Risk assessment of the asthma-induction potential of substances in spray products for car cabin detailing – based on EU’s Chemical Agents Directive, using harmonised classifications and quantitative structure-activity relationship (QSAR)

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Risk assessment of the asthma-induction potential of substances in spray products for car cabin detailing – based on EU’s Chemical Agents Directive, using harmonised classifications and quantitative structure-activity relationship (QSAR)

Kasper Mikkelsen, Jorid B. Sørlø, Marie Frederiksen, Niels Hadrup

1. Introduction

Car cabin detailing is done by both consumers and professionals. It may involve extensive use of spray-formulated products such as textile cleaning, vinyl treatment, leather treatment, and glass cleaning. The use of spray products creates aerosols consisting of airborne droplets and particles that workers may inhale. At the same time, the volume of air inside a car cabin is small (~3.5 m³), and thus exposure of the person inside the car can be substantial. The use of cleaning agents has previously been linked to an increased risk of asthma (Karljalsen et al., 2002; Makela et al., 2011). We recently reported that spray-formulated cleaning products contain substances with some risk of asthma induction (Hadrup et al., 2022). Carder et al. investigated respiratory sensitisation (monoethanolamine, bronopol, glycerol, methyl salicylate, benzoic acid, ammonium benzoate, and sodium benzoate). Two vinyl treatment products had a risk ratio > 1 based on the level of sodium benzoate and its DNEL set on respiratory irritation. Two products had risk ratios of 0.69 and 0.73, respectively, based on 2-methyl-2 H-isothiazol-3-one and its acute DNEL set on respiratory irritation. Four substances had a harmonised classification for respiratory irritation (bronopol, 2-phenoxyethanol, 2-methoxypropanol, and butan-1-ol). Seven substances were positive in the QSAR model for respiratory sensitisation (monoethanolamine, bronopol, glycerol, methyl salicylate, benzoic acid, ammonium benzoate, and sodium benzoate). Two vinyl treatment products had a risk ratio > 1 based on the level of sodium benzoate and its DNEL set on respiratory irritation. Two products had risk ratios of 0.69 and 0.73, respectively, based on 2-methyl-2 H-isothiazol-3-one and its acute DNEL set on respiratory irritation. In conclusion, 10 substances that may pose a risk for asthma induction were identified in the products. Two of the 71 products had a risk ratio > 1, meaning they may pose an asthma-induction risk in the modelled exposure scenario and using respiratory irritation DNELs from ECHA.

ABSTRACT

Exposure to spray-formulated products for car cabin detailing is a potential risk for asthma induction. With a focus on the asthma-related endpoints sensitisation and irritation of the lungs, we performed an occupational risk assessment based on requirements in the EU Chemical Agents Directive. We identified 71 such spray products available in Denmark. We identified ingredient substances in safety data sheets and screened for harmonised classifications of respiratory sensitisation and airway irritation. For respiratory sensitisation, we also applied quantitative structure-activity relationship (QSAR). We modelled the exposure during 15 min of work inside a car cabin, and determined the risk ratio of the products by further applying occupational exposure limits – mainly derived no-effect levels (DNELs) from the European Chemicals Agency (ECHA) set on respiratory irritation. Four substances had a harmonised classification for respiratory irritation (bronopol, 2-phenoxyethanol, 2-methoxypropanol, and butan-1-ol). Seven substances were positive in the QSAR model for respiratory sensitisation (monoethanolamine, bronopol, glycerol, methyl salicylate, benzoic acid, ammonium benzoate, and sodium benzoate). Two vinyl treatment products had a risk ratio > 1 based on the level of sodium benzoate and its DNEL set on respiratory irritation. Two products had risk ratios of 0.69 and 0.73, respectively, based on 2-methyl-2 H-isothiazol-3-one and its acute DNEL set on respiratory irritation. In conclusion, 10 substances that may pose a risk for asthma induction were identified in the products. Two of the 71 products had a risk ratio > 1, meaning they may pose an asthma-induction risk in the modelled exposure scenario and using respiratory irritation DNELs from ECHA.

Keywords:
Respiratory sensitisation
Respiratory irritation
Inhalation
Toxicology
In silico
Trigger spray
overview of the identity of substances in sprays for car cabin detailing published in the peer-reviewed literature, let alone their asthma-induction potential.

One option to fill these knowledge gaps is to use the requirements stipulated in section II, Employers’ Obligations, of the EU Chemical Agents Directive (CAD) (European Council, 1998). CAD places the responsibility of ensuring the health and safety of the workers on the employer. It describes the steps that the employer needs to conduct to combine hazard and exposure in a risk assessment, with the most important steps being: a) identification of the hazardous properties of the chemical agents; b) the level, type, and duration of exposure; c) available occupational exposure limit values; and d) the effect of preventive measures to be taken. Nevertheless, CAD does not outline precisely how this is done in practice.

