International Journal of Hygiene and Environmental Health 229 (2020) 113592

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Review

Chemicals inhaled from spray cleaning and disinfection products and their respiratory effects. A comprehensive review

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ARTICLE INFO

Keywords:
Spray cleaning and disinfection products
Exposure
Respiratory effects
Asthma
Allergy
Hypotheses

ABSTRACT

Spray cleaning and disinfection products have been associated with adverse respiratory effects in professional cleaners and among residents doing domestic cleaning. This review combines information about use of spray products from epidemiological and clinical studies, *in vivo* and *in vitro* toxicological studies of cleaning chemicals, as well as human and field exposure studies. The most frequent chemicals in spray cleaning and disinfection products were compiled, based on registrations in the Danish Product Registry. The chemicals were divided into acids, bases, disinfectants, fragrances, organic solvents, propellants, and tensides. In addition, an assessment of selected cleaning and disinfectant chemicals in spray products was carried out. Chemicals of concern regarding respiratory effects (e.g. asthma) are corrosive chemicals such as strong acids and bases (including ammonia and hypochlorite) and quaternary ammonium compounds (QACs). However, the evidence for respiratory effects after inhalation of QACs is ambiguous. Common fragrances are generally not considered to be of concern following inhalation. Solvents including glycols and glycol ethers as well as propellants are generally weak airway irritants and not expected to induce sensitization in the airways. Mixing of certain cleaning products can produce corrosive airborne chemicals. We discuss different hypotheses for the mechanisms behind the development of respiratory effects of inhalation of chemicals in cleaning agents. An integrative assessment is needed to understand how these chemicals can cause the various respiratory effects.

1. Introduction

Use of cleaning agents and disinfection products may lead to a broad range of exposure scenarios, whereof some are associated with respiratory effects that range from acute temporary upper airway irritation to obstructive lung disease. Numerous studies published from 1975 to 2020 have been reviewed and relate the use of cleaning agents to compromised respiratory health, most importantly asthma (Folletti et al., 2014, 2017; Mirabelli et al., 2007; Quirce and Barranco, 2010; Siracusa et al., 2013; Vincent et al., 2017b; Wiszniewska and Walusiak-Skorupa, 2014). None of the reviews focused specifically on spray products for cleaning, though several original studies have investigated the association between the use of spray cleaning products and the risk of respiratory symptoms and asthma within professional cleaners, professional domestic cleaners, and healthcare or hospital workers (Dumas et al., 2012; Lee et al., 2014; Medina-Ramón et al., 2006). Furthermore, three studies have investigated cleaning and asthma in populations of non-professional domestic household cleaners (Bédard et al., 2014; Le Moual et al., 2012; Mirabelli et al., 2007; Zock et al., 2007). Evidence of a deleterious role of cleaning products mostly derives from studies on occupational exposure and risk of, or exacerbation of, asthma, but adverse respiratory effects from non-professional home-cleaning exposure have also been observed, mainly among women (Le Moual et al., 2014; Lipinska-Orjzanowska et al., 2017; Svanes et al., 2018). Clinical data is scarce; for instance, the Finnish Institute of Occupational Health diagnosed 20 occupational asthma (OA) cases in professional cleaners during an 11 year study period, which resulted in 1.8 OA cases/year among an estimated number of

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https://doi.org/10.1016/j.ijheh.2020.113592
Received 21 February 2020; Received in revised form 20 May 2020; Accepted 3 July 2020
Available online 15 August 2020
1438-4639/

professional cleaners of around 56000, far less than suggested from the epidemiological literature (Mäkelä et al., 2011).

Potential mechanisms underlying the development of asthma and decline in lung function due to occupational risk factors have been proposed (Siracusa et al., 2013; Svanes et al., 2018; Tarlo and Lemiere, 2014). These include sensitizer-induced asthma, involving non-IgE, and IgE dependent pathways, as well as irritant-induced asthma (Tarlo and Lemiere, 2014). The two sensitizer-induced pathways are diagnostically difficult to separate, for instance after exposure to quaternary ammonium compounds (QACs) (Bellier et al., 2015). Accidental high-level exposure to cleaning chemicals is believed to induce acute-onset irritant-induced asthma (Quinn et al., 2015; Vandenplas et al., 2014b); however, frequent daily low-level exposure has also been proposed to cause irritant-induced asthma (Vandenplas et al., 2014b). Furthermore, health effects may be further aggravated by the interaction of cleaning chemicals with the ubiquitous ozone resulting in generation of oxidation products such as formaldehyde and reactive oxygen species (Carslaw et al., 2017; Nørgaard et al., 2014b). Thus, the exact mechanisms continue to be a "black box" (De Matteis and Cullinan, 2015).

The main causative scenario might involve spray application of products, either by trigger sprays (pump) or pressurized spray cans, as suggested in many studies and reviews, e.g. (Nielsen and Bach, 1999; Quirce and Barranco, 2010; Svanes et al., 2018; Weinmann et al., 2017; Zock et al., 2010). Recommendations to eliminate the use of spray cleaning products have already been put forward (Cummings and Virji, 2018). Several cases of lung injury have been reported due to the use of spray coating and impregnation products (usually waterproofing) (Duch et al., 2014; Garnier et al., 2018; Scheepers et al., 2017; Sørli et al., 2018). These products' content of fluoro-silicone polymers may be the causative chemical (Hahn and Begemann, 2012; Larsen et al., 2014; Nørgaard et al., 2014a). There are only few cases of lung injury reported following the use of spray products for surface cleaning and disinfection, e.g. (Bédard et al., 2014; Burge and Richardson, 1994; Houtappel et al., 2008; Le Moual et al., 2012; Purohit et al., 2000). The use of cleaning sprays was, however, associated with lower evening forced expiratory volume (FEV_1), showing a positive dose–response effect with the frequency of spraying (Vizcaya et al., 2015).

Spray cleaning and disinfection products generally contain complex mixtures of chemicals, including volatile organic compounds (VOCs) mainly used as solvents and fragrances, preservatives, disinfectants, and tensides (Gerster et al., 2014b). Spray products release chemicals as gasses and aerosols, which also contain non-volatile chemicals that are inhaled during the cleaning process. Intuitively, inhalation exposure may therefore be higher following spray application compared to other means of application of liquid products (Zock et al., 2007). However, the causative chemical(s) and their link to respiratory disorders in occupational and general populations have not been clearly identified. Ammonia, bleach (chlorine, hypochlorite), reaction products from mixing products (e.g. hypochlorite with acid or ammonia), detergents, disinfectants (QACs), glass cleaners, limescale removers (e.g. acids), cleaning sprays, and air fresheners (occasionally mentioned) have all been suggested as causative chemicals or product categories based on survey studies, e.g. (Carder et al., 2019; Siracusa et al., 2013; Vizcaya et al., 2015), see Table S1. A special focus has been on QACs as causative chemicals (Gonzalez et al., 2014; Paris et al., 2012; Vandenplas et al., 2013), but many chemicals or mixtures have only been associated with non-specific respiratory effects like lung function decline.

Clearly, there is a need for accurate measures of gas- and particle phase chemicals released by spray-type cleaning and disinfection products to assess their adverse respiratory effects in acute and longitudinal exposure studies. The main objective of this review is to identify specific chemicals potentially causing adverse respiratory effects in defined scenarios by reviewing the epidemiological and toxicological literature. Furthermore, we aim to assess how exposure to spray cleaning aerosols may result in respiratory effects.

2. Method

2.1. Search approach

This comprehensive review integrates and analyzes studies about cleaning agents with focus on spray cleaning products and their associated respiratory effects in cleaning personnel. Searches in PubMed and Google Scholar were carried out with a number of different combinations of keywords: "cleaning" and "airway effects", or "asthma" or "health" or "lung effects" or "respiratory effects"; further different combinations of "spray products" and "cleaning" or "asthma" or "lung effects" or "lung injury" or "inflammation" or "dyspnea" or "pulmonary effects" were used. Finally, our own collection of literature compiled during the last decade up to December 2019 was included. The search excludes use of spray impregnation/coating products as already reviewed by Garnier et al. (2018). High molecular weight compounds like proteins and enzymes were excluded as well.

2.2. Identification of chemicals used in spray cleaning and disinfection products from the Danish Product Registry

The Danish Product Registry is a database on substances and materials for professional use in Denmark run by the Danish Working Environment Authority. Products are included in the Registry if it is produced or imported to Denmark in volumes >100 kg/y and the product is hazardous (a detailed definition of substances and materials included can be found in Supplementary Information). Products solely used by private consumers do not need to be in the Product Registry, but household cleaning agents are expected to be well covered by the registry due to a large overlap in professional and private use. The database is updated every second year and contains detailed information on product composition and 'volume' put on the Danish market as well as industry and feature codes, e.g. general cleaning in buildings, multipurpose cleaning agent. The Product Registry is used by the Danish authorities for market surveillance purposes and trend analyses as well as by medical professionals in case of poisoning or acute allergic reactions; finally, researchers can be granted access for specific studies.

The Product Registry was searched for products with the following feature codes: 'general cleaning', 'window polish' and 'disinfection'. In this way spray products for industrial cleaning and disinfection, such as high-pressure cleaning or spray products used in the auto business were excluded. As the Product Registry lacks information on application type, spray products could not be identified in the Product Registry. Products on pressurized cans were identified by a simultaneous search for propellants such as propane and butane. Trigger spray products identified in the Product Registry were subsequently verified by a search on the internet, Table 1.

2.3. Selection of chemicals of concern from the literature

A large number of chemicals have been mentioned in the literature in connection with cleaning and respiratory effects, see overview in Table S1. A starting point for identification of chemicals of concerns in the current review was Table S1, together with Tables 2 and 3 which shows the most frequently used chemicals in 101 spray cleaning and disinfection products identified in the Danish Product Registry. The information from the tables was combined with the epidemiological literature and other exposure effect studies. The finally identified chemicals or groups of chemicals are stated in Section 9.

2.4. Hazard assessment of specific chemicals in spray cleaning and disinfection products

The chemicals in Tables 2 and 3 were assessed according to previous assessments by Baur et al. (2012) and Hahn et al. (2010) with specific focus on respiratory effects.

