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REVIEW ARTICLE

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Asthma-inducing potential of 28 substances in spray cleaning products—Assessed by quantitative structure activity relationship (QSAR) testing and literature review

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Abstract

Exposure to spray cleaning products constitutes a potential risk for asthma induction. We set out to review whether substances in such products are potential inducers of asthma. We identified 101 spray cleaning products for professional use. Twenty-eight of their chemical substances were selected. We based the selection on (a) positive prediction for respiratory sensitisation in humans based on quantitative structure activity relationship (QSAR) in the Danish (Q)SAR Database, (b) positive QSAR prediction for severe skin irritation in rabbits and (c) knowledge on the substances' physico-chemical characteristics and toxicity. Combining the findings in the literature and QSAR predictions, we could group substances into four classes: (1) *some indication in humans for asthma induction:* chloramine, benzalkonium chloride; (2) *some indication in animals for asthma induction:* ethylenediaminetetraacetic acid (EDTA), citric acid; (3) *equivocal data:* hypochlorite; (4) *few or lacking data:* nitriloacetic acid, monoethanolamine, 2-(2-aminoethoxy) ethanol, 2-diethylaminoethanol, alkyldimethylamin oxide, 1-aminopropan-2-ol, methylisothiazolinone, benzisothiazolinone and chlormethylisothiazolinone; three specific sulphonates and sulfamic acid, salicylic acid and its analogue sodium benzoate, propane-1,2-diol, glycerol, propylidynetrimethanol, lactic acid, disodium malate, morpholine, bronopol and benzyl alcohol. In conclusion, we identified an asthma induction potential for some of the substances. In addition, we identified major knowledge gaps for most substances. Thus, more data are needed to feed into a strategy of safe-by-design, where substances with potential for induction of asthma are avoided in future (spray) cleaning products. Moreover, we suggest that QSAR predictions can serve to prioritise substances that need further testing in various areas of toxicology.

KEYWORDS
asthma, chemical, in silico, inhalation, QSAR, sensitisation, toxicology

1 | INTRODUCTION

Asthma is a disease characterised by chronic airway inflammation and variable airflow obstruction and bronchospasms. The causes of asthma are diverse and involve both genetic and environmental factors (Papi et al., 2018). Environmental factors include exposure to allergens but also to substances that are not suspected to induce sensitisation. Several workplace exposures imply a potential risk for induction of occupational asthma (Baur et al., 2012). Proposed, underlying mechanisms for development of occupational asthma can be subdivided into (a) allergic asthma via IgE mediated sensitisation, (b) allergic asthma with latency time, not involving IgE dependent pathways and (c) nonallergic asthma due to irritating effects of substances (without latency) (Tarlo & Lemiere, 2014). Irritant-induced asthma can be further subdivided into (i) acute onset irritant-induced asthma—formerly known as reactive airways dysfunction syndrome [RADS], (ii) subacute irritant-induced asthma and (iii) low-dose irritant-induced asthma (Vandenplas et al., 2014). Finally, occupational asthma can be subdivided into (1) occupationally induced asthma and (2) occupationally exacerbated asthma.

Professional cleaning has been associated with increased risk of asthma induction in several epidemiological studies (Clausen et al., 2020). It is therefore important to know which substances in cleaning products can induce (or exacerbate) asthma. This enables their substitution or informs limitation of their use in spray cleaning products. We therefore set out to review whether substances present in spray cleaning products, common to the occupational setting, are potential inducers of asthma.

The aim of the current study was to identify and evaluate substances in spray cleaning products with regard to their potential for asthma induction. Application of cleaning products by spraying on surfaces is suggested to constitute a main causative scenario in development of asthma. Spray products release chemicals as gases and aerosols. This means that even nonvolatile chemicals, such as quaternary ammonium compounds, can be aerosolised upon spraying and enter the airways (Clausen et al., 2020; Luz et al., 2020). We screened the substances in 101 spray cleaning products (described in (Clausen et al., 2020)) based on the following criteria: (a) positive prediction for respiratory sensitisation in humans based on quantitative structure activity relationship (QSAR) in the Danish (Q)SAR Database, (b) positive prediction for severe skin irritation in rabbits based on QSAR (also from the Danish (Q)SAR Database) and (c) knowledge on substances' physico-chemical characteristics and prevalence. Based on these criteria, we selected 28 substances, for which we provide knowledge on the asthma induction potential based on literature review as well as the QSAR findings.

2 | METHODS

2.1 | Identification of substances

The Danish Product Registry is the Danish Working Environment Authority's database on hazardous substances and materials for professional use in Denmark. For 101 spray cleaning products identified in the Danish Product Registry (described in (Clausen et al., 2020)), we retrieved CAS numbers of all constituent substances. Product information in this database is confidential, but we were granted permission to retrieve the CAS numbers of substances for the current work and to report on a general level.

2.2 | Selection of substances to be included in the literature review

The selection of substances of interest was performed based on screening with QSAR and knowledge on the substances' physico-chemical characteristics and association with induction of toxicity based on experience of the involved researchers (See Figure 1 for an overview of the process).

QSAR screening QSAR predictions on (1) respiratory sensitisation in humans and (2) severe skin irritation in rabbits were retrieved from the Danish (Q)SAR Database (Division of Diet, Disease Prevention and Toxicology, National Food Institute, 2021). The Danish (Q)SAR Database includes estimates from more than 200 QSAR models from free and commercial platforms related to physico-chemical properties; ecotoxicity; environmental fate; absorption, distribution, metabolism and excretion (ADME); and toxicity. QSAR predictions for more than 600,000 substances can be searched. Information on the data underlying the QSAR models for respiratory sensitisation in humans and for severe skin irritation in rabbits is provided in supporting information File S1, Tables S1 and S2 and documentation of all the underlying models in the international QSAR Model Reporting Format is available from the Danish (Q)SAR Database (Division of Diet, Disease Prevention and Toxicology, National Food Institute, 2021).

The Danish (Q)SAR Database returns predictions based on a battery of three (Q)SAR software systems each using a different technology (CASE Ultra, Leadscope and SciQSAR) (Division of Diet, Disease Prevention and Toxicology, National Food Institute, 2021). Only substances with a positive battery prediction, that is, positive inside the applicability domain in at least two of the three models, were considered as positive for human respiratory sensitisation in this study. Battery predictions here designate a combined majority vote between the three models that are developed on the same

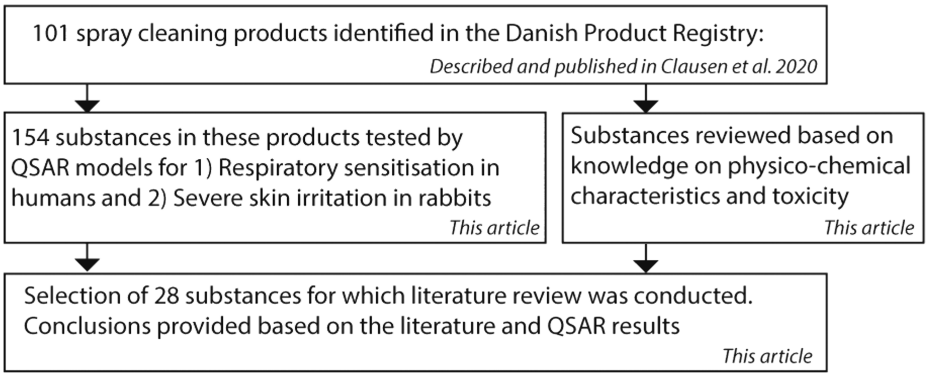


FIGURE 1 Overview of the selection and evaluation process of the 28 selected spray cleaning substances

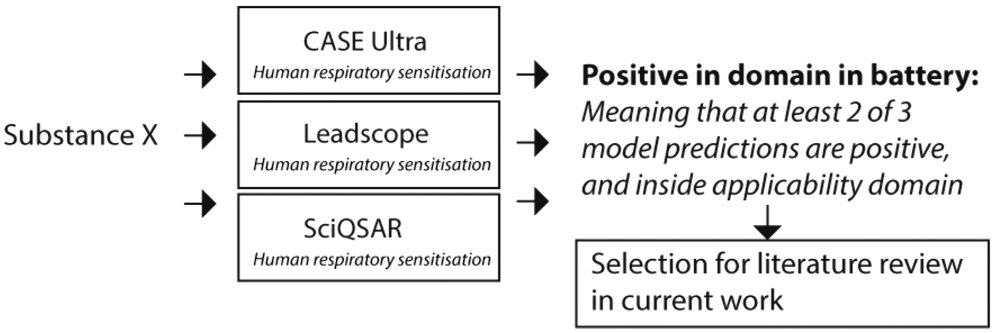


FIGURE 2 Illustration of the positive-predictions-in-battery approach for selection of substances for literature review. The figure represents the quantitative structure activity relationship (QSAR) model for respiratory sensitisation in humans. The same approach pertains to severe skin irritation in rabbits

training set of chemicals, but use different QSAR software systems, each applying a different technology (Figure 2 provides an illustration of this). Positive and in-domain mean that the substance is predicted to have potential to induce the endpoint in question and is within the applicability domain of the model. And vice versa for substances that are negative and in-domain. The CAS numbers of the substances in the 101 spray cleaning products were searched in the Danish (Q)SAR Database. The subset of substances that were positive for Respiratory Sensitisation in Humans (positive battery prediction in-domain) and/or for Severe Skin Irritation in Rabbits (positive battery prediction in-domain) was used to prioritise substances of interest for the current review. The Danish (Q)SAR Database also gives access to the experimental data underlying the models used for this project (training set substances). Thus, the substances of the current work were monitored for presence in the training set.