We here provide an overview of car detailing products and the risk of asthma induction, and at the same time demonstrate an approach that can be used to fulfil the requirements of CAD. Finally, we modelled the exposure during 15 min of work in a car cabin and compared this value with derived no-effect levels (DNELs) from the European Chemicals Agency (ECHA) and Danish occupational exposure limits (OELs). With this information, we determined whether the risk ratios of the products were below or above 1 – with the latter indicating that the exposure is higher than the level at which there is an asthma risk.

2. Methods

In the next sections, we describe our methods in the context of the requirements of CAD (European Council, 1998) (Fig. 1 provides a short overview of our procedure, Supplemental Materials Fig. S1 provides a more detailed overview). One difference compared to the procedure that an employer has to follow is that we focused on substances that have a potential for asthma induction, while an employer has to take into account all potential toxicological endpoints. Our approach deviated from the requirements in CAD in two steps: first, instead of considering specific workplace exposure, we used a two-box exposure model to describe exposure in standard situations; second, we did not consider biological monitoring, which is not relevant in a literature-based risk assessment.

2.1. Selection and categorisation of spray products

The first part of a CAD-based risk assessment is the identification of chemical agents present in the workplace. We focused on products used for detailing and treating the interior of cars, including leather care products, odour removers, textile cleaners, glass cleaners, and products for refreshing surfaces. We identified 71 spray products from 12 different suppliers from September to December 2022 by internet search using Google Chrome with the search terms ‘car interior detailing products’, ‘vinyl treatment spray’, and ‘car cabin leather care’. Each supplier and product was given an identification number. The products’ formulations and usages vary according to whether the product is sprayed onto a seat or dashboard or into the air. Therefore, the products were divided into the following categories: leather treatment (4 products), rubber treatment (2), textile treatment (12), vinyl treatment (30), vinyl cleaning (4), glass cleaning (8), general cleaning (3) and air fresheners (8).

The products were all formulated in packaging for spraying, either as non-pressurised products such as trigger spray bottles or as pressurised products in aerosol spray cans. The aerosols generated by spraying by either type of packaging can be expected to vary substantially in e.g., size due to the difference in outlet pressure and nozzle type (Sorli et al., 2022). Aqueous mixtures are often sold in trigger bottles, while organic mixtures are sold in aerosol spray cans pressurised with CO₂ or a mixture of propane, butane, and isobutane. Products creating foam after dispersion were omitted, as they were not expected to give rise to the same airborne concentration levels as conventional spray products (Clausen et al., 2023).

2.2. Identification of hazardous properties

2.2.1. Retrieval of substance information from safety data sheets and retrieval of harmonised classifications

We gathered the newest safety data sheets available on the producers’ websites. The names, CAS numbers, and concentrations of all substances listed in the safety data sheets were entered into an Excel data library (Supplemental Materials File S2). If the concentration of a substance was given as a range, the average concentration was included. The substances were categorised based on their function in the product, such as surfactants, preservatives, perfumes, or propellants. The term ‘other’ was used for a few substances with either unknown or diverse purposes or unique properties such as UV protection. Furthermore, information on the recommended protective measures was collected for each product.

We used harmonised classifications of substances found in Annex VI ATP 18 of EU’s Classification, Labelling and Packaging (CLP) Regulation (ECHA, 2023). Asthma can be induced by respiratory sensitisation or respiratory irritation, and these were the two main endpoints looked at (Table 1). Skin sensitisation and irritation were included as supportive endpoints as there is a substantial overlap between substances that are skin sensitisers and respiratory sensitisers (Arts et al., 2008; Burge et al., 2012; Roach et al., 2020; Tsui et al., 2020), as there is between substances that cause skin irritation and respiratory irritation as reviewed in Hadrup et al. (2022). The overlap in sensitisation is based on the limited

<table>
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<td>1. Respiratory sensitising by harmonised classification (H334)</td>
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<td>3. Irritation (respiratory tract) by harmonised classification (specific target organ toxicity — single exposure, Category 3, H335,’may cause respiratory irritation’)</td>
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* This category includes substances with no harmonised classification but which ECHA highlights as skin sensitising by a majority of registrants.
human data on respiratory sensitisers (Graham et al., 1997; Hadrup et al., 2022). There is a lack of validated animal or in vitro models to detect respiratory sensitisers, warranting that some care is to be taken in considering skin sensitisers as respiratory sensitisers, although Chapter R.8 of the ECHA guidance on information requirements and chemical safety assessment states: ‘there is evidence from both human and animal studies which indicate that effective sensitisation of the respiratory tract can result from dermal contact with a chemical respiratory allergen’ (ECHA, 2012).

An additional source of information was considered. For substances that do not have a harmonised classification, ECHA still highlights whether they are considered skin sensitising by a minor or major part of the registrants. If a majority of registrants have classified a substance as skin sensitising, we thus marked it as ‘potentially sensitising’ (Table 1).