Table 1
Distribution of products in different product categories[a] of 101 spray cleaning and disinfection products identified in the Danish Product Registry. The 101 products consist of 72 trigger sprays, 24 pressurized can sprays, and 5 non-aerosol forming sprays (foam sprays).

Product category	Number of products	Comments
Glass cleaners	37	
Disinfectants	15	
Sanitary + bathroom cleaners	13	
Oven + grill cleaners	9	
Multipurpose cleaners	7	
Graffiti removers	4	
Limescale removers	3	
Stain removers	3	
Basic cleaners	2	For very thorough cleaning, e.g. before painting
Others	4	Kitchen, textile, steel, deodorizer
Other multifunction cleaners	4	Disinfectant + multipurpose, Glass + multipurpose, Bathroom + kitchen

[a] We carried out the categorization based on information from manufacturers, information in the Danish Product Registry, and the products' content of active chemicals.

3. Asthma phenotypes of relevance for exposure to cleaning and disinfection chemicals

Cleaning and disinfection chemicals may lead to respiratory effects ranging from acute temporary upper airway irritation to obstructive lung disease, including asthma and asthma like disease. Some of the cleaning chemicals or mixtures thereof in the products could potentially cause chronic obstructive lung disease (COPD) (Dumas et al., 2019; Svanes et al., 2015), but the literature is scarce, and will not be touched upon. Asthma is characterized by chronic airway inflammation. It is defined by respiratory symptoms such as wheezing, shortness of breath, chest tightness, and coughing that vary over time and in intensity, together with variable expiratory airflow limitation (https://ginasthma.org/). Pathologically, asthma is characterized by inflammation and remodeling of the airways by thickening of the smooth muscle layer and changes in the submucosal mucous glands and lamina propria.

Asthma is common, affecting 1–18% of the population in different countries (https://ginasthma.org/). For adult-onset asthma, a large European population-based cohort showed that the prevalence of asthma increased from 4.8% in the early 1990's when the participants were between 22 and 44 years old to 7.3% 20 years later (Jarvis et al., 2018). It has been suggested that about 15% of adult-onset asthma is attributable to occupational exposure (Torén and Blanc, 2009). Work-related asthma is either caused by occupational exposures (OA), or exacerbated by occupational exposures (work exacerbated asthma, WEA), e.g. cleaning chemicals (Baur et al., 2012). OA, like asthma in general, can be divided into sensitizer induced and non-sensitizer (non-allergic) induced asthma.

The mechanism underlying development of asthma is poorly understood, but has been suggested to include complex interaction between inflammation and airway remodeling leading to bronchial hyper-responsiveness (King et al., 2018). Sensitizer induced asthma often has a high eosinophilic count in the sputum and blood, and is characterized by activation of T-cells (T-helper type 2) (Pelletier and Savignac, 2018), leading to release of inflammatory cytokines (i.a. IL4, IL5, and IL13), and promotion of IgE synthesis. Occupational exposures are common causes of sensitizer induced asthma (Tarlo and Lemiere, 2014). Occupational sensitizers are commonly high molecular weight compounds (>10 kD, usually a protein, e.g. an enzyme). Low molecular weight compounds can also cause sensitization and, subsequently, asthma (Quirce and Bernstein, 2011) and production of specific IgE antibodies (Pralong et al., 2012).The mechanisms are however poorly understood for most low molecular weight chemical (Tarlo et al., 2017). Sensitizer induced asthma has been reported after exposure to cleaning agents with QAC, ethanolamine, and glutaraldehyde (Folletti et al., 2017; Quirce and Barranco, 2010; Vandenplas et al., 2013; Walters et al., 2018).

Non-sensitizer induced asthma is generally characterized by a low eosinophilic count in sputum and blood (Esteban-Gorgojo et al., 2018). Irritant-induced asthma is considered the most important mechanism in relation to cleaning agents (Folletti et al., 2017) and accidental high-level exposure to cleaning chemicals is believed to induce acute-onset irritant-induced asthma (Vandenplas et al., 2014a). Common exposures during cleaning work are chlorine and ammonia, especially after mixing hypochlorite with acid or ammonia (Quirce and Barranco, 2010; Sastre et al., 2011). Frequent daily low-level exposure to irritants, which is the typical scenario for cleaners, has also been proposed to cause irritant-induced asthma (Vandenplas et al., 2013, 2014a), e.g. chlorine, ammonia, hydrochloric acid, chloramine, and sodium hydroxide. QACs and ethanolamine have been considered to be both sensitizers and irritants (Quirce and Barranco, 2010), though the mechanisms for QAC-related asthma is not clear (Bellier et al., 2015) and that existing knowledge is inadequate (LaKind and Goodman, 2019).

4. Epidemiological findings

A broad range of study types show work in professional and non-professional cleaning to be associated with asthma (Folletti et al., 2014, 2017; Quirce and Barranco, 2010; Siracusa et al., 2013; Vincent et al., 2017b; Zock et al., 2010). Most studies use self-report of spray exposure (Dumas et al., 2012; Lee et al., 2014; Nielsen and Bach, 1999; Zock et al., 2007), with a few studies applying Job Exposure Matrices (JEMs) (Dumas et al., 2012, 2017, 2020). The outcomes are mainly assessed by self-response to one or more questions on asthma attacks, physician diagnosed asthma, breathlessness, or wheezing (Bédard et al., 2014; Dumas et al., 2012; Nielsen and Bach, 1999). Epidemiological studies on exposure to cleaning sprays and asthma are summarised in Table 4.

4.1. Studies using job exposure matrices

In a case-control study, hospital worker exposure was assessed by self-report and by expert assessment combined with an asthma specific JEM for 22 asthmagens (Dumas et al., 2012). The risk for current asthma was increasesed among self-reported cleaning spray users, odds ratio (OR) = 1.36 (0.74–2.50). Using the JEM, a dose-dependent association between use of spray products and prevalence of asthma was found, OR 2.87 (1.02–8.11) for moderate/high compared to no exposure. However, only 8 workers were categorized as exposed to cleaning spray.

Two studies from the US Nursing cohort (Dumas et al., 2017, 2020) applied a Job-Task Exposure Matrix (JTEM) (Quinot et al., 2017) for disinfectant exposure with 24 groups (8 subcategories of nurses and 3 on tasks). Use of disinfectants for cleaning of medical instruments (both spray and not spray) was associated with poorly (OR 1.37 ([1.05–1.79]) and very poorly (1.88 [1.38–2.56]) controlled asthma compared to no use of disinfectants. Similar associations were found for self-reported spray exposure, Table 4. Also specific disinfectants, i.e. formaldehyde, glutaraldehyde, hypochlorite, hydrogen peroxide and enzymatic cleaners were associated with poor asthma control, but exposure to QACs and alcohol was not (Dumas et al., 2017). In a subsequent follow-up of the cohort no association between disinfections (spray and not spray) and incident asthma was observed (Dumas et al., 2020).

4.2. Other epidemiological studies

Among female professional domestic cleaners, in two small cross-sectional panel studies, the use of degreasing and cleaning sprays was associated with lower respiratory tract symptoms and bronchial hyper-

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Table 2
The most frequently used chemicals in 101 spray cleaning products (frequency ≥ 9 products) identified in the Danish Product Registry. Chemicals are grouped together in homologous series of chemicals and otherwise closely related chemicals. The indicated Min-Max quantities may be subject to large uncertainty.

CAS numbers	Chemicals	Class[a]	Function of chemical	Number of products	Min – Max content (%)	Respiratory effect
7732-18-5	Water 5 products did not contain water, for 2 products water information was missing	In-organic	Solvent	94	25–99.66	–
	Fragrances (usually mixtures e.g. plant extracts)		Fragrance	36	0.00015–0.25	–
68439-46-3 68439-50-9 68439-51-0 68002-97-1 69227-22-1 71060-57-6 78330-20-8 69011-36-5	Alcohols, C9-11, ethoxylated Alcohols, C12-14, ethoxylated Alcohols, C12-14, ethoxylated propoxylated Alcohols, C10-16, ethoxylated Alcohols, C10-16, ethoxylated propoxylated Alcohols, C8-10, ethoxylated Alcohols, C9-11-iso-, C10 rich, ethoxylated Poly (oxy-1,2-ethanediyl),.alpha.-tridecyl-.omega.-hydroxy-, branched	NVOC	Tenside	30	0.01–4.00	?
67-63-0	2-propanol	VVOC	Solvent	31	0.01–2.10	–
64-17-5	Ethanol	VVOC	Solvent	26	0.15–67.90	–
68891-38-3 68585-34-2	Poly (oxy-1,2-ethanediyl),.alpha.-sulfo-.omega.-hydroxy-, C12-14-alkyl ethers, sodium salts Poly (oxy-1,2-ethanediyl),.alpha.-sulfo-.omega.-hydroxy-, C10-16-alkyl ethers, sodium salts	NVOC	Tenside	26	0.03–3.41	?
1310-73-2 1310-58-3	Sodium hydroxide Potassium hydroxide	Salt	Base	25	0.0002–10	Strong bases +
1336-21-6 7664-41-7	Ammonium hydroxide Ammonia	In-organic	Base	20	0.04–0.90	+,[b]
77-92-9 5949-29-1	Citric acid Citric acid monohydrate	Organic	Acid	15	0.0005–14.00	?
63449-41-2 68391-01-5 68424-85-1 68989-01-5 8001-54-5 7173-51-5	Quaternary ammonium compounds, benzyl-C8-18-alkyldimethyl, chlorides Quaternary ammonium compounds, benzyl-C12-18-alkyldimethyl, chlorides Quaternary ammonium compounds, benzyl-C12-16-alkyldimethyl, chlorides Quaternary ammonium compounds, benzyl-C12-16-alkyldimethyl, chlorides, salts with 1,2-benzisothiazol-3 (2 h)-one 1,1-dioxide (1:1) Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides 1-decanaminium, N-decyl-N,N-dimethyl-, chloride	NVOC	Disinfectant/ Tenside	12	0.0001–10	-,[b], ?[c]
74-98-6	Propane	VVOC	Propellant	11	0.8–10.0	–
106-97-8	Butane	VVOC	Propellant	11	0.48–28.6	–
57-55-6	1,2-Propanediol	VOC Glycol	Solvent	10	0.0024–15	–
111-76-2	2-butoxyethanol	VOC Glycol ether	Solvent	10	0.28–11.90	–
124-38-9	Carbon dioxide	In-organic gas	Propellant	9	4–5	–

(continued on next page)

Table 2 (*continued*)

CAS numbers	Chemicals	Class[a]	Function of chemical	Number of products	Min – Max content (%)	Respiratory effect
141-43-5	2-aminoethanol	VOC	Solvent	9	0.09–8.28	-,[b]
7647-14-5	Sodium chloride	Salt		9	~0–0.1	–
34590-94-8	(2-methoxymethylethoxy)-propanol (dipropylenglycolmonomethylether (uspec.))	VOC Glycol ether	Solvent	9	0.0048–14	–

-) Not suspected to be associated with respiratory effects or inadequate evidence according to Baur et al. (2012). +) Suspected to be associated with pulmonary effects as a corrosive, irritative, or surface-active chemical. ? No information available.
[a] Classes of organic compounds: VVOC (very volatile organic compound); VOC (volatile organic compound); NVOC (non-VOC).
[b] According to Baur et al. (2012).
[c] According to Hahn et al. (2010).