Concerning the relevance of the QSAR model for respiratory sensitisation in humans to prioritise substances according to their asthma induction potential, respiratory sensitisation is a health hazard that can occur after exposure to substances. It is an allergic-type airway response that may manifest as asthma. The Severe Skin Irritation in Rabbit model was employed with the rationale that if a substance is irritating to skin by damage of the surface, then it might also irritate the airways and indicate that the chemical has potential for induction of irritant-induced asthma. In support of this notion, an overlap in skin and irritation of the airways is seen in a range of substances in both humans and animals. These include the following: acetaldehyde plastics, acetic acid, acid anhydrides, acrolein plastics, ammonia fertilisers, methyl bromide, calcium hydroxide, chloroacetophenone, formaldehyde, hydrochloric acid, hydrofluoric acid, isocyanates, mercury, osmium tetroxide, phosgene, sulphuric acid, phosphoric acid aerosol, perchlorethylene, polyurethane foam, mono-, di-, and triethanolamine, formic acid, hydrogen peroxide, sodium hydroxide and sodium hypochlorite (Andersen & Maibach, 1995; Blain, 2003; Boulet, 1988; Czerwinska-Dihm & Rudzki, 1981; Dahlin et al., 2013; Division of Diet, Disease Prevention and Toxicology, National Food Institute, 2021; Ernstgård et al., 2012; Harris et al., 1981; Hooker, 2008; Kieć-Świerczyńska et al., 2014; Kishi et al., 1991; Knaak et al., 1997; Larsen, 2001; I Makarovsky et al., 2007; Makarovsky et al., 2008; Nielsen, 2018; Nowak, 2002; Plavec et al., 1993; Preisser et al., 2011; Roudabush et al., 1965; Rubin et al., 1992; Sekizawa et al., 1994; Slaughter et al., 2019; Tewari-Singh et al., 2017; Tovar & Leikin, 2015; Yelon et al., 1996).

2.3 | Literature search strategy and evaluation of asthma induction potentials

2.3.1 | Search strategy

We searched the PubMed database for the prioritised substances and their potential for induction of asthma following inhalation. Acknowledging that the database on inhalation of chemicals and development of asthma might be limited, we initially made a broad search regarding

toxicity. The following search string was applied for citric acid (CAS number: 77-92-9) as example: "(citric acid OR citric acid[Mesh] OR 77-92-9) AND ("Asthma"[Mesh] OR asthma OR"Allergy and Immunology"[Mesh] OR adverse effects[Mesh] OR toxicity) AND inhalation" The number of identified articles for each chemical substance is given in supporting information File S1 and Table S2. The abstracts of identified references were studied, relevant articles were retrieved in full and their reference lists were reviewed to identify relevant articles that we had not identified via the PubMed search.

2.3.2 | Evaluation criteria for indication of asthma induction

Besides inclusion of articles that describe respiratory sensitisation, we also included studies on substance exposure and lung function changes, irritation of the airways and asthma and respiratory symptoms and disease. Asthma is diagnosed by recurrent obstructive changes in lung function as measured by peak expiratory flow (PEF) or forced expiratory volume in the first second (FEV_1). Diagnostics for asthma involves identification of significant variability in FEV_1 and/or PEF, assessed by unspecific or specific bronchial challenge test, reversibility test or diurnal or weekly variation (e.g. spontaneously or at work or at home). In addition, we included data on injuries on the airways as an indication of the potential for induction of irritant-induced asthma.

2.4 | Statistics performed to test for overrepresentation of specific chemical fragments in the QSAR models

Specific functional groups, fragments or moieties can be significantly associated with characteristic chemical reactions and hence also for the toxicity of substances. The Danish (Q)SAR database allowed us to assess whether specific chemical fractions and moieties were associated with positive prediction for respiratory sensitisation in humans. To determine the potential overrepresentation of specific fragments and moieties in the QSAR model for respiratory sensitisation in humans, we employed the Matthews Correlation Coefficient (MCC). We first counted how many of the total predictions from the battery model that were positive and in-domain, and negative and in-domain, and calculated their ratio. Then, selected chemical fragment/moiety was searched for in the Danish (Q)SAR Database, and we counted how many of the substances containing a given fragment/moiety were predicted positive in-domain or negative in-domain for respiratory sensitisation and calculated their ratio. MCC was calculated according to Chicco and Jurman (2020)) (Formula and further description are provided in the supporting information File S1, Table S3). The Chi-squared test was employed to test for the potential overrepresentation of chemical groups, for example. carboxylic acids (–COOH), in the group of substances that were positive for battery for respiratory sensitisation in humans in the QSAR model (GraphPad Prism v. 8.0.2, GraphPad Software, San Diego, CA, USA). Notably, in all calculations we only considered substances that were positive or negative in-domain in battery, thus omitting all inconclusive substances.

3 | RESULTS

3.1 | Overview of the selected substances and their QSAR predictions

The 101 products contained substances with 206 unique CAS numbers of which 154 could be found in the Danish (Q)SAR Database. The database, for example, does not contain substances with less than 2 carbon atoms. Eighteen substances were positive in battery for respiratory sensitisation in humans, and 44 were negative in battery. The remaining substances were inconclusive or outside the applicability domain. One substance, monoethanolamine, was present in the training set of the Danish (Q)SAR Database, with positive outcome in a respiratory sensitisation test. Severe skin irritation in rabbits was found positive in battery for 34 substances, while 63 were negative in battery.

We aimed at selecting approximately 30 substances to limit the extent of the literature review. We selected 28 substances for review, based on the QSAR findings and knowledge on the substances' physico-chemical characteristics and toxicity. The selected substances are presented in Table 1, organised according to their chemical or functional groups or, for some, according to their properties such as calcium chelation. Twenty substances were selected for literature review based on a positive QSAR prediction, while eight were selected based on previous experience.

3.2 | Review of the literature on the asthma induction potentials

3.2.1 | Calcium chelators

Ethylenediaminetetraacetic acid (EDTA), citric acid and nitrilotriacetic acid

EDTA, citric acid and nitrilotriacetic acid are added to cleaning products due to their ability to chelate calcium and thereby improve the performance of soaps and detergents. A case series study looked at patients with work-related rhinitis—Alone or in combination with asthma—With a history of exposure to aerosols containing EDTA. A nasal EDTA-provocation test was positive in 10 of 28 patients. Of note, the majority of the 10 positive patients were cleaners or healthcare workers who used cleaning products formulated as sprays (Laborde-Castérot et al., 2012).