2.2.2. Quantitative structure-activity relationship (QSAR)

QSAR is a statistical method used to predict a substance’s biological or toxicological activity based on its structural features. QSAR models are built by analysing a dataset of substances, of the so-called training set, and their known properties and by using statistical techniques to identify the structural features that are most predictive of that property (National Food Institute, 2021). We previously demonstrated the use of the Danish (Q)SAR database for risk assessments of the asthma-inducing potential of spray cleaning products (Hadrup et al., 2022), and in the hazard assessment of the carcinogenic potential of spray-formulated cleaners and lubricating agents for machine maintenance (Sørl et al., 2022). In the current project, we retrieved QSAR predictions on: 1) respiratory sensitisation in humans, 2) severe skin irritation in rabbits, and 3) allergic contact dermatitis in guinea pigs and humans, from the Danish (Q)SAR Database (National Food Institute, 2021). The Danish (Q)SAR Database has predictions based on a battery of three QSAR software systems each using a different technology (CASE Ultra, Leadli and SciQSAR) (National Food Institute, 2021). Substances with a positive battery prediction were considered positive, i.e., positive inside the applicability domain in at least two of the three models. Battery predictions are thus a combined majority vote among the three models, which have been developed on the same training set of substances. The sensitivity, specificity and concordance of the QSAR models as well as the number and characteristics of reference chemicals used for building the models are provided in the Supplemental Materials.

2.3. Estimating the level, type and duration of exposure

CAD states that the employer should consider ‘the level, type and duration of exposure’ (European Council, 1998). We estimated the airborne concentration of substances during work with a two-box exposure model covering the spraying/breathing zone and the remaining cabin volume (Steiling et al., 2014), with an exposure duration of 15 min. We assumed that the substances are completely mixed into the air (in both boxes). We considered a standard-sized passenger car with an internal volume of 3.5 m$^3$ (Tenning et al., 2009). The two zones applied in the model were: a) the spraying zone (1.5 m$^3$), approximately above the surfaces sprayed upon; and b) the breathing zone (2 m$^3$) near the worker (ECHA, 2016). Some assumptions were made: a) when the worker sprays against a surface, the initial airborne concentration of the product is only present in the spraying zone next to the surface; b) all relevant surfaces are sprayed upon initially so that no more spraying occurs within the following 15 min during which the worker wipes off the surfaces; c) the overall air change rate of the workshop (3 h$^{-1}$) in which it was parked was used to estimate the interzonal air exchange (Keil and Zhao, 2017); d) the breathing zone was centred in the car and was assumed to be in contact with the surrounding air through the open car doors, and each door opening had an area of 1 m$^2$ that we used to calculate the ventilation of the breathing zone; e) the area connecting the spraying and breathing zones were assumed to have the same random air velocity as the ventilation area and a connected area of 4 m$^2$ (Keil and Zhao, 2017; Tenning et al., 2009). Larger droplets are more likely to land on a surface as they have more inertia than smaller droplets (Lee et al., 2022). Spray products packaged in aerosol cans generally produce smaller droplets compared to trigger bottles (Delmaar and Bremmer, 2009). To account for the above phenomena, we assumed that only 5% of the product dispensed from a trigger bottle, and 10% of the product dispensed from an aerosol spray can, will stay suspended after the surface is initially covered. Further details of the model are provided in the Supplemental Materials.

2.4. Occupational exposure limits

CAD states that the employer should take into consideration any occupational exposure limit values or biological limit values established on the territory of the Member State in question (European Council, 1998). As our main focus was to use exposure limits that were set based on respiratory sensitisation or irritation of the respiratory tract, we looked at DNELs, for which the most sensitive endpoint was noted as one of these. The DNELs were obtained by searching ECHA’s website for the substance in question, viewing the REACH registered substance factsheets, navigating to Details and choosing Toxicological Summary under Toxicological Information. If no acute DNEL existed for inhalation, the chronic one was noted and multiplied by two to estimate a short-term DNEL (the process is illustrated in Fig. 2).

In addition to looking at the endpoint of asthma, which was our main focus, we added information on the general toxicity to screen for exposure limits on all endpoints. This enabled us to determine the extent of asthma-related endpoints in comparison to other endpoints. For this, we used DNELs set on other endpoints, as well as OELs that are implemented through national legislation. The short-term (15 min) OEL for each substance was acquired from the Danish Working Environment Authority (Beskæftigelsesministeriet, 2022) (process illustrated in Fig. 2).

2.5. Risk assessment

If the air concentration of a single substance exceeds the exposure limit of the substance, the risk must be controlled. In the current work, we had mixtures of substances in the products and in that situation we calculated the risk ratio, based on the concept of dose addition, and determined whether it exceeded 1. We used Eq