Table 3
Frequency of products (<9) with chemicals that in the literature have been suspected to be involved in development of respiratory effects in 101 spray cleaning and disinfection products (if not listed in Table 2) as identified in Danish Product Registry.

CAS numbers	Chemicals	Class	Number of products	Min – Max content (%)	Properties	Respiratory effect
7681-52-9	Sodium hypochlorite	Salt	5	0.63–4.5	Chlorine precursor, corrosive	+,[a,b]
52-51-7	2-bromo-2-nitro-1,3-propanediol Bronopol (formaldehyde releaser)	Organic solid	4	0.00002–0.15	Disinfectant, skin allergen	-,[b]
111-42-2	2,2′-iminodiethanol	VOC	3	0.01–0.06	Surfactant	-,[a]
75-75-2	Methanesulfonic acid	Organic acid	3	0.1–0.7	Strong acid, corrosive	n/a
7664-93-9	Sulfuric acid	In-organic	3	0.07–10	Strong acid, corrosive	+,[a]
7722-84-1	Hydrogen peroxide	In-organic	3	0.28–5	Peroxide, oxidant	-,[b]
7664-38-2	Phosphoric acid	In-organic	2	1.68–6	Weak acid	n/a
110-91-8	Morpholine	VOC	2	0.13–0.5	Additive, weak base	(+,[a])
929-06-6	2-(2-aminoethoxy)-ethanol	VOC Glycolamine	1	- 0.95	Surfactant	–

- Not suspected to be associated with respiratory effects or inadequate evidence according to Baur et al. (2012). +) Suspected to be associated with respiratory effects as a corrosive/irritative or surface-active chemical. ?) No information available.
[a] According to Baur et al. (2012).
[b] According to Hahn et al. (2010). n/a: No information available.

responsiveness, but study size precluded significant associations (Medina-Ramón et al., 2006; Whitworth et al., 2019). A cross-sectional study among cleaning workers in Northern California also found association between cleaning spray use and respiratory symptoms. Exposure to cleaning tasks using spray at either medium or high levels, based on frequency (days/week) and duration (hours/day), increased the risk of respiratory symptoms (OR = 3.16, 95% confidence interval (CI) 1.24–8.04 and OR = 1.98 (0.87–4.51), respectively) (Lee et al., 2014).

Three studies within private domestic cleaning all showed association between self-reported spray use in cleaning and asthma or symptoms of asthma (Bédard et al., 2014; Le Moual et al., 2012; Zock et al., 2007). Using two or more cleaning sprays at least weekly was significantly associated with current asthma and to a high score for asthma symptoms ($\geq$2) (Le Moual et al., 2012). Bédard et al. (2014) showed that elderly women without household help had increased risk of current asthma with increasing use of spray product (0, 1 or $\geq$ 2 times per week, trend, $p = 0.04$). A similar observation was done in a study from the European Community Respiratory Health Survey (ECRHS) on the use of spray within households and risk of asthma, measured as asthma symptoms/use of medication, or as self-reported physician-diagnosed asthma (Zock et al., 2007).

A follow-up study among 22 European study centers as part of the large ECRHS studied new-onset asthma among health care workers compared to administrative workers. Participants who reported use of spray cleaning products had an increased risk of new-onset asthma (relative risk (RR) = 2.36 (0.99–5.64) (Mirabelli et al., 2007). Another follow-up study comparing current and former female cleaners, risk of respiratory symptoms among was increased among current cleaners and among spray users in current cleaners; symptoms decreased upon cessation of spray use (Nielsen and Bach, 1999).

Professional cleaners (n = 42) with a history of asthma and/or recent respiratory symptoms were identified together with symptom-free controls (n = 53) in a case-control study (Vizcaya et al., 2013). Information on occupational and domestic use of cleaning products was obtained by interview. FeNO (Fractional exhaled Nitric Oxide (biological marker of inflammation)), FEV_1, FVC (forced vital capacity), and $FEF_{25–75\%}$ (mean forced expiratory flow between 25% and 75% of the FVC) were measured at a clinical examination. Total IgE, pulmonary surfactant protein D and the 16 kDa Club Cell secretory protein were measured in blood serum and inflammatory biomarkers in exhaled breath condensate (EBC). Asthma was found to be associated with an 8% lower FEV_1, a higher prevalence of atopy (42% vs. 10%), and a 2.9 times higher level of total IgE. Asthma status was not associated with the other respiratory biomarkers. Asthmatics that frequently used multi-use cleaning sprays were more often atopic, and use of multipurpose cleaning agent sprays was associated with higher FeNO. Elevated FeNO was not observed in a cross-sectional study of cleaners (n = 40) and controls (n = 40) (Corradi et al., 2012). However, the use and abundance of spray products is not clear. Exhaled breath condensate analyses revealed slightly higher levels of H_2O_2, pH, and NH_4^+, respectively, in cleaners than in controls; 4-hydroxynonenal (oxidative stress marker) did not differ significantly between the groups.

In a 15-day panel study with 21 asthmatic female cleaners, participants self-reported use of cleaning products and respiratory symptoms. In addition to the conclusion that cleaning products may exacerbate asthma, the study also showed that among participants without atopy, lower respiratory tract symptoms were associated with the use of strong irritants like hydrochloric acid and detergents (Vizcaya et al., 2015). Similarly, FeNO levels were higher among females without asthma using sprays with acids, whereas no associations were seen among females

Table 4
Epidemiological findings of associations between spray use in occupational or in household cleaning and asthma or respiratory symptoms.

Author	Design	Sector	Population	Exposure	Type of health effect	Primary findings
Bédard et al. (2014) France	Nested case-control (8th quetionnaire, 2005 and alive in 2009)	Private household cleaning	235 women with current asthma (cases) 335 women without asthma (controls) At least 68 years	Spray use assessed 1. Self-reported 2. Principal component analysis 3. Composite score for sprays	Self-reported ever asthma: "Have you ever had asthma attacks?" "Have you ever had attacks of breathlessness at rest with wheeze?" Current asthma/combined with yes to one of two questions: In the past 12 months 1. Asthma attack. 2. One of five asthma-like symptoms (wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath exercise, woken by attack of shortness of breath).	**Current asthma** (Reference = 0 spray) Spray use ≥1: aOR = 1.45 (0.94–2.24) Current asthma (without household help) Spray use ≥1 weekly: aOR = 1.86 (1.04–3.33) Trend Spray use 1 weekly: aOR = 1.29 (0.63–2.66) Spray use ≥2 weekly: aOR = 2.63 (1.03–6.67) Decreasing spray Weekly: aOR = 3.32 (1.34–8.22) Current asthma (with household help) Spray use ≥1: aOR = 0.98 (0.47–2.03) Decreasing spray Weekly: aOR = 0.76 (0.23-2.49-8.22)
Brooks et al. (2020) New Zealand	Cross-sectional (2008–2010)	Professional cleaners (hospitals, schools, commercial buildings, and hospitality and industrial settings)	425 cleaners 281 references (retail/service workers and bus drivers)	Self-reported information on spray use (cleaning products)	Self-reported current asthma: In the past 12 months 1. Woken by shortness of breath 2. Asthma attack Currently using: 3. Asthma medication	**Current asthma** Reference = No use of the exposure (internal reference) or external reference **Internal comparison** Self-reported assessment of spray Furniture spray: aOR = 1.41 (0.78–2.55) Glass-cleaning spray: aOR = 1.07 (0.68–1.69) Sprays for carpets, rugs, curtains: aOR = 3.25 (1.16–9.10) Sprays for mopping the floor: aOR = 1.20 (0.71–2.04) Oven sprays: aOR = 0.66 (0.08–5.85) Air-refreshing sprays: aOR = 0.97 (0.59–1.60) Multi-purpose antibacterial cleaning spray: aOR = 1.28 (0.80–2.04) Other sprays: aOR = 1.16 (0.54–2.49) **External comparison** Self-reported spray use Furniture spray: aOR = 2.50 (1.27–4.91) Glass-cleaning spray: aOR = 1.88 (1.17–3.02) Sprays for carpets, rugs, curtains: aOR = 5.57 (1.94–16.03) Sprays for mopping the floor: aOR = 2.13 (1.18–3.87) Oven sprays: aOR = 1.24 (0.14–11.03) Air-refreshing sprays: aOR = 1.81

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Table 4 (*continued*)