EDTA has been used in nebuliser bronchodilators for treatment of asthma (Asmus et al., 1999). To investigate the effect of EDTA inhalation in asthmatics, 18 subjects with asthma (and bronchial hyperresponse to methacholine) were randomly subjected to

TABLE 1 Overview of the 28 selected substances: Structure, QSAR predictions and availability of literature

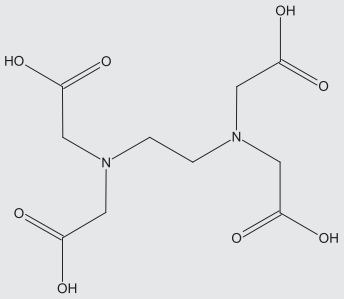
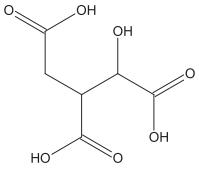
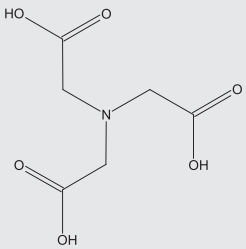
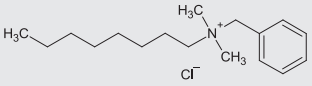
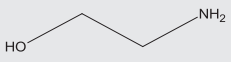
Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
Calcium chelators			
Ethylenediaminetetraacetic acid (EDTA) CAS no 64-02-8 Ethylenediaminetetraacetic acid Molecular formula: $C_{10}H_{16}N_2O_8$ MW: 416.20		**Respiratory sensitisation in humans:** Battery: POS_OUT CASE ultra: POS_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: INC_OUT CASE ultra: POS_IN Leadscope: INC_OUT SciQSAR: NEG_IN **Selected based on knowledge?** Yes	Yes
Citric acid CAS no 77-92-9 Molecular formula: $C_6H_8O_7$MW: 192.12		**Respiratory sensitisation in humans:** Battery: POS_OUT CASE ultra: POS_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_IN SciQSAR: NEG_IN Experimental QSAR training data: Negative **Selected based on knowledge?** Yes	Few data
Nitrilotriacetic acid CAS no 139-13-9: Molecular formula: $C_6H_9NO_6$ MW: 191.14		**Respiratory sensitisation in humans:** Battery: POS_OUT CASE ultra: POS_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_IN SciQSAR: NEG_IN **Selected based on knowledge?** Yes	No data

TABLE 1 (Continued)

Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
Chlorine substances			
Hypochlorite /sodium hypochlorite/chlorine CAS No 14380-61-1: Hypochlorite ion Molecular formula: ClO^- MW: 51.45 CAS No 7681-52-9: Sodium hypochlorite Molecular formula: NaOCl MW: 74.44 CAS No 7782-50-5: Chlorine Molecular formula: Cl_2 MW: 70.91	Hypochlorite ion:  Sodium hypochlorite:  Chlorine: 	Not inlcuded in the Danish (Q) SAR Database[1] **Selected based on knowledge?** Yes	Yes
Chloramine CAS No 10599-90-3 Chloramide Molecular formula: NH_2Cl MW: 51.48		Chlormanine is not included in the Danish (Q)SAR Database[1] **Selected based on knowledge?** Yes	Few data
Benzalkonium chloride CAS No 8001-54-5: Alkylbenzyldimethylammonium chloride Molecular formula: $C_9H_{13}NCl$-R (R = C_8H_{17} to $C_{18}H_{37}$) Example shows: R = C_8H_{17} MW: 283.88		**Respiratory sensitisation in humans:** Battery: NEG_OUT CASE ultra: INC_OUT Leadscope: NEG_OUT SciQSAR: NEG_IN **Severe skin irritation in rabbits:** Battery: POS_IN CASE ultra: INC_OUT Leadscope: POS_IN SciQSAR: POS_IN **Selected based on knowledge?** Yes, and selected based on QSAR predicted potential for irritation	Yes
Amines			
Monoethanolamine CAS no 141-43-5: 2-aminoethanol Monoethanolamine Molecular formula: C_2H_7NO Mw: 61.08		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_OUT SciQSAR: POS_IN Experimental QSAR training data: Positive **Severe skin irritation in rabbits:** Battery: POS_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Selected based on knowledge?**	Yes

(Continues)

TABLE 1 (Continued)

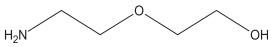
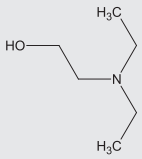
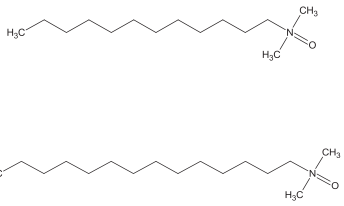
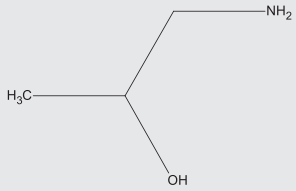
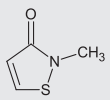
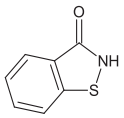
Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		No, selected based on QSAR predicted potential for sensitisation	
2-(2-aminoethoxy)ethanol CAS no 929-06-6: Diethylene glycolamine Molecular formula: $C_4H_{11}NO_2$ MW: 105.14		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_OUT SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: INC_OUT CASE ultra: INC_OUT Leadscope: NEG_IN SciQSAR: POS_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	No data
2-diethylaminoethanol CAS no 100-37-8: *N*,*N*-Diethylethanolamine Molecular formula: $(C_2H_5)_2NCH_2CH_2OH$ MW: 117.19		**Respiratory sensitisation in humans:** Battery: INC_OUT CASE ultra: POS_OUT Leadscope: POS_OUT SciQSAR: INC_OUT **Severe skin irritation in rabbits:** Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_IN SciQSAR: POS_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for irritation	Few data
Alkyl dimethyl aminoxide Mixture of c12 and c14 alkyl-chains: CAS No 1643-20-5: *N*,*N*-Dimethyldodecylamine *N*-oxide Molecular formula: $C_{14}H_{31}NO$ MW: 229.40 CAS No 3332-27-2: *N*,*N*-Dimethyltetradecylamine *N*-oxide Molecular formula: $C_{16}H_{35}NO$ MW: 257.46		**Respiratory sensitisation in humans:** Battery: NEG_OUT CASE ultra: INC_OUT Leadscope: NEG_OUT SciQSAR: NEG_IN (pertains to both CAS numbers) **Severe skin irritation in rabbits:** CAS: 1643-20-5 Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_IN SciQSAR: POS_IN Experimental QSAR training data: Positive	No data

TABLE 1 (Continued)

Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		CAS: 1643-20-5: Battery: POS_IN CASE ultra: NEG_IN Leadscope: POS_IN SciQSAR: POS_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for irritation	
1-aminopropan-2-ol CAS no 78-96-6 Molecular formula: C_3H_9NO MW: 75.11		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: NEG_OUT Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: POS_OUT SciQSAR: NEG_IN Experimental QSAR training data: Negative **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	
Isothiazolinones			
Methylisothiazolinone CAS No 2682-20-4: 2-Methyl-4-isothiazolin-3-one Molecular formula: C_4H_5NOS MW: 115.15		**Respiratory sensitisation in humans:** Battery: INC_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: POS_OUT **Severe skin irritation in rabbits:** Battery: INC_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: NEG_OUT **Selected based on knowledge?** Yes	Few data
Benzisothiazolinone CAS No 2634-33-5: 1,2-Benzisothiazol-3(2H)-one Molecular formula: C_7H_5NOS MW: 151.19		**Respiratory sensitisation in humans:** Battery: INC_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: POS_OUT **Severe skin irritation in rabbits:** Battery: NEG_OUT CASE ultra: INC_OUT Leadscope: INC_OUT SciQSAR: NEG_IN	Few data

(Continues)

TABLE 1 (Continued)

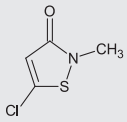
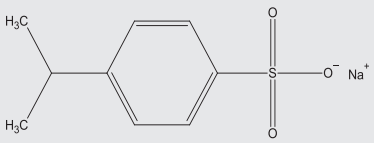
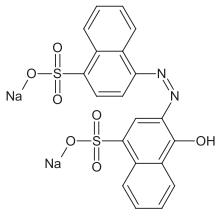
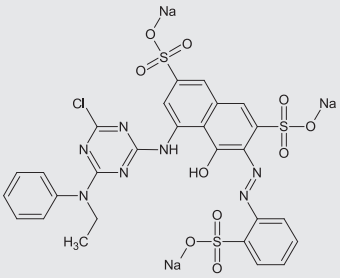
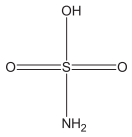
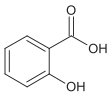
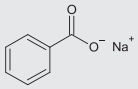
Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		Selected based on knowledge? Yes	
Chlormethylisothiazolinone CAS No 26172-55-4: 5-Chloro-2-methyl-4-isothiazolin-3-one Molecular formula: C_4H_4ClNOS MW: 149.6		**Respiratory sensitisation in humans:** Battery: INC_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: POS_OUT **Severe skin irritation in rabbits:** Battery: POS_OUT CASE ultra: INC_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Selected based on knowledge?** Yes	Few data
Sulphonates and sulfamic acid			
Sodium p-cumenesulphonate CAS No 15763-76-5 Molecular formula: $C_9H_{11}NaO_3S$ MW: 222.24		**Respiratory sensitisation in humans:** Battery: POS_OUT CASE ultra: POS_IN Leadscope: POS_OUT SciQSAR: INC_OUT **Severe skin irritation in rabbits:** Battery: POS_IN CASE ultra: POS_IN Leadscope: INC_OUT SciQSAR: POS_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for irritation	No data
Disodium 4-hydroxy-3-[(4-sulphonatonaphthyl)-azo]naphthalenesulphonate CAS No 3567-69-9: Carmoisine, acid red 14 Molecular formula: $C_{20}H_{12}N_2Na_2O_7S_2$ MW: 502.43		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_OUT Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_OUT CASE ultra: POS_OUT Leadscope: NEG_OUT SciQSAR: NEG_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	No data