Author	Design	Sector	Population	Exposure	Type of health effect	Primary findings
						(1.02–3.23) Multi-purpose antibacterial cleaning spray: aOR = 2.15 (1.25–3.68) Other sprays: aOR = 2.14 (0.96–4.76)
Dumas et al. (2012) France	A case-control and family-based study (EGEA2[a], follow-up 2003–2007)	Hospital workers	179 female hospital workers 545 non-hospital female workers (controls) Age 18–79 years	Exposure to cleaning agents 1. Self-reported 2. Expert assessment 3. Asthma-specific job exposure matrix	Self-reported ever asthma asthma: “Have you ever had asthma attacks?" “Have you ever had attacks of breathlessness at rest with wheezing?" Current asthma/combined with yes to one of two questions: In the past 12 months 1. Asthma attacks 2. Respiratory symptoms 3. Asthma treatment	**Current asthma** (reference = non hospital workers) Self-reported assessment of spray Spray use ≥1 day/week: aOR = 1.36 (0.74–2.50) Expert assessment of spray Spray use ≥1 day/week: aOR = 1.21 (0.67–2.18) Expert assessment of spray Low or environmental intensity: aOR = 0.75 (0.34–1.65) Moderate to high intensity: aOR = 2.06 (0.87–4.88) Expert and JEM assessment of spray Low or environmental intensity: aOR = 1.51 (0.46–4.98) Moderate to high intensity: aOR = 2.87 (1.02–8.11)
Dumas et al. (2017) US	Cohort study using prospectively collected data (Nurses Health Study II. 2011–2015; enrolled in 1989)	Nursing population	4,102 female nurses with asthma Mean age 58 years (2013)	Self-reported information on weekly spray use (yes/no). Information on disinfection task (2013) summing up to a Job-Task-Exposure Matrix (JTEM) based on information from a random sample of women without asthma (n = 9,073). JTEM combines types of nursing job and general disinfection tasks. Exposure level: Low, Medium, High	Asthma Control Test score (range 5–25). Five questions including information concerning the past four months: Activity limitations Frequency of symptoms Frequency of use of quick-relief medication 25: Controlled 20-24: Partly controlled 16-19: Poorly controlled ≤15: Very poorly controlled	**Asthma control** (reference = Asthma, controlled) Weekly use of sprays Partly controlled: aOR = 1.13 (0.94–1.36) Poorly controlled: aOR = 1.50 (1.16–1.94) Very poorly controlled: aOR = 1.38 (1.00–1.92)
Dumas et al. (2020) US	Prospective cohort (Nurses Health Study II. 2009–2015; enrolled in 1989)	Nursing population	61,539 female nurses without asthma Mean age 55 years (2009)	Self-reported information on weekly spray use (yes/no). Information on disinfection task (2013) summing up to a Job-Task-Exposure Matrix (JTEM) based on information from a random sample of women without asthma (n = 9,073). JTEM combines types of nursing job and general disinfection tasks. Exposure level: Low, Medium, High	Physician diagnosed asthma and use of any asthma medication within the past year (yes/no)	**Self-reported physician diagnosed asthma** (reference = no weekly use of sprays) Self-reported cleaning/disinfection, weekly spray use Yes: aHR = 1.10 (0.76–1.59)
Le Moual et al. (2012) France	Case-control (EGEA[a], 2003–2007)	Private household cleaning	244 women with asthma (cases) 439 women without asthma (controls) Mean age 44 years	Self-reported current domestic exposures/spray exposure weekly 1. Furniture 2. Glass-cleaning 3. Carpet 4. Mopping the floor 5. Oven 6. Ironing	Self-reported asthma symptoms High score = two or more symptoms in the past 12 months: 1. Wheezy breathlessness 2. Woken up by chest tightness 3. Woken up by an attack of shortness of breath	**Spray use ≥2 types of sprays day/week (self-reported)** (reference = never symptoms) Self-reported symptom score Symptom score 1: aOR = 0.99 (0.59–1.73) Symptom score ≥2:

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Table 4 (*continued*)

Author	Design	Sector	Population	Exposure	Type of health effect	Primary findings
				7. Air-refreshing 8. Other use	4. Attack of shortness of breath at rest 5. Attack of shortness of breath after exercise Self-reported current asthma/combined with yes to one of two questions: In the past 12 months 1. Asthma attack 2. Asthma treatment 3. Asthma-like symptoms	aOR = 2.50 (1.54–4.03) Self-reported current asthma All: aOR = 1.67 (1.08–2.56) Controlled: aOR = 1.32 (0.75–2.34) Poorly controlled: aOR = 2.04 (1.25–3.32)
Le Moual et al. (2014) France	Case-control (EGEA[a], 2003–2007)	Household cleaning	116 females with asthma (cases) 197 females without asthma (controls) Mean age 42 years Self-reported current asthma in the past 12 months: 1. Asthma attack 2. Asthma treatment 3. Asthma-like symptoms	Cleaning agents (five) and eight types of spray in four groups (times use/week): 1. Furniture 2. Glass cleaning 3. Air freshener 4. Other use (carpet, mopping the floor, oven, ironing, or other use) A combined exposure: Spray, at least one out of eight weekly	Exhaled nitric oxide fraction (FeNO) measurements: 1. Log transformed FeNO 2. Forced vital capacity (FVC) 3. Forced expiratory volume in 1 s (FEV_1) 4. FEV_1% predicted values	**Exhaled nitric oxide fraction and forced expiratory volume in 1 s (FEV_1)** (reference = no spray use) Exhaled nitric oxide fraction Spray, at least one out of eight Non-asthmatics: GM ratio = 1.09 (1.03–1.16) Asthmatics: GM ratio = 0.97 (0.86–1.09) Forced expiratory volume in 1 s (FEV_1) Spray, at least one out of eight Non-asthmatics: mL β = −89 (−197, −18) Asthmatics: mL β = −159 (−326, −9)
Lee et al. (2014) US	Cross-sectional (2010)	Hospital and campus cleaners	183 cleaning workers (142 patient support assistants [hospital workers] and 41 campus cleaners) Age <30 - >60 years	Self-reported work tasks including cleaning tasks using spray and and exposure to cleaning products	Self-reported respiratory symptoms In the past 12 months symptoms involving the respiratory tract: 1. Stuffy, itchy or runny nose 2. Burning in nose or throat 3. Cough 4. Phlegm from chest 5. Chest tightness 6. Shortness of breath 7. Wheezing Response: Daily; several times weekly; several times monthly; several times yearly; never in the past 12 months.	**Respiratory symptoms** (reference = no/low exposure) Self-reported assessment of cleaning tasks using spray Medium exposure: aOR = 3.16 (1.24–8.04) High exposure: aOR = 1.98 (0.87–4.51)
Medina-Ramón et al. (2006) Spain	Two week Panel study (June 2001–April 2002)	Domestic cleaners (profes-sional)	43 female cleaning workers with current asthma symptoms/ asthma attack (within the past 12 months) Age 34–65 years	Self-reported cleaning exposure/two-week diary. Self-reported checklist - each day assessing exposure both at work and at home including hours of cleaning.	Self-reported short-term respiratory effect. Lower respiratory tracts symptoms was based on a daily symptom severity score based on scores for: 1. Chest thightness 2. Wheezing 3. Shortness of breath 4. Cough	**Lung function/Lower respiratory tract symptoms daily** (reference = days without exposure to the cleaning task/ product) Based on 582 days Self-reported use of cleaning products Furniture spray: aOR = 2.2 (0.9–5.4) Glass cleaning spray: aOR = 2.9 (1.3–6.4) Degreasing spray: aOR = 6.9 (2.9–16.0) Air refreshing spray: aOR = 7.8 (2.6–24.0)
Mirabelli et al. (2007) 22 European sites (10 countries)	Prospective population-based cohort study (ECRHS[b], Baseline 1991/Follow-up 1998–1999)	Hospital	332 nurses and healthcare professionals at ECRHS II (symptom-free at baseline) 2,481 professional	Self-reported cleaning product use (less than once/week vs. 1–7 days/ week)	Self-reported new-onset asthma based on current asthma (at follow-up) Positive response to one of the following: 1. Have you had an attack of	**New-onset asthma** (reference = professional, administrative occupations) Self-reported use of

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Table 4 (*continued*)

Author	Design	Sector	Population	Exposure	Type of health effect	Primary findings
			and/or administrative ECRHS II (symptom-free at baseline) Age 28–56 years		asthma in the last 12 months? 2. Have you been woken by an attack of shortness of breath at any time in last 12 months? 3. Are you currently taking any medication for asthma?	cleaning products (≥1 day/week) Any products in spray form: aRR = 2.36 (0.99–5.64)
Nielsen and Bach (1999) Danmark	Prospective population study (Baseline 1989/ follow-up 1991)	Profes-sional cleaners (nursing home, schools, offices)	1,011 female cleaners Age <30 to >50 years	Self-reported use of cleaning products (Range: never to all the time)	Self-reported asthma 1. Defined as attacks with wheezing breathing during the last 12 months. 2. If yes, variation of symptoms in relation to work and leisure time. 3. Consultation at a medical doctor during the last 12 months due to airway symptoms.	**Asthma** (reference = former cleaners/never) Self-reported employment status in 1991 Cleaner: OR = 1.0 (0.4–2.7) Use of sprays Ceased: OR = 1.6 (0.3–7.3) Started: OR = 2.4 (0.6–10.0) Continuously: OR = 3.0 (0.9–10.0)
Vizcaya et al. (2013) Spain	Nested case-control (December 2008 to September 2009)	Cleaning workers	42 cleaning workers with a history of asthma and/or recent respiratory symptoms (cases) 53 symptom-free (controls) (Around 90% females) Cases Mean age 42 years Controls Means age 48 years	Self-reported use of cleaning products within the past 12 months including average hours using products; occupationally and domestically.	Self-reported asthma and respiratory symptoms	**Asthma** (reference = no use of the product in the past year/0) Self-reported product use, occupationally use in the past year - spray or aerosol form Multi-use products: aOR = 4.1 (1.0–18) Degreases: aOR = 1.1 (0.4–3.1) Dust mop products: aOR = 1.5 (0.6–3.9) Limescale removers: aOR = 1.5 (0.5–5.0) Glasscleaners: aOR = 1.2 (0.3–5.9) Number of differentt sprays: 1-2: aOR = 0.8 (0.3–2.4) 3-5: aOR = 2.1 (0.6–7.4)
Vizcaya et al. (2015) Spain	Panel study (15-day period, 2008)	Cleaning workers	21 cleaning workers with asthma symptoms Median age 45 years	Self-reported information on use of cleaning products - types and forms of application (e.g., spray)	Symptom severity scale (No symptoms to a lot of symptoms) Upper respiratory tract symptoms (URTS): Sore throat, a runny nose, watery eyes. Lower respiratory tract symptoms (LRTS): Breathlessness, wheeze, chest tightness, cough.	**Respiratory tract symptoms** Upper Number of different sprays: 1-2: MR = 1.7 (0.9–2.9) ≥3: MR = 1.6 (1.0–2.6) Lower Number of different sprays: 1-2: MR = 1.4 (0.8–2.4) ≥3: MR = 1.4 (0.7–2.7)
Whitworth et al. (2019) US	Cross-sectiotional (2017)	Professional domestic cleaners	56 hispanic, informal, self-employed, domestic cleaners Age 23–74 years	Self-reported use of cleaning products	Self-reported information combined into bronchial hyper-responsive (BHR) symptoms: ever had trouble breathing; wheezing/ shortness of breath/ awakened in the night by cough/chest/tightness in the last 12 months; itchy or watery eyes or feelings of tightness in the chest when near animals, feathers or dust; and itchy or watery eyes when near trees, grass or flowers.	**Bronchial hyper-responsive (BHR) symptoms** (reference = unexposed) Self-reported product use/cleaning sprays (*use product 4–7 days/week;[§] use of product 1–7 days/ week) Cleaning furniture*: aOR = 0.5 (0.1–2.1) Cleaning glass*: aOR = 0.8 (0.3–2.7) Cleaning rugs or carpet[§]: aOR = 2.1