TABLE 1 (Continued)

Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
Trisodium 5-[[4-chloro-6-(ethylphenylamino)-1,3,5-triazin-2-yl]amino]-4-hydroxy-3-[(2-sulphonatophenyl)azo] naphthalene-2,7-disulphonate CAS No 72829-25-5 Molecular formula: $C_{27}H_{19}ClN_7Na_3O_{10}S_3$ MW: 802.10		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: INC_OUT Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: POS_OUT Leadscope: NEG_IN SciQSAR: NEG_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	No data
Sulfamic acid CAS No 5329-14-6: Amidosulfonic acid Molecular formula: H_3NO_3S MW: 97.09		No data[1] **Selected based on knowledge?** Yes	Few data
Salicyclic acid-like substances			
Salicylic acid CAS no 69-72-7: 2-Hydroxybenzoic acid Molecular formula:$C_7H_6O_3$ MW: 138.12		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_OUT Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: INC_OUT SciQSAR: NEG_IN Experimental QSAR training data: Negative **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	Yes
Sodium benzoate CAS no 532-32-1 5329-14-6: Molecular formula: $C_7H_5NaO_2$ MW: 144.10		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_IN SciQSAR: POS_IN Note that the prediction is on the acid not the sodium salt **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_OUT SciQSAR: NEG_IN	Few data

(Continues)

TABLE 1 (Continued)

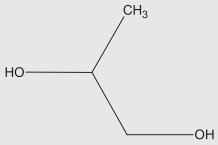
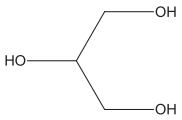
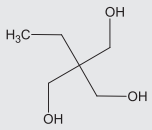
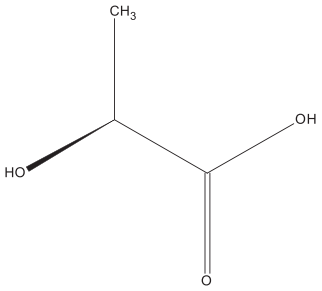
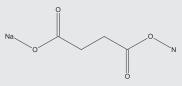
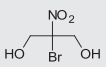
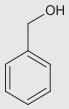
Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		Experimental QSAR training data: Negative **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	
Short-chain aliphatic alcohols and acids			
Propane-1,2-diol CAS no: 57-55-6: Propylene glycol Molecular formula: $C_3H_8O_2$ MW: 76.09		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: NEG_IN Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: POS_OUT SciQSAR: NEG_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	Few data
Glycerol CAS no 56-81-5: 1,2,3-Propanetriol, glycerin Molecular formula: $C_3H_8O_3$ MW: 92.09		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: NEG_IN Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_OUT SciQSAR: NEG_IN Experimental QSAR training data: Negative **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	No data
Propylidynetrimethanol CAS no 77-99-6: Trimethylolpropane, 1,1,1-Tris (hydroxymethyl) propane Molecular formula: $C_6H_{14}O_3$ MW: 134.17		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: NEG_IN Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_IN SciQSAR: NEG_IN	No data

TABLE 1 (Continued)

Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		Selected based on knowledge? No, selected based on QSAR predicted potential for sensitisation	
L-(+)-lactic acid CAS no 79-33-4 Molecular formula: $C_3H_6O_3$ MW: 90.08		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_OUT Leadscope: POS_IN SciQSAR: POS_IN Notably the QSAR model does not distinguish between the 3D isomers **Severe skin irritation in rabbits:** Battery: POS_IN CASE ultra: POS_IN Leadscope: INC_OUT SciQSAR: POS_IN Experimental QSAR training data: Positive	Few data
		Selected based on knowledge? No, selected based on QSAR predicted potential for sensitisation and irritation	
Disodium malate CAS no 676-46-0: DL-malic acid disodium salt Molecular formula: $C_4H_4O_5Na_2$ MW: 178.05		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: POS_OUT Leadscope: POS_IN SciQSAR: POS_IN Note that the prediction is on the acid not the sodium salt **Severe skin irritation in rabbits:** Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_IN SciQSAR: NEG_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	Few data
Other substances			
Bronopol CAS no 52-51-7: 2-brom-nitro-1,3-propandiol Molecular formula: $C_3H_6BrNO_4$ MW: 199.99		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: INC_OUT Leadscope: POS_IN SciQSAR: POS_IN	No data

(Continues)

TABLE 1 (Continued)

Substances Name(s), CAS, synonyms, linear formula, number and molecular weight (MW)	Structure	QSAR predictions and criteria for selection (see explanation below table)	Relevant literature available?
		Severe skin irritation in rabbits: Battery: NEG_IN CASE ultra: NEG_IN Leadscope: NEG_OUT SciQSAR: NEG_IN Experimental QSAR training data: Negative **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	
Morpholine CAS no 110-91-8: Tetrahydro-1,4-oxazine Molecular formula: C_4H_9NO MW: 87.12		**Respiratory sensitisation in humans:** Battery: POS_OUT CASE ultra: POS_OUT Leadscope: POS_OUT SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: POS_IN CASE ultra: POS_IN Leadscope: POS_OUT SciQSAR: POS_IN Experimental QSAR training data: Positive **Selected based on knowledge?** No, selected based on QSAR predicted potential for irritation	No data
Benzyl alcohol CAS no 100-51-6: Benzenemethanol Molecular formula: C_7H_8O MW: 108.14		**Respiratory sensitisation in humans:** Battery: POS_IN CASE ultra: INC_OUT Leadscope: POS_IN SciQSAR: POS_IN **Severe skin irritation in rabbits:** Battery: INC_OUT CASE ultra: NEG_IN Leadscope: INC_OUT SciQSAR: POS_IN **Selected based on knowledge?** No, selected based on QSAR predicted potential for sensitisation	No data

Note: QSAR predictions and experimental training set data (only monoethanolamine) were retrieved from the Danish (Q)SAR Database. Experimental values are as given in the Danish (Q)SAR Database and originate from the DTU QSAR models training set (Division of Diet, Disease Prevention and Toxicology, National Food Institute, 2021). Supporting toolbox alerts and supporting information on the substances QSAR predictions for allergic contact dermatitis in guinea pig and human are found in the supporting information File S2. Substances selected based on QSAR predictions are those that are positive in domain, while the rest were selected based on previous knowledge on the chemicals. The Danish (Q)SAR Database only contains organic substances (with at least two carbon atoms).

Abbreviations: IN: inside applicability domain of the models; INC: inconclusive meaning: a definite call within the defined applicability domain could not be made; NEG: negative; OUT: outside applicability domain; POS: positive; QSAR, quantitative structure activity relationship.

inhalation of 600-μg EDTA, 600-μg benzalkonium chloride (positive control) or placebo (saline) in a double-blind cross-over study. The inhalation of each substance was repeated until the FEV_1 had decreased by 20% or more, for a maximum of four times. The effect of EDTA inhalation did not differ from that of saline, whereas benzalkonium chloride decreased FEV_1. The authors concluded that EDTA did not induce significant bronchospasms at the maximum recommended dose for nebulised bronchodilators (Asmus et al., 2001).

Studies in dogs suggest that EDTA treatment might contribute to hyperresponsive airways, as dogs pretreated with an EDTA containing aerosol displayed increased airway responsiveness to methacholine compared to saline treated controls (Downes & Hirshman, 1985). In addition, bronchial inhalation challenge with aerosolised EDTA was shown to induce bronchoconstriction in several breeds of dogs, evidenced by measurement of collateral system resistance using a wedged bronchoscope (Lindeman et al., 1990; Lindeman et al., 1991).