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Table 4 (*continued*)

Author	Design	Sector	Population	Exposure	Type of health effect	Primary findings
						(0.5–10.5) Mopping floor*: aOR = 0.5 (0.1–1.8) Cleaning tile*: aOR = 1.0 (0.3–3.3) Cleaning the oven[§]: aOR = 2.1 (0.5–8.1) Decreasing[§]: aOR = 2.0 (0.6–7.0) Ironing clothes[§]: aOR = 0.3 (0.03–2.4) Air freshening*: aOR = 4.6 (1.3–16.5)
Zock et al. (2007) 22 European sites (10 countries)	Prospective population-based cohort study (ECRHS[b], Baseline 1991/Follow-up 1998–1999)	Private household cleaning	3,503 without asthma at baseline Age at follow-up 28–57 years	Self-reported use of cleaning products	Self-reported new-onset asthma based on current asthma (at follow-up) Positive response to one of the following: 1. Have you had an attack of asthma in the last 12 months? 2. Have you been woken by an attack of shortness of breath at any time in last 12 months? 3. Are you currently taking any medicine for asthma? Physician-diagnosed asthma Asthma confirmed by a doctor with reported first asthma between ECRHS I and II	**Asthma** (reference = use of cleaning products less than weekly) **Current asthma** Self-reported spray use (at least weekly) Furniture spray: aRR = 1.49 (0.99–2.23) Glass-cleaning spray: aRR = 1.35 (0.98–1.85) Sprays for carpets, rugs, curtains: aRR = 1.24 (0.47–3.21) Sprays for mopping the floor: aRR = 1.05 (0.59–1.85) Oven sprays: aRR = 0.87 (0.33–2.28) Ironing sprays: aRR = 1.66 (0.92–3.00) Air-freshener sprays: aRR = 1.71 (1.22–2.39) Any spray: aRR = 1.49 (1.12–1.99) Cleaning sprays (at least weekly) Women: aRR = 1.45 (1.04–2.02) Men: aRR = 1.76 (0.99–3.15) **Physician-diagnosed asthma** Self-reported spray use (at least weekly) Furniture spray: aHR = 2.46 (1.26–4.80) Glass-cleaning spray: aHR = 1.43 (0.84–2.44) Sprays for carpets, rugs, curtains: aHR = 0.80 (0.11–5.93) Sprays for mopping the floor: aHR = 0.93 (0.30–2.85) Oven sprays: aHR = 0.63 (0.09–4.64) Ironing sprays: aHR = 1.51 (0.46–4.96) Air-freshener sprays: aHR = 1.46 (0.78–2.70) Any spray: aHR = 1.28 (0.78–2.09) Cleaning sprays (at least weekly) Women: aHR = 1.51 (0.87–2.64) Men: aHR = 0.61 (0.16–2.25)

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; GM = geometric mean; OR = odds ratio; aRR = adjusted rate ratio; MR = mean ratio. 95% CI = 95% confidence interval presented in brachets after the ratio estimate.
[a] Epidemiological study on Genetics and Environment of Asthma.
[b] European Community Respiratory Health Survey.

with asthma (Le Moual et al., 2014; Nadif et al., 2014). It has previously been speculated that asthmatic cleaners are protected towards certain irritants compared to non-asthmatic subjects, possibly by elevated production of mucus acting as a trap for water soluble compounds like formaldehyde, a strong sensory irritant. This was observed for sensitized mice exposed to formaldehyde (Larsen et al., 2013) and in asthmatics that were exposed to a reaction mixture of ozone and limonene and compared with healthy subjects (Fadeyi et al., 2015).

In a recent cross sectional study from New Zeeland among 425 cleaners and 281 reference workers, several types of cleaning sprays were investigated, and most had estimates above one for current asthma, both compared to an internal and an external control group (Brooks et al., 2020). The most commonly used spray was glass cleaning spray, with OR compared to internal control 1.07 (0.68–1.69) and to external control, OR 1.88 (1.17–3.02).

Overall, the epidemiological studies give some evidence of increased risk of asthma or exacerbation of asthma symptoms related both to professional and non-professional use of spray cleaning products. The dose-effect relationship between use of cleaning spray and asthma or respiratory symptoms were indicated in a single study. However, most studies are small, rely on self-reports of both exposure and outcome, and are predominantly cross-sectional, which reduces the ability to make inferences on the causality of the association between the use of cleaning sprays and asthma.

5. Mechanistic studies

5.1. Animal exposure studies

Some animal exposure studies have been carried out to elucidate cases of reported asthma or lung injury closely related to handling of or being near a surface recently treated with cleaning and disinfectant products e.g. QACs (Burge and Richardson, 1994; Houtappel et al., 2008; Purohit et al., 2000; Villar-Gómez et al., 2009). One inhalation study in mice showed that benzalkonium chloride was the most potent among a series of aerosolized QACs in causing acute pulmonary inflammation evidenced by neutrophil and macrophage influx in bronchial alveolar lavage fluid (BALF) and rapid shallow breathing (without indication of trigeminal stimulation). A No Observed Adverse Effect Level (NOAEL) of 0.049 mg/m^3 was determined (Larsen et al., 2012). Further, intratracheal installation studies in rats and mice with didecyldimethyl ammonium chloride caused both pulmonary damage and inflammation, (Kwon et al., 2016; Ohnuma et al., 2011). Based on the findings, it was suggested that alteration of the pulmonary defense system may increase vulnerability to exogenous infectious agents (Ohnuma et al., 2011). When ethylene glycol was added to didecyldimethyl ammonium chloride, both at a sub-toxic dose, an amplifying and dose-dependent effect was observed in BALF one day after instillation. This indicates that lung cytotoxicity and inflammation arose by the mixture, but not by the chemicals alone (Kwon et al., 2016). Even slight changes of product composition might therefore change the toxicity of cleaning spray products. Similar observations have been made for impregnation products with perfluoro alkyl silanes which have shown to cause atelectasis, emphysema, and hemorrhages by interaction with lung surfactant in mice and with a steep dose-response relationship (Nørgaard et al., 2010). In another study, rats were exposed for 13 weeks by whole-body inhalation to aerosols of didecyldimethyl ammonium chloride (three concentrations ranging from 0.11 to 1.4 ± 0.7 mg/m^3) (Kim et al., 2017). Body weights were significantly lower at the highest concentration compared to control animals, but otherwise effects were relatively mild. Lung weight and neutrophil counts increased somewhat and inflammatory cell infiltration and pneumonia were partially present (without histopathological changes) at the middle and high exposure level. For the 13-week exposure a NOAEL value of 0.11 mg/m^3 was suggested.

5.2. Inhalation studies in patients and workers

A few human inhalation studies on exposure to cleaning chemicals have been reported. Not all are specific to sprays, but they illustrate well the airway effects upon controlled exposure. For instance, hypochlorite (bleach) is a common chemical often nominated as an important contributor of respiratory effects among cleaning personnel (Quirce and Barranco, 2010; Vandenplas et al., 2014b). Hypochlorite is sometimes accidently used together with acid, which result in generation of chlorine vapors. Thus, in one study, patients (n = 55; housewives) with reactive airways dysfunction syndrome presented at the emergency department after accidental being exposed to a mixture of hypochlorite and hydrochloric acid most often during cleaning of bathrooms or kitchens. Fifty of these patients were followed for 3 months. Symptoms of dyspnea, coughing, wheezing, and chest tightness, and PEF (Peak Expiratory Flow) rate improved significantly after medical treatment (Gorguner et al., 2004). In another study, cleaning workers (n = 19) with asthma-like symptoms inhaled an aerosolized 5% hypochlorite solution resulting in a concentration of 0.4 ppm pure chlorine in a climate chamber (Sastre et al., 2011). The results appear erratic, but suggest that 0.4 ppm chlorine, a concentration below the 8-h permissible TLV-TWA of 0.5 ppm (Threshold Limit Value – Time Weighted Average), may produce a substantial decrease of FEV_1, but not FVC, in subjects with and without bronchial hyper-reactivity. Sham exposed individuals showed no general effects, but asthmatic reactions were elicited in three individuals.

QACs are another group of cleaning chemicals (disinfectants) that have been associated with respiratory effects among cleaning personnel (Gonzalez et al., 2014; Vandenplas et al., 2013), and some specific inhalation challenge (SIC) studies have been published. In one study, asthmatic patients (n = 30) inhaled up to three successive aerosolized 0.6 mg doses of benzalkonium chloride in water, causing a significant reduction in FEV_1, while controls (n = 10) were unaffected. Bronchoconstriction was observed in 20% of the patients exposed to benzalkonium chloride, and this was most pronounced among severe asthmatics (Lee and Kim, 2007). SIC of asthmatic patients (n = 22; cleaners) to a QAC solution (0.1–1%) was carried out in a climate chamber; the exposure concentration was not described. Twelve patients (55%) reacted to the QAC provocation. These patients were characterized by higher FeNO at work, FEV_1 reduction and atopy, and reported rhinitis and conjunctivitis more often relative to those unaffected by the SIC. Didecyldimethyl ammonium chloride most often resulted in a positive SIC. The authors concluded that the cause of QAC-related asthma is not clear, but may involve both irritation and sensitization, which are difficult to separate (Bellier et al., 2015). This agrees with the conclusion by LaKind and Goodman (2019) that there is inadequate information about the active mechanism(s) by which QACs act.