In the same studies, also citric acid induced bronchoconstriction in dogs. This seemed to be mediated by chelation of calcium rather than acidification, since inhalation of 10% acetic acid did not increase pulmonary resistance. Furthermore, citric acid has been described to induce bronchoconstriction (and cough) in guinea pigs (Lai et al., 1999; Ricciardolo et al., 1999; Yasumitsu et al., 1996). In some studies, citric acid has even been used to induce bronchoconstriction. These studies sought to investigate other substances' inhibition of such constriction (Daoui et al., 1998; Girard et al., 1996; Satoh et al., 1993).

Nitrilotriacetic acid binds calcium like EDTA. No relevant studies on inhalation exposure and toxicity were identified.

In the Danish (Q)SAR database, EDTA, citric acid and nitrilotriacetic acid are outside the applicability domain of the respiratory sensitisation in humans model. Thus, QSAR cannot indicate whether these substances are sensitisers or not. Citric acid is negative in-domain in the QSAR model for skin irritation, while EDTA is inconclusive. Nitrilotriacetic acid was negative inside domain for skin irritation. Overall, there is some support from animal studies that EDTA and citric acid might induce bronchoconstriction.

Overall discussion of calcium chelators' potential for induction of asthma

EDTA, citric acid and nitrilotriacetic acid were out of domain in the QSAR for respiratory sensitisation in humans. EDTA is a common (but not pharmacologically active) substance in bronchodilators for treatment of asthma. Nevertheless, there is some indication from animal studies that EDTA and citric acid might induce bronchoconstriction upon airway exposure. There is a structural similarity of EDTA and citric acid (Table 1). In addition, there are data indicating that the two substances cause bronchoconstriction upon inhalation, possibly by chelation of calcium. Based on these phenomena, it is warranted to test whether calcium chelators as a group, including the structurally related nitrilotriacetic acid, induce bronchoconstriction in general. The three calcium chelators contain multiple carboxylic acid groups. Substances with carboxylic acid groups are more likely to be positive in the QSAR model for respiratory sensitisation in humans than substances without (MCC of 0.31). Ninety percent of the substances with carboxylic acid-groups are positive in battery for respiratory sensitisation in humans, whereas 10% are negative for battery (inconclusive substances not considered). This, taken together with the above considerations, supports that these calcium chelators should be studied further.

3.2.2 | Chlorine substances

Chlorine

Chlorine (Cl_2) releasing hypochlorite (ClO^-) can be added to cleaning agents as a bleaching and disinfecting agent due to hypochlorite's and chlorine's strong oxidation properties. Several studies pertain to investigation of chlorine instead of the specific chlorine containing substances (described in the next sections) that are often found in cleaning products. Yet data on chlorine could facilitate hazard assessment of the specific substances, as chlorine containing substances release chlorine upon oxidative reactions.

A range of epidemiological studies have observed association between exposure to chlorination products for disinfection of pool water at lower exposure levels and increased risks of respiratory or allergic disease, among swimmers, lifeguards and pool workers, as reviewed in (Bernard, 2007; Fisk et al., 2010; Kanikowska et al., 2018). Yet, and notably, a Cochrane review concluded that swimming training was well-tolerated by children and adolescents with stable asthma, that is,, existing asthma was not aggravated, at least not in younger people (Beggs et al., 2013). The review did however not address the risk of *developing* asthma.

In a case study, a 39-year-old woman inhaled released gases from a mixture of sodium hypochlorite and hydrochloric acid and developed asthma that persisted 2 years later. The asthma was suggested to be nonimmunologic asthma caused by irritation. Pathological findings in bronchial tissue supported that irritation was the initiating event (Deschamps et al., 1994).

Concerning data from animal studies, one study in mice investigated the effect of chlorine on respiratory mechanics as determined during exposure to increased concentrations of methacholine. Naïve mice inhaling 80 ppm of chlorine exhibited a marked increase in respiratory resistance (Johansson et al., 2017). Tuck et al. exposed mice to chlorine gas at 800 ppm for 5 min and observed airway epithelial cell apoptosis and sloughing and a modest increase in airway responses to methacholine (Tuck et al., 2008). In two studies, mice were exposed to chlorine gas at 100 ppm for 5 min. Airway responsiveness to aerosolised methacholine was increased 24 h later (McGovern et al., 2015, 2010).

Hypochlorite

Hypochlorite (ClO^-) is also called chlorine bleach and is often used for surface cleaning and disinfection (Nickmilder et al., 2007). Hypochlorite decomposes to chlorine gas (Cl_2), which is the active substance (Bernard, 2007). An epidemiological study on asthma control in US

nurses suggested that increased risk of poor asthma control was associated with exposure to, among other substances, hypochlorite bleach (odds ratio: 1.18) (Dumas et al., 2017). In one case study, sodium hypochlorite was accidentally mixed with a "residual acidic antimicrobial solution" producing chlorine. Of 545 potentially exposed workers, three developed acute onset irritant-induced asthma (Centers for Disease Control and Prevention (CDC), 2012).

In mice, FEV_1 and airway resistance following challenge with methacholine did not differ between control mice and mice after intranasal instillation with 40 μl of 0.003% active chlorine dosed as sodium hypochlorite. The administered concentration of chlorine was tenfold higher than in public swimming pool water. When the airway barrier had been compromised by intraperitoneal injection of the airway damaging agent of naphthalene, intranasal administration of hypochlorite did, however, induces an immediate irritant sensory response, and 24 h later the mice showed airway hyperreactivity (Van Den Broucke et al., 2018). Similarly, when mice were sensitised with ovalbumin and subsequently challenged with ovalbumin in combination with a naturally vaporised gas of a 5% hypochlorite solution, airway inflammation and hyperresponsiveness were increased by hypochlorite (aerosol) exposure (Kim et al., 2014).

Hypochlorite is not included in the (Q)SAR Database. Taken together, the above-described data are inconsistent to conclude that hypochlorite inhalation is a risk factor for induction of occupational asthma.

Chloramine

The disinfectant chloramine has previously been linked to development of occupational asthma as reviewed by (Baur et al., 2012). Out of 80 English patients with occupational asthma caused by cleaning products, chloramine was attributed to 31% of the asthma cases (Walters et al., 2018). After using chloramine-T, seven brewery workers experienced asthmatic symptoms. Skin-prick tests with chloramine were positive (Bourne et al., 1979). In another case, five individuals had been exposed to chloramine-T while dissolving it as a cleaning-agent powder. Four patients noticed that nasal irritation and wheezing started within minutes after dissolving a chloramine-T-powder in water. The fifth patient noticed wheezing several hours after the procedure. Three of the patients later had an inhalation challenge with the substance. One showed early onset bronchial obstruction (FEV_1 decreased to 65%), whereas the other two showed no bronchial obstruction. Four had a skin prick test and all had "an immediate type of wheal and flare reaction followed by a late-type infiltrative reaction" (Dijkman et al., 1981). Kramps et al. described a number of patients who developed asthmatic symptoms post exposure to chloramine-T (Kramps et al., 1981). One male nurse had for more than 14 years worked in departments, where he was exposed to Chloramine-T and glutaraldehyde, which were used to disinfect surgical instruments. He noticed what was described as the beginning of an asthmatic reaction. He was positive for Chloramine-T in a skin (prick) test and, following inhalation challenge with this substance, FEV_1 decreased, while no effect was observed after inhalation of glutaraldehyde (Sartorelli et al., 2010).

Chloramine is not included in the Danish (Q)SAR database because it is inorganic. Overall, we assess that there is some indication for an asthma induction potential of chloramine.

Benzalkonium chloride and other quaternary ammonium substances

Benzalkonium chloride includes organic salts classified as "quaternary ammonium substances with lengths of the alkyl chain ranging from C8 to C18" (Sanders, 2006). Benzalkonium chloride is used in cleaning products as disinfectants, detergents and preservatives. Notably, benzalkonium chloride has been used as an additive (preservative) in bronchodilator solutions (Asmus et al., 1999).

Out of 80 English patients with occupational asthma originating from exposure to cleaning products, benzalkonium chloride was attributed to 11% of the cases (Walters et al., 2018). One study was undertaken to investigate benzalkonium chlorides due to their role as preservative in anti-asthma respirator solutions. Twenty-eight subjects with stable asthma inhaled 0.04- to 5-μmol benzalkonium chloride. Seventeen subjects showed at least 20% decrease in FEV_1 following dosing with 0.4- to 5-μmol benzalkonium chloride (Zhang et al., 1990). In another study with the same purpose, 30 subjects with asthma, as well as 10 nonasthmatic controls, inhaled nebulised benzalkonium chloride. Dosing was repeated until their FEV_1 was lowered by at least 15% (up to three doses, each of 600 μg). The effect was most pronounced in asthmatics (Lee & Kim, 2007). Nine asthmatic subjects were tested for the effect of different pharmaceuticals on benzalkonium chloride-induced bronchoconstriction. Benzalkonium chloride was found to provoke bronchoconstriction via a combination of mast cell activation and stimulation of peripheral and central neural pathways (Miszkiel, Beasley, & Holgate, 1988). Another study by the same group measured FEV_1 in 12 asthmatic subjects, which were challenged with benzalkonium chloride in the presence of other pharmacological agents. The authors concluded that the initial bronchoconstrictor effect of benzalkonium chloride was partially caused by histamine release. Yet the main cause of the effect was not identified (Miszkiel, Beasley, Rafferty, & Holgate, 1988). Ten women and 12 men with asthma were tested for whether they responded to a nebuliser solution that contained benzalkonium chloride solution, defined as a fall in FEV_1 of more than 20%. Those that did subsequently inhaled 4 ml of benzalkonium chloride aerosol at increasing concentrations. The dose was increased until bronchoconstriction occurred, defined as above. The cumulative concentration of benzalkonium chloride causing 20% decrease was 0.3 g/L (Beasley et al., 1987).

Several case studies have been published. Three female nurses developed asthma after exposure to a disinfection solution with benzalkonium chloride. A challenge test with benzalkonium chloride showed decreased FEV_1 of 25%, 30% and 40% in the three nurses (Purohit et al., 2000). A 44-year-old male pharmacist developed asthma, and a bronchial challenge test showed *lauryl dimethyl benzyl ammonium chloride*, a benzalkonium chloride, to be the eliciting substance (Burge & Richardson, 1994). A 22-year-old woman presented with occupational asthma that was suspected to originate from benzalkonium chloride exposure. She exhibited positive responses to

challenges with a liquid toilet bowl cleaner containing benzalkonium chloride but did not react to other substances. The asthmatic symptoms resolved after discontinued use of the toilet cleaning product (Bernstein et al., 1994). A 17-year-old woman inhaled nebulised Albuterol containing benzalkonium chloride (cumulative dose: 32 mg) over 3.5 days. Persistent bronchospasm was observed. The respiratory status improved dramatically after switching to a benzalkonium chloride-free nebulisation fluid (George et al., 2017). In another case, benzalkonium chloride was suspected to induce life-threatening toxicity in a 16-month-old girl receiving bronchodilator solutions. The girl did not react to a solution with no benzalkonium chloride (Menendez et al., 1989).

Conclusion on benzalkonium chloride

Benzalkonium chlorides are out of the domain of the QSAR model for respiratory sensitisation in humans. Nonetheless, the substance is positive in-domain in the QSAR model for skin irritation suggesting a potential for irritation of the airways too. In addition, there is some indication from human studies that this substance might induce asthma.

Overall assessment of chlorine containing substances

There is some indication in the literature that chloramine and benzalkonium chloride have potential for inducing asthma, whereas data for hypochlorite are equivocal. Chloramine and hypochlorite are not included in the Danish (Q)SAR Database, as both are inorganic substances. Overall, chlorine containing substances in the QSAR model for respiratory sensitisation in humans, present with an MCC of 0.28 for positive respiratory sensitisation in humans, pointing towards the presence of Cl in substances is a positive predictor for asthma.

3.2.3 | Amines

Amines are generally used in cleaning products as surfactants and/or anti-bacterial agents.

Monoethanolamine

Monoethanolamine serves as a surfactant in cleaning products. Data on monoethanolamine and asthma are sparse: One study investigated the mechanism underlying monoethanolamine induced bronchoconstriction. Guinea pigs were exposed by inhalation to monoethanolamine at the air concentration of 3.3%. This induced bronchoconstriction, measured as a change in airway opening pressure in anaesthetised ventilated animals. This exposure level is very high and to a higher degree reflects levels encountered during a chemical accident rather than air concentrations during cleaning (Kamijo et al., 2009).

In QSAR, monoethanolamine was positive for respiratory sensitisation in humans. Monoethanolamine is also reported to be positive in the underlying experimental data used to develop the QSAR model. We were however unable to retrieve this original study. Overall, we assess that more experimental data are needed to firmly assess whether monoethanolamine has an asthma induction potential.

2-(2-aminoethoxy)ethanol

There is to our knowledge no relevant literature on the asthma-inducing potential of this substance. In QSAR, this substance is positive for respiratory sensitisation in humans (Table 1).

2-diethylaminoethanol

After a leak in a heating system 2500 people were potentially exposed to 2-diethylaminoethanol and most experienced irritative symptoms in the airways. During the next 3 months, 14 were diagnosed with asthma. Diagnoses were confirmed in seven subjects according to the: "National Institute for Occupational Safety and Health surveillance case definition of occupational asthma" (Gadon et al., 1994). In experimental animals, rats inhaled diethylethanolamine at 10 to 301 ppm, 6 h/day for 9 days. Nasal irritation was observed at 56 and 301 ppm, and mortality was increased at 301 ppm (males, 90%; females, 50%). A follow-up 14-week study was undertaken with rats inhaling 11, 25 or 76 ppm, 6 h/day, 5 days/week. Mild to moderate signs of respiratory irritation in the form of noises or rales occurred in a dose-dependent fashion. These symptoms reversed within 1 h at the two lowest concentrations and overnight at the highest concentration. Some exposure-related lesions were observed in the upper respiratory tract at the two highest dose levels, including among other, hyperplasia and inflammatory cell infiltrations. Bronchoconstriction was not measured, so the indication of asthma induction potentials is solely based on the symptoms of irritation (Hinz et al., 1992).

In QSAR, 2-diethylaminoethanol was inconclusive for respiratory sensitisation in humans but positive in the model for skin irritation. Overall, the literature data are sparse, and we asses that more knowledge is needed to provide a conclusion on this substance.

Alkyldimethylamin oxide

We have not found any relevant studies on the toxicity of this substance. It was inconclusive in the QSAR model for respiratory sensitisation in humans but positive for skin irritation. It is not known whether this substance has an asthma induction potential, but the QSAR prediction indicates that it might have potential for irritation of the airways.

1-Aminopropan-2-ol

There is a lack of studies in the literature, but the substance was positive for respiratory sensitisation in humans in the QSAR model. Thus, only this QSAR prediction points to an asthma induction potential.

Overall assessment of amines

Despite a positive QSAR prediction for respiratory sensitisation in humans, we assess that additional data are needed to determine whether monoethanolamine has an asthma induction potential. Two other amine substances, 2-(2-aminoethoxy)ethanol and 1-aminopropan-2-ol, were positive in the QSAR predictions but lacked data on airway toxicity (Baur et al., 2012). Two other amines were neither positive in QSAR for respiratory sensitisation in humans nor was experimental data available to provide support as to their potential for induction of asthma. Both showed positive predictions for skin

irritation, indicating that they might have potential for irritation of the airways.

The presence of an NH_2 group in a substance seems to increase the likelihood of respiratory sensitisation as inferred by QSAR. The MCC is 0.27 for the presence of -NH_2 and positivity for respiratory sensitisation (MCC: 0.28 for secondary amines). Notably the tertiary amines are not overrepresented among the positive predictions for respiratory sensitisation in humans (MCC: 0.02). Overall, more data are needed to reach conclusions on these substances.

3.2.4 | Isothiazolinones

Methylisothiazolinone, benzisothiazolinone and chloromethylisothiazolinone

Isothiazolinones are added to cleaning products to prevent microbial growth. We located only few studies on airway effects of these substances. In one case study, a 26-year-old male chemical worker poured raw materials containing, among others, 1,2-benzisothiazolin-3-one. Two months after having started on the job, he developed asthma. Challenge with 1,2-benzisothiazolin-3-one provoked an asthmatic response. The responses to other raw materials tested in the same way were negative (Moscato et al., 1997).