Other SIC studies with asthmatic workers using cleaning and disinfection products (n = 44) confirm that QACs containing products may cause sensitizer-induced asthma, but that also glutaraldehyde and ethanolamine containing products were associated with significant reduction of FEV_1 after SIC (Vandenplas et al., 2013). Thus, challenge with the cleaning products suspected to cause asthma induced a >20% drop in FEV_1 in 17 workers (39%). Workers showed a bronchial reaction with sensitizer-induced OA. Data indicates that a substantial proportion of workers who experience asthma symptoms related to cleaning products show a pattern of bronchial reaction consistent with sensitizer-induced OA.

Subjects (n = 178) were investigated for possible OA in a prospective observational study. They underwent a SIC to several chemicals in a 5 m^3 chamber under realistic exposure conditions. These included both high (e.g. flour) and low molecular weight compounds (e.g. unspecified cleaning agents). The test was positive in 98 patients, based on increased exhalation of FeNO. The tested low molecular weight compounds were not associated with increase in FeNO. The authors concluded that FeNO increased more consistently in subjects with OA caused by high molecular weight compounds than in those with OA caused by low molecular weight compounds (Lemiere et al., 2014).

Female patients (n = 20) diagnosed with OA and working as professional cleaners, experienced asthma when undergoing SIC in a climate chamber. The patients responded to chemicals in nine cases (45%) and to molds in 11 cases (55%). The chemicals were cleaning chemicals like wax-removing compounds containing ethanolamines in five cases, a chloramine agent in one case, and chemicals used in the industrial processes at workplaces in 3 cases (Mäkelä et al., 2011).

In a study of 50 female cleaners that reported work-related respiratory symptoms, a questionnaire, skin prick tests, serum specific IgE antibodies, and SICs with latex, chloramine, formaldehyde, glutaraldehyde, and benzalkonium chloride were performed. Work-related asthma was recognized in 46% of the symptomatic cleaners, of whom 15 were considered as having work-exacerbated asthma and eight as having OA. It was concluded that sensitization to disinfectants and latex played an important role as causative agents in OA of the cleaners (Lipinska-Orjzanowska et al., 2017).

The hypothesis that the use of cleaning products for private domestic cleaning induces inflammation in the airways was tested by studying the exhalation of FeNO following airway challenge to cleaning products in females (n = 313; 116 with current asthma; 53% never-smokers) (Le Moual et al., 2014). It was confirmed that adult exposure to domestic spray cleaning products was associated with elevation of FeNO in exhaled air. Furthermore, lower FEV_1 was found to be associated with use of sprays, especially air freshening sprays, in both females with and without asthma. This agrees with a study of FeNO measured in children (age 10–13) apparently exposed from use of a variety of domestic cleaning products including spray products (Casas et al., 2013).

In summary, a limited number of studies show that inhalation of aerosolized chlorine, chloroamines, ethanolamines, hydrochloric acid, formaldehyde, glutaraldehyde, benzalkonium chloride, and other QACs may initiate inflammatory reactions in the airways as reflected by the elevation of FeNO. Even slight changes of product composition might change the toxicity of cleaning spray products.

6. Field exposure studies of spray cleaning and disinfection products

Most studies, which associates asthma among cleaners with exposure to cleaning chemicals, are based on self-reported exposure assessment, e.g. via questionnaires, rather than field measurements. This probably owes to the large number of different cleaning products in combination with their complex chemical composition, which would require an extensive battery of measurement and analytical techniques. The diversity in type and frequency of product use depending on the specific cleaning task, duration of peak concentrations, and the need for full-shift time-weighted average concentrations further complicates field measurements.

Less than 20 field/chamber/simulation studies of the exposure during use of cleaning and disinfectant products were identified in our literature search. Of these, only five studies qualified as field exposure studies of spray cleaning or disinfection products, see Table 5. The studies vary in quality and size; furthermore, the reported exposure concentrations show, as expected, large variations.

Vincent et al. (1993) measured 2-butoxyethanol from surface and glass cleaning sprays and found 7.3 ppm 2-butoxyethanol as the highest time-weighted-average concentration. This is below the ACGIH (American Conference of Governmental Industrial Hygienists) threshold limit of 25 ppm but above NIOSH's recommended limit value of 5 ppm (National Institute of Occupational Safety and Health). Furthermore, biomonitoring suggested that skin penetration of 2-butoxyethanol was the predominant route of exposure. Garrod et al. (1998) measured QACs from remedial in-situ masonry treatment by spraying in a more industrial type of spraying and showed that spraying QACs may result in high air concentrations rising with increasing spray pressure. Fedoruk et al. (2005) measured ammonia from spray-on glass cleaners while washing several large windows in an office setting and concluded that routine household uses of ammonia are unlikely to produce significant exposures when using standard cleaning solutions (0.1–0.2%), but spillage or use of concentrated ammonia solutions (3%) in poorly ventilated areas can lead to potentially hazardous airborne ammonia exposures. Peak airborne ammonia concentrations within 3–5 min were 36–90 ppm and 125–4200 ppm 2–5 min after floor and tile cleaning with 0.2% and un-diluted cleaner (0.3% ammonia), respectively. Gerster et al. (2014a) measured mono-ethanolamine, glycol ethers, and benzyl alcohol during professional cleaning in an apartment, an industrial space, and some public spaces. They found that professional cleaners were exposed to multiple airborne irritants at low concentrations. They concluded that these chemicals should be considered in investigations of respiratory dysfunctions in the cleaning industry, particularly in specialized cleaning tasks such as intensive floor cleaning. However, it is unclear how the authors define "irritants", because glycols and glycol ethers are not considered strong sensory irritants, cf. (Nielsen et al., 2007a; Wolkoff, 2013). Exposure to a surface disinfectant containing peracetic acid in a mixture of hydrogen peroxide and acetic acid has been studied in a hospital (Casey et al., 2017; Hawley et al., 2017). Exposure to this mixture has shown association to elevated prevalence of work-related eye, nasal, and asthma-like symptoms among hospital staff compared to no use. Formerly, application of the product was by spraying, but in this study it was applied by disposable cloth wipes using gloves. Highest average air concentrations of hydrogen peroxide, peracetic and acetic acid were measured to 169, 25, and 250 ppb, respectively.

6.1. *Quasi-experimental exposure studies of spray cleaning and disinfection products*

A few studies have dealt with simulated exposure scenarios in climate chambers, gloveboxes, or simulated bathrooms, often combined with modeling. Bello et al. (2013) measured 2-butoxyethanol and TVOC (Total VOCs) as function of the air exchange rate (AER), bathroom volume, type of cleaning task, and product type. The AER showed the strongest correlation with TVOC after spraying followed by wiping. The cleaning person had been exposed to an average concentration in the breathing zone below 0.8 ppm 2-butoxyethanol. Singer et al. (2006) measured 2-butoxyethanol and 2-hexyloxyethanol in a 50 m^3 climate chamber (AER = 0.5 h^{-1}) after cleaning a tabletop with a trigger spray cleaning product followed by wiping. The concentrations of 2-butoxyethanol exceeded 0.2–0.8 mg/m^3 for 4 h and a maximum initial concentration up to 1.5 mg/m^3 was found. These findings are compatible with maximum airborne concentrations sampled over 4–8 h in offices after floor cleaning, highest for 2-butoxyethanol (13.5 mg/m^3) and lowest for 2-propoxyethanol (1.6 mg/m^3) (Fromme et al., 2013). Rogers et al. (2005) simulated post-application inhalation levels of fragrances (0.06% in spray liquid) in a surrogate air freshener formulation expelled from a pressurized spray can in an environmentally controlled room (14.5 m^3) after a 5-s spray release. The experiments showed that the higher the volatility of the fragrance material, the higher the airborne concentration. At the height of adult breathing zone (1.5 m), the maximum concentrations of the nine fragrances ranged from 108 to 347 $\mu g/m^3$ during the first minute post-application. In the height of child breathing zone (0.5 m), the maximum fragrance material concentrations

Table 5
Field exposure studies of spray cleaning and disinfection products.

Spray event	Location	Spray duration min	Chemicals/ conc. in product	Number personal samples	Time weighted average concentrations μg/m^3 (ppm)	Biomonitoring/ surface sampling	Comments/conclusions	Reference
Spraying, then wiping of cars and office	4 garages, town hall	15–320	2-butoxyethanol	29	<480–35400 (<0.1–7.33)	Butoxy acetic acid <2–371 mg/g creatinine	Results suggest: Skin penetration predominant	Vincent et al. (1993)
Pumped spraying of masonry	Main hall, cottage, living room, chapel	6–35	QAC[a]	4	130–12900	Coveralls (total) 44–247 mg	Inhalation exposure and deposition rose with spray pressure	Garrod et al. (1998)
Trigger spray-on, then wiping off large windows	Office setting	15	NH_3/0.1%	1	450 (0.65)	n/a	Cleaning tiles in bathroom with 0.1% NH_3 using a sponge resulted in >10-fold higher conc. Diluting 3% NH_3 and spillage even higher concentration	Fedoruk et al. (2005)
Spray disinfection	Hospital	15 (sampling time)	QAC[b]	1	<187	n/a	Below limit of detection (187 μg/m^3)	Vincent et al. (2007)
Spraying is only one of several cleaning activities during measurements. Professional cleaning	Apartment, industry, public spaces. Sampling in 12 different cleaning companies	30 - 281 (sampling time) 30–281 (sampling time) 30–186 (sampling time)	Mono-ethanolamine Glycol ethers[c] Benzyl alcohol	68 79 15	5–559 9–58700[d] 864–4300	n/a	Nearly all concentrations far below OEL. Exposure to mono-ethanolamine is influenced by amount and spraying and to butoxy ethanol by spraying	Gerster et al. (2014a)

[a] Benzalkonium chloride + dialkyl dimethyl ammonium chloride.
[b] Dialkyl dimethyl ammonium chloride.
[c] Seven different glycol ethers.
[d] Highest concentration: Ethylene glycol mono-n-butyl ether. n/a: No information available.

ranged from 125 to 362 μg/m^3 during 2–6 min post-application. Particle bound fragrance exposure accounted for approximately 47% and 72% of the total exposures during the first minute post-application period in the adult and child breathing zone heights, respectively; the rest is in the gas-phase. Clausen et al. (2020) carried out a 6 s spraying of a 2% aqueous solution of benzalkonium chloride in a 20 m^3 chamber (AER 0.5 h^{-1}). The maximum air concentration measured after 9 min was 0.01 mg/m^3 and benzalkonium chloride was measurable in air for more than half an hour. A study of aerosols from pressurized spray cans containing nanoparticles (propellant driven) observed higher exposure concentrations of nanoparticles compared to aerosols from trigger sprays (pump) with nanoparticles. The latter exposure concentration was negligible and could not be distinguished from the background concentration (Lorenz et al., 2011). Park et al. (2017) made similar observations when comparing pressurized can and trigger sprays. A Norwegian study (reported in Norwegian (STAMI, 2017):) measured aerosols from 17 products in seven different trigger spray cans in a simulated bathroom (14.4 m^3). The air exchange rate was not specified. The sprays were directed towards two opposite walls and the trigger was pressed 180 times in 3 min. Airborne mass fractions ranged from 4 to 47%. The air concentrations of inhalable aerosols ranged from below the limit of detection (0.64 μg/m^3) to 140 μg/m^3. Foam sprays gave the lowest airborne concentrations.