In an animal study, mice were dermally exposed to methylisothiazolinone. Challenge with the substance by intranasal instillation 15 days later resulted in increased breathing frequency, lymph node T- and B-cell proliferation and increased IFN-γ and IgE in serum, confirming dermal sensitisation. Airway challenge with the substance decreased breathing frequency, an indication of acute sensory irritation. The mice did not present an allergic respiratory response 24 h after the airway challenge, when airway resistance in response to methacholine was assessed nor was pulmonary inflammation observed. The authors concluded that methylisothiazolinone did not induce asthma but was a dermal sensitiser and airway sensory irritant (Devos et al., 2015).

Summary of isothiazolinones

The isothiazolinones were outside of the applicability domains of the QSAR models for respiratory sensitisation in humans or skin irritation in rabbits. Together with the lack of experimental evidence, no overall conclusion can be reached as to whether these substances are respiratory sensitisers or asthmogens.

3.2.5 | Sulphonates and sulfamic acid

Sulphonates are surfactants. Sulfamic acid is a powerful descaling agent but not as corrosive for metals as, for example, hydrochloric acid.

Sodium p-cumenesulphonate

There is virtually no toxicity data available on this substance, and we identified no studies relating to respiratory toxicity. The QSAR prediction for respiratory sensitisation in humans is outside the applicability domain of the model, while that for skin irritation is positive in-domain. More data are needed to determine if this substance has an asthma-inducing potential.

Two large sulphonate substances (names detailed in Table 1)

There is to our knowledge no relevant literature on their asthma-inducing potentials, but the QSAR predictions on respiratory sensitisation in humans are positive in-domain (Table 1).

Sulfamic acid

A woman aged 22 mixed a bleaching agent containing 4.9% sodium hypochlorite with a detergent containing 10% malic acid and 2% sulfamic acid. Thereafter, she developed dry cough, breathlessness and chest tightness. She further presented with severe airway hyperresponsiveness against methacholine during an inhalation challenge. She already had a history of allergic asthma, rhinitis, and aspirin sensitivity prior to mixing of the substances. The authors concluded that she had severe asthma and that acute respiratory distress syndrome was triggered by mixing of the cleaning products (Mapp et al., 2000). Likely, this effect is due to released chlorine gas, rather than to sulfamic acid. Sulfamic acid is inorganic and therefore not included in the Danish (Q)SAR Database.

Overall assessment of sulphonates and sulfamic acid

The literature data base on these substances are sparse. Two of the sulphonates were positive in QSAR for respiratory sensitisation in

TABLE 2 Matthews correlation coefficient (MCC) values and chi-squared *p*-values for selected chemical fragments and moieties reflecting the substance classes chosen in this work

Fragment/moiety	Matthews correlation coefficient (MCC)	Chi-squared *p*-value
-COOH (carboxylic acid)[a]	0.31	<0.0001
Chlorine	0.28	<0.0001
-NH_2	0.27	<0.0001
Secondary amine	0.28	<0.0001
Tertiary amine	0.02	<0.001
Bromine	0.10	<0.0001
-N-O	0.08	<0.0001
 From sulfamic acid	0.06	<0.0001

Note: Values are calculated based on their presence in substances with positive in-domain QSAR predictions relative to their presence in substances with negative in-domain predictions from the battery model for respiratory sensitisation in humans in the Danish (Q)SAR Database with 650,000 substances.

[a]The carboxylic acid was searched as bound to a carbon atom in the substances.

humans, and one was positive for skin irritation. Yet when the fragment: -SO_3 (see drawing in Table 2) is run in the Danish (Q)SAR Database with predictions, the MCC is low (0.06). We assess that more data are needed before a conclusion can be reached on whether sulphonates and sulfamic acid might contribute to development of asthma.

3.2.6 | Salicylic acid-like substances

These substances are widely used as preservatives in cleaning agents and many other products. Salicylic acid has been associated with asthma induction or exacerbation in some reports. But in these reports the acetyl salicylic acid is administered by orally; for instance, Botey et al. studied four paediatric patients described to have aspirin-induced asthma. An oral provocation test with acetyl salicylic acid was positive in all four patients (Botey et al., 1988). Sanak et al. described airway overexpression of leukotriene C_4 (LTC_4) synthase (LTC_4 is a potent lipid mediator in asthma and inflammation) in aspirin sensitive asthmatic patients (Sanak, 2000). The prevalence of aspirin intolerant asthma was approximately 10% in two Australian asthmatics cohorts (Vally, 2002). Sodium benzoate is an analogue of salicylic acid. There is some support for association with asthma: A girl had developed asthma in her early life and was given bronchodilator therapy. At the age of 7 years, she had what was described as exacerbations of the asthma. When challenged orally with sodium benzoate, she showed heightened sensitivity to this substance. When this substance was avoided, the episodes of coughing and wheezing disappeared (Petrus et al., 1996). A group of asthma patients had a history of asthma exacerbation after ingestion of orange drinks. Therefore, 14 of 272 asthma patients were tested for the response on FEV_1 of sodium benzoate—a substance in these drinks. Four of the 14 reacted to this substance with a drop in FEV_1 (Freedman, 1977).

Salicylic acid and sodium benzoate (neutralised to benzoic acid for QSAR prediction) were both predicted positive in-domain in the QSAR model for respiratory sensitisation in humans (Table 1). Yet as the described cases occurred after oral exposure, it is unknown whether inhalation would have similar effects in humans. Overall, we assess that further studies are needed to provide a conclusion.

3.2.7 | Short-chain aliphatic alcohols and acids

Propane-1,2-diol (propylene glycol)

Propane-1,2-diol (propylene glycol) is used as a solvent in cleaning products. Airway irritation as well as slight airway obstruction were observed in nonasthmatic subjects inhaling 309-mg propane-1,2-diol/m^3 for 1 min (Wieslander et al., 2001). Ten women and 10 men were exposed to propylene glycol at 20 and 100 mg/m^3 for 4 h or to 200 mg/m^3 for 30 min (concentrations amounted to 96, 442 and 871 mg/m^3 when both droplets and gas phase were considered). No effects were seen on pulmonary function assessed as FEV_1 (Dalton et al., 2018).

There is limited data on airway obstruction for this substance. The QSAR prediction is positive in-domain for respiratory sensitisation in humans. We assess that more data are needed to conclude as to whether propane-1,2-diol is a potential asthma inducer.

Glycerol and propylidynetrimethanol

Glycerol and probably also propylidynetrimethanol are used as solvents in cleaning products. These substances have positive QSAR predictions for respiratory sensitisation in humans. Nonetheless, the literature on these substances and sensitisation or irritation of the airways seems limited to studies of glycerol from the tobacco industry, where glycerol was investigated as a component of tobacco smoke. It is therefore not possible to conclude on these substances' potential to induce asthma.

Lactic acid and malic acid

Lactic acid and probably also malic acid have descaling properties. As aforementioned, a 22-year-old female inhaled vapours from mixing of a bleaching agent containing 4.9% sodium hypochlorite with a detergent containing 10% malic acid and 2% sulphamic acid, after which she developed dry cough, breathlessness and chest tightness. She already had a history of allergic asthma and rhinitis and had salicylic acid sensitivity. She presented with severe airway hyperresponsiveness by methacholine inhalation challenge. The authors concluded that she had severe asthma and adult respiratory distress syndrome triggered by the cleaning agents, but this could be due to an effect of the hypochlorite (Mapp et al., 2000).

In the QSAR models, these substances were predicted positive for respiratory sensitisation in humans. Yet experimental data are virtually absent and a conclusion on whether they have an asthma induction potential cannot be reached.

Overall assessment of aliphatic alcohols and acids

There are only sparse data in the literature on the asthma induction potential of *aliphatic alcohols and acids*. Yet all five included substances have positive predictions for respiratory sensitisation in humans in the Danish (Q)SAR Database. Overall, we assess that further testing is needed to determine whether there is an asthmogenic potential of aliphatic alcohols and acids.

3.2.8 | Other substances

Morpholine

Morpholine is an alkaline and corrosive chemical solvent used in cleaning products such as oven cleaners. The experimental data in the literature on bronchoconstriction are absent, although some findings indicate that morpholine might induce local irritation to the airways (Conaway, 1984; Harbison, 1989). The QSAR prediction for respiratory sensitisation in humans is outside the applicability domain, while that for skin irritation is positive inside domain. Overall, data are needed to assess a possible asthma induction potential, although there is an indication for irritation of the airways by the QSAR prediction.