Chemical reactions by mixing of cleaning chemicals, e.g. from different products, should also be considered because new chemical species, of which some may be of toxicological concern, may be formed (Siracusa et al., 2013; Weschler and Carslaw, 2018). For instance, new species (i.a. formaldehyde) were formed by the reaction between ozone and fragrances (terpenes) during simulated cleaning in 20 m^3 climate chamber (Nørgaard et al., 2014b). Chloramine derivatives can be formed by the reaction between hypochlorite (precursor of chlorine) and ammonia, chlorine from hypochlorite and acids, and a variety of substances from reactions of hypochlorite and proteins or soap (Massin et al., 2007; Mattila et al., 2020; Wong et al., 2017). Elevated concentrations of chloroform has also been reported after cleaning activities in hospitals (Su et al., 2018), while a number of chlorinated hydrocarbons, including carbon tetrachloride in surprisingly high concentrations, have been observed when mixing tensides with hypochlorite under laboratory conditions (Odabasi, 2008).

7. Routes of exposure to chemicals from spray cleaning and disinfection products

It is important to consider all possible exposure routes for an in-depth risk assessment (Vincent et al., 2017a). The exposure to cleaning and disinfection products during and after the application is sixfold: i) Inhalation of aerosols and gasses during the spray event and for up to some hours after; ii) Deposition from air to skin of aerosols and gas-phase semi-VOCs (SVOCs) during and for up to some hours after the spray event (Weschler and Nazaroff, 2012); iii) Post application exposure by skin contact with treated (sprayed) surfaces; iv) Oral exposure from hands/fingers; v) inhalation exposure to thermal degradation products from burning cigarettes that are contaminated with product (Scheepers et al., 2017), and vi) Inhalation of re-suspended product(s) from floor by walking activity (Burge and Richardson, 1994; Qian et al., 2014). However, for a quantitative exposure assessment "There are still too many gaps in understanding real-time exposure and, without continuous, real-time exposure monitoring, clinicians and researchers cannot truly understand the causal exposures needed to elicit respiratory effects" as it was stated by Vincent et al. (2017a). Elicitation of the respiratory effects caused by deposition of cleaning chemicals, and in particular associated particles, in the airways, is complex; many parameters, e.g. the deposition of particles, depends on the dynamics of the breathing pattern, inhalation airflow, particle size, and influence of the deposition in different parts of the airways (Ganguly et al., 2019). Finally, it should be pointed out that exposure to cleaning chemicals is not limited to cleaning and disinfection tasks since these chemicals are also constituents of many other products, e.g. paints.

8. Results from search in the Danish Product Registry on spray cleaning products

Table 1 shows the distribution of products in different categories and spray types (pressurized can, trigger, and non-aerosol forming sprays) for 101 spray cleaning and disinfection products identified in the Danish Product Registry. Limitations of data from the Danish Product Registry are described in section 2.2. Table 2 shows the most frequent chemicals in 101 cleaning and disinfection spray products (frequency $\geq$ 9 products). Most of the products (n = 94) contained water as solvent, additional common solvents are ethanol, 2-propanol, glycols, glycol ethers, and 2-aminoethanol. Other major groups of constituents are fragrances (n = 36), non-ionic tensides (n = 30), ethoxylated sulfate salts (n = 26), disinfectants (QACs) (n = 12), ammonia (n = 20), strong bases (n = 25), and acids (n = 15). Products with chemicals suspected to be of concern regarding respiratory effects, but which occurred in less than 9 products are listed in Table 3. Bonnet et al. (2018) published a table similar to Tables 2 and 3, based on results from a French study of 299 cleaning products, including general cleaning products, spray products, and air fresheners. Information on the composition of the products was collected from their MSDS (Materials Safety Data Sheets); but these do not always report the exact composition. The table furthermore lists chemicals for each CAS registry number whereas in the current Tables 2 and 3, similar chemicals and chemical mixtures are grouped together, even if their CAS registry numbers are different. Hence, all fragrance chemicals in Table 2 are in one group, even though these are not similar chemicals. In the table of Bonnet et al. (2018) single fragrance chemicals are listed. In spite of that, and if we exclude fragrance chemicals and group similar chemicals, our tables are similar regarding chemical identity and occurrence of the individual chemicals and groups. A major difference between the lists is the frequent occurrence of QAC-containing products in the French study. Gerster et al. (2014b) published a similar table for all chemicals identified from information in MSDS of 105 of the most used cleaning products in the Swiss cleaning sector. The content of this table is also similar to the content of Tables 2 and 3.

9. Assessment of respiratory effects of selected chemicals identified in the literature and in 101 spray cleaning and disinfection products

Baur et al. (2012) and Hahn et al. (2010) have reported a limited number of cleaning and disinfection chemicals of concern as indicated in Tables 2 and 3. Using the modified RCGP three-star grading system (Royal College of General Practitioners), the strength of evidence for unspecified cleaning agents as a group, is graded with “low to moderate evidence” or “limited evidence” for their role as an “irritative agents causing OA or occupational chronic obstructive pulmonary disease” (Baur et al., 2012). Vandenplas et al. (2014b) state that epidemiological studies provide evidence that occupational exposure to cleaning agents increases the risk of chronic irritant-induced asthma. Irritative chemicals can be divided into corrosive or reactive irritants, which may damage tissue on the cellular level, and sensory irritants that gives the feeling of irritation through activation of the trigeminus nerve but do not damage the tissue (Nielsen and Wolkoff, 2017). Inhalation of corrosive or reactive chemicals may induce asthma (Bardana, 2008; Le Moual et al., 2018). In Tables 2 and 3, corrosive or reactive chemical irritants include the strong bases sodium and potassium hydroxide, the base ammonia, the corrosive chlorine releaser sodium hypochlorite, the strong acids sulfuric acid and methanesulfonic acid, and the oxidizing chemical hydrogen peroxide. The other chemicals in Tables 2 and 3 are non-corrosive and mostly to be considered as weak airway irritants. In the following, single chemicals in groups of compounds are briefly assessed regarding concerns of their potential to induce of respiratory effects.

Acids: Sulfuric acid and methanesulfonic acid are very strong and corrosive acids, while phosphoric acid in the presented concentrations and citric acids are weak. Baur et al. (2012) consider the evidence for respiratory effects caused by sulfuric acid as limited or contradictory.

Alkyloxylated alcohols (non-ionic tensides): No information has been found about this type of chemicals to be associated with respiratory effects. They are relatively high molecular weight substances, being structurally homologues that mimic glycols and glycol ethers. Thus, they are assumed to have little effect on respiration, see below for organic solvents.

Bases: Ammonia, a strong base, has repeatedly been suggested as a chemical of concern. Baur et al. (2012) graded the strength of evidence for “limited or contradictory” for its role as an “irritative agent causing OA or occupational chronic obstructive pulmonary disease”. NOAEL for irritation in the upper airways is in the order of 25 ppm (Nielsen et al., 2007b). The EU OEL is 20 ppm (SCOEL, 1992). Morpholine is a weak base without indication of being a sensitizer; evidence for respiratory effects caused by N-methyl-substituted morpholine was graded as limited or contradictory and further downgraded due to inadequate methodology by Baur et al. (2012), who also graded evidence for respiratory effects caused by 2-aminoethanol as “no scientific evidence”.

Disinfectants: Quaternary ammonium compounds (QACs) are common disinfectants. A few cases of asthma after handling of disinfectants have been reported, see Section 5. Baur et al. (2012) graded the strength of evidence for respiratory effects caused by benzalkonium chloride and lauryl dimethyl benzyl ammonium chloride as “no scientific evidence”, while Hahn et al. (2010) assessed the sensitizing potential of OA as uncertain. Both animal and human exposure studies indicate inflammatory reaction and bronchoconstriction following inhalation of elevated concentrations of benzalkonium chloride, the most reactive QAC on the basis of a mice inhalation study (Larsen et al., 2012). In the thorough health evaluation of case reports, challenges, and epidemiological studies, LaKind and Goodman (2019) concluded that the assessments of QACs suffers from uncertainties about exposure, type of QACs investigated, and the presence of other concurring chemicals. More severely, there was inadequate information about whether QACs act as sensitizers or irritants or by other mechanisms, as the studies not clearly distinguish between spray and wet cleaning with QACs. QACs are highly water-soluble and should be trapped in the upper airways depending on aerosol size, but clearly ultrafine aerosols can reach the pulmonary region. It is well established that exposure of the eyes to QACs aggravate the precorneal tear film leading to instability and irritative effects (Wolkoff, 2017). Bronopol, another disinfectant and preservative, is a known skin allergen and also a weak sensory and mucous membrane irritant (Hahn et al., 2010). It is noteworthy, however, that Bronopol decomposes to formaldehyde under weak to strong alkaline conditions (Kajimura et al., 2008). Formaldehyde is a well-known and strong eye and upper airway sensory irritant but is not considered to cause or exacerbate asthma by gaseous inhalation (Nielsen et al., 2013; Wolkoff and Nielsen, 2010). Glutaraldehyde, also a common disinfectant, is a relatively strong sensory irritant (Wolkoff, 2013), but there is only low to moderate scientific evidence for sensitizing properties as assessed by Baur et al. (2012).

Fragrances: This group of chemicals usually occurs in mixtures of essential oils. Mono-terpenes and oxidized species thereof are common fragrance chemicals, particularly limonene, linalool, pinenes, geraniol, and terpinols. Neither the mono-cyclic terpenes (e.g. limonene) nor the bicyclic terpenes (e.g. α-pinene) are considered to be of concern by inhalation, apart from their function as signaling a pleasant smell (Basketter et al., 2019; Baur et al., 2012; Johnson et al., 2019; Wolkoff and Nielsen, 2017). Reduced lung function has been observed at elevated terpene concentrations (above OELs) in the wood industry (Eriksson et al., 1996, 1997); however, these findings are hampered by concurrent wood dust exposure. Lung function effects of α-pinene and 3-carene have never been observed in controlled human exposure studies, see references in Wolkoff and Nielsen (2017). The most common mono-terpenes (α-pinene, geraniol, limonene, linalool, and terpineol) are considered weak sensory irritants (Wolkoff, 2013; Wolkoff and Nielsen, 2017). Many fragrances, however, like limonene, are well-known dermal allergens (Schnuch et al., 2007).

Gases (propellants): propane, butane, and carbon dioxide are not considered sensitizers or airway irritants.

Organic solvents: Two major alcohols used as solvents, ethanol and propanol, are weak sensory irritants (Wolkoff, 2013). They are not expected to induce sensitization (Nielsen et al., 2007a) (Nurmatov et al., 2015). It has been observed in one study that occupational long-term exposure to organic solvents doubled the risk of chronic bronchitis related to smoking (Ebbehøj et al., 2008). However, the identity of the solvents was not specified except that a large fraction was assumed to be chlorinated organic solvents. Glycols and glycol ethers are common organic solvents of which some are SVOCs. They are also very weak sensory irritants (Wolkoff, 2013) but like other common solvents are they not expected to induce sensitization. Mangelsdorf et al. (2016) have assessed several of this type of chemicals of which 1,2-propanediol, 2-butoxyethanol, and 2-methoxymethylethoxy)-propanol were considered weak airway irritants. Some glycols, however, have siccative properties, which might desiccate the airways, thus making these more vulnerable due to a reduced mucociliary clearance rate, see Wolkoff (2018).

Incorrect or accidental mixing of products can produce corrosive chemicals such as chlorine, see section 6.1 and Siracusa et al. (2013). The combination of cleaning chemicals has been further elaborated by analyzing asthma health clusters with exposure clusters, however, none of the latter clusters contained spray products, specifically (Su et al., 2019).

10. Discussion of potential mechanisms

Numerous studies and reviews have reconfirmed that adverse respiratory effects are associated with the use of spray cleaning products in cleaners, as observed by Nielsen and Bach (1999) two decades ago. A household survey study of consumer product uses and user patterns among home-based population groups in four EU regions within the EPHECT project (Emission, Exposure Patterns, and Health Effects of Consumer Products) showed that use of spray products was substantial (Dimitroulopoulou et al., 2015). The products included all-purpose cleaners, bathroom cleaning products, kitchen cleaning products, and glass, window, and furniture cleaners. Garza et al. (2015) argued that use of environmentally friendly ("safer") cleaning products might be beneficial health-wise in comparison to traditional products with elevated contents of ethanolamines, glutaraldehyde, QACs, and VOCs. However, except for avoidance of glutaraldehyde and possibly aggressive chemicals (not mentioned), such approach might not be safer per se, in view of our assessment. It requires also an assessment of the potential exposure, duration, and inhalation of generated aerosols as function of the spray technique, i.e. particle size distribution. For instance, the deposition of spray generated aerosols can vary substantially from the eyes to the lips (Duan et al., 2020). Intuitively, aerosol exposure can be reduced substantially by substitution of the spray-surface working process with wet-cloth-surface cleaning. This agrees with the recommendation to abandon the use of spray cleaning products (Cummings and Virji, 2018).

The pathogenesis of the respiratory effects is clearly complex and remains broadly a black box (De Matteis and Cullinan, 2015), although many mechanistic proposals and hypotheses can be forwarded. It is evident that inhalation of aggressive and corrosive chemicals can aggravate airway tissue injuries, and that daily repeated exposures will further exacerbate injury of the respiratory mucosa causing inflammatory reactions, and ultimately "irritant-induced" asthma (Siracusa et al., 2013; Svanes et al., 2018). It has also been suggested that the concentration and duration of exposure are important determinants of "irritant-induced asthma" (Vandenplas et al., 2014b). Furthermore, it has been suggested that cleaning agents may act as adjuvants (Rosenman, 2006). Finally, inflamed airways will likely be more vulnerable to subsequent inhalation exposures, e.g. re-suspended dirt particles and their reactive surface chemistry. For instance, elevated exposure to re-suspended dust/dirt particles during domestic cleaning and use of spray products reduced heart-rate variability, a marker of autonomic cardiac dysfunction (Huang et al., 2014; Metha et al., 2012); this might impact the general health of the cleaning personnel. The reduction of the heart-rate variability appeared more severe among those with obstructive lung diseases (Metha et al., 2012).

Evidently specific allergic mechanisms, most importantly IgE mediated allergy, plays a limited role, but it is still unclear to which extent specific immunological mechanisms drives health effects caused by for example QACs and glutaraldehyde.

Siccative cleaning chemicals, like some glycol ethers, should also be considered, because they can desiccate the mucous membranes, cf. (Dalton et al., 2018). This may exacerbate the vulnerability of the respiratory system by reduction of the mucociliary clearance rate, cf. Wolkoff (2018).

It could be speculated whether repeated low-dose inhalation might be able to initiate an autoimmune response in the lungs, resulting in asthma-like disease. An alternative mechanism could be that repeated exposure of skin without barrier function could initiate allergen sensitization via the skin as a critical step (Redlich, 2010). Thus, skin exposure to airborne cleaning chemicals may cause delayed-type hypersensitivity leading to asthma-like effects from inhalation of the chemicals by an immunological mechanism (Folletti et al., 2017), i.e. skin allergens like limonene, linalool, and 3-carene. Furthermore, repeated exposure of the respiratory tract to cleaning chemicals can disrupt the microbiome, consequently modulating the immune system (Scherzer and Grayson, 2018); this could increase the vulnerability to inhalation of resuspended debris of microbiological origin.

As shown above, several mechanisms and hypotheses can be forwarded, which calls for a more integrated and holistic approach in delineation of the pathogenesis of respiratory effects of spray cleaning products. This should also include the indoor microclimatic conditions before and during the cleaning activities. For instance, extended exposure to low indoor air humidity desiccates the airways becoming more vulnerable (Wolkoff, 2018). Other issues to include in the overall assessment are early life disadvantages such as maternal smoking according to Svanes et al. (2015), airway vulnerability (low, moderate, severe asthmatic) as well as prognostic issues. The psychological working conditions could also be included in an integrated assessment as stress induced inflammatory mechanisms may add to the vulnerability of the airways (Karvala et al., 2018).

11. Conclusion

Identification of casual interference between the use of cleaning spray products and asthma (respiratory effects) in epidemiological studies is hampered by the self-reporting of both exposure and outcome, and dose-dependence has only been seen in one study. Few studies provide reliable and detailed exposure data for the many co-occurring cleaning chemicals and proper aerosol characterization. Health assessment based on field studies is therefore not possible.

Animal exposure studies have mostly focused on QACs that resulted in both pulmonary inflammation and lung damage. Studies are few and extrapolation to real life (daily) exposure conditions is hampered by the short-term exposure duration. Long-term repeated studies are lacking in experimental animals.

Several clinical and experimental exposure/challenge studies indicate induction of pulmonary inflammation from inhalation of aerosolized benzalkonium chloride, chlorine, chloroamines, ethanolamines, hydrochloric acid, formaldehyde, and glutaraldehyde. The overall picture is not consistent, among others because vulnerability among atopics differ from that of healthy subjects, while asthmatics at the same time appear to be protected from the effects of certain water-soluble chemicals.

Survey of the Danish market identified 101 spray cleaning and disinfection products among three different spray types, pressurized can, trigger, and non-aerosol forming sprays. Overall, the distribution of cleaning chemicals was similar to a French survey. Most products contained water as solvent and a minor part contained common organic solvents. Major groups of potential concern were disinfectants, fragrances, non-ionic tensides, bases, acids, and certain salts.

Overall, the assessment of exposure regarding respiratory effects after inhalation of spray generated aerosols must include corrosive chemicals like strong acids and bases including ammonia and hypochlorite. Mixing of certain cleaning products can produce corrosive airborne chemicals like chlorine. Also quaternary ammonium compounds (QACs) are considered, but the evidence for their respiratory effect is ambiguous. The most common fragrances are generally not considered of concern. Common solvents (glycols, glycol ethers, and propellants) are generally weak airway sensory irritants but are not expected to induce sensitization of the airways. Clearly, cleaning and disinfectant products are complex chemical mixtures, which would require unaffordable resources to test by human exposure studies; this warrants the development of *in vitro* methods, which reliably can test both single chemicals and mixtures.

The search for a rationale of respiratory effects caused by inhalation of cleaning chemicals calls for an integrative assessment, both at group and individual level. This should integrate externally caused vulnerability (e.g. microclimate), individual susceptibility (e.g. disadvantages), in combination with the exposure to the chemicals of concern.

Based on this review suggestions for future research are presented:

- Better characterization of personal exposure should be obtained from controlled experimental exposure studies combined with objective health measures of asthma versus healthy subjects.
- *In vitro* methods should be further explored and validated against *in vivo* methods and ultimately also objective health data in cleaning subjects. As an example, the effect of cleaning products could be analyzed for effect on lung surfactant function *in vitro*, as this method has been shown to be predictive for lung effects of impregnation spray products.
- Skin sensitization should be tested as a promotor relative to induction of airway sensitization.
- Repeated exposure as aggravating potential of irritation effects in the airways should be explored.

Author responsibilities

PW conceptualized and wrote first draft with assistance from PAC, CSS, EMF, JBS, HWM, KSH, TKC, and VS. All authors have proofread and accepted the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgement

The project is supported by a grant from the Danish Working Environment Research Fund (06-2017-03/20175100199).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113592.

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