Bronopol

Bronopol has antimicrobial properties, and, to our knowledge, there are no available data on this substance on respiratory irritation or sensitisation, although dermal sensitisation has been described in several cases (e.g. Cheng et al., n.d.; Warshaw et al., n.d.; Choudry et al., 2002; Podmore, 2000; Shaughnessy et al., 2014). In the Danish (Q)SAR Database, bronopol was positive for both respiratory sensitisation in humans and skin irritation in rabbits. We searched two chemical fragments of bronopol (Br, NO) in the Danish (Q)SAR Database in combinations with predictions for respiratory sensitisation in humans and found low MCCs: Br has an MCC of 0.10, while that of NO was 0.08, suggesting that these fragments are not heavily associated with respiratory sensitisation. Overall, we assess that there is a need for more data before a conclusion on the asthma induction potential of this substance can be reached.

Benzyl alcohol

Benzyl alcohol is predicted positive in the QSAR model for respiratory sensitisation in humans. We found no literature on the asthma induction potential of this substance. Thus, experimental data are needed to provide a conclusion on the asthma induction potential of benzyl alcohol.

4 | DISCUSSION

In the current work, we gathered data to assess the potential for induction of asthma for some specific substances in spray formulated cleaning products. We collected CAS numbers from 101 products and searched QSAR predictions in the Danish (Q)SAR Database from two models: (1) Respiratory Sensitisation in Humans and (2) Severe Skin Irritation in Rabbits. The first model represents the induction pathway of asthma via sensitisation; the other irritation pathway to asthma, with the underlying assumption that skin irritants, would also be irritants of the airways. Twenty substances were selected for further review based on these QSAR predictions. In addition, we included eight substances based on prior knowledge of the substances' physico-chemical characteristics and toxicity. In total, 28 substances were reviewed, and conclusions drawn on literature findings together with the QSAR predictions. Notably, we did not look for other toxicities, for instance carcinogenicity.

4.1 | Evaluation of the selected substances

Based on our evaluations, we could categorise the substances according to their potential for induction of asthma and the level of knowledge supporting this: (1) *some indication in humans for asthma induction:* chloramine, benzalkonium chloride; (2) *some indication in animals for asthma induction:* EDTA, citric acid; (3) *equivocal data:* hypochlorite; (4) *few or lacking data:* nitriloacetic acid, monoethanolamine; 2-(2-aminoethoxy)ethanol, 2-diethylaminoethanol, alkyldimethylamin oxide, 1-aminopropan-2-ol, methylisothiazolinone, benzisothiazolinone, and chlormethylisothiazolinone; three specific sulphonates and sulfamic acid, salicylic acid and its analogue sodium benzoate, propane-1,2-diol, glycerol, propylidynetrimethanol, lactic acid, disodium malate, morpholine, bronopol and benzyl alcohol. In no instance was the level of knowledge sufficient to conclude that a substance with all probability did not have potential to induce asthma.

4.2 | Data gaps and consideration of mixture effects

One important finding in this work is the scarcity of data on the potential for induction of asthma for numerous substances, for example, sulphonates, glycerol and bronopol. This is even the case for substances for which QSAR predictions point towards a potential for human respiratory sensitisation. Data are therefore highly warranted to allow for assessment of the asthma-inducing potential of a wide range of substances in spray cleaning products on the Danish market. A major reason for this is the lack of validated predictive assays for assessing induction or elicitation of asthma (Vincent et al., 2017). We therefore included animal studies where chemical exposure was subsequently followed up by assessment of airway function by a variety of methods, for example, airway responsiveness to methacholine (Downes & Hirshman, 1985), measurement of collateral system resistance by wedged bronchoscope (Lindeman et al., 1990, 1991) or the animals were sensitised with ovalbumin and subsequently challenge with ovalbumin in combination with the chemical (Kim et al., 2014). Robust and predictive assays have been developed for predicting skin sensitisation, such as the Local lymph node assay. Indication that a chemical is not a respiratory sensitizer might be obtained indirectly by the mechanistic assumption that chemicals that do not sensitise skin will also not sensitise the airways. However, until a respiratory equivalent for assessment of airway sensitisation is developed, quantitative risk assessment for respiratory allergens will probably be limited (Vincent et al., 2017).

Likewise, knowledge is completely absent for mixture effects, that is, if and how substances in cleaning products might interact to potentiate the effect of each other (synergism), so that the resulting combined effects are larger than what can be expected from addition of the effects of the individual substances (Hadrup et al., 2015; Hadrup, 2014; Kortenkamp, 2007; Nørgaard et al., 2014; Olmstead & LeBlanc, 2005). Another aspect of mixtures of chemicals is that some substances with extreme pH may be buffered by other substances and therefore act differently in combination, for example, in a spray product, compared to in pure form.

4.3 | The usefulness of QSAR as a tool for prioritising substances with asthma induction potential

Due to lack of experimental data on potential for asthma induction, we suggest that QSAR is a valuable tool in prioritisation of substances for further testing. We applied this in silico method in the selection of constituents in cleaning spray products to increase the probability

of identification of asthma inducers. We used the Danish (Q)SAR Database to assess potential for respiratory sensitisation in humans as well as for severe skin irritation in rabbits. We put most emphasis on the first model as it builds on positive experimental data on respiratory sensitisation in humans. Eighteen out of 154 substances in cleaning sprays were positive in battery for respiratory sensitisation in humans. Yet we propose that the latter model provides supplementary information for prioritising substances for further testing. This is based on the notion that if a substance is a skin irritant, it might also irritate or corrode tissue in the lower airways and have potential for induction of irritant-induced asthma. This is substantiated by the considerable number of substances outlined in the methods section that are both skin and airway irritants. One limitation in the applied QSAR predictions source was that only about 75% of the unique CAS numbers for the assessed product substances were included in the Danish (Q)SAR Database. This reflects that inorganic and organic substances with less than two carbon atoms are not included in the database.

The QSAR models helped us prioritise substances to be included in our literature review. The QSAR predictions furthermore enabled identification of gaps in the field of potential asthma inducing chemicals in spray cleaning products. Hence, several chemicals were positive for respiratory sensitisation in humans but without such toxicity having being adequately assessed in for example, experimental animals. We foresee a role of QSAR in safe-by-design product development in which potential new substances are screened before being considered in spray products.

In addition to assessment of specific substances, the QSAR predictions for 650,000 substances in the Danish (Q)SAR Database also allowed for study of overrepresentation of specific chemical fragments or moieties in substances predicted positive for respiratory sensitisation compared to substances predicted negative. Based on the 28 substances evaluated in this work, we selected eight relevant fragments and moieties for test in the QSAR model for respiratory sensitisation (Table 2). We found that in particular substances containing primary and secondary amines, carboxylic acid groups, Cl and -SO_3 were overrepresented relative to a positive outcome in respiratory sensitisation in humans, with MCC's (Matthews correlation coefficients) around or above 0.3 (Table 2). All these fragments were significantly overrepresented as tested by the Chi-squared test, but this likely reflects that in large datasets even small differences may become statistically significant. We propose that the search for fragments in QSAR predictions provides an additional tool to prioritise substances for further study for asthma induction potentials.

A point of criticism of the training set for the used QSAR model on respiratory sensitisation in humans (based on: [Graham et al., 1997]) is that we did not have access to the identity and content of the primary references for the underlying experimental data, to probe their validity. Yet we performed our own literature search and thereby ensure that there was primary literature underlying most of the positives in the dataset (supporting information File S1, Table S4). Another important point is the predictive performance of in silico models. Dik et al. evaluated QSAR models as a method of identifying low molecular weight (including chemicals) respiratory sensitisers, based on a dataset of identified respiratory sensitisers and non-sensitisers not included in the models' training sets. Both positive and negative predictive values were high when the models were used in combination (96% and 89%, respectively). However, this combination approach was not able to predict two-thirds of the chemicals, suggesting that other testing methods should supplement current in silico models (Dik et al., 2014) but not excluding QSAR models for prioritisation purposes.

5 | CONCLUSION

Based on data from the scientific literature and QSAR predictions, we were able to divide 28 specific substances into four groups according to effect and evidence level. We identified knowledge pointing towards an asthma induction potential of some substances. We identified major knowledge gaps for several substances, and overall, more data are needed on the potential for induction of asthma. This is even more important in the light of the prediction of potential for respiratory sensitisation for 18 substances in spray cleaning products. Knowledge on asthma induction potential on the potential for induction of asthma can feed into a safe-by-design strategy for development of future cleaning products on spray form by avoiding potential asthma inducers. Finally, we suggest that QSAR predictions can serve to prioritise substances that need further testing in various areas of toxicology.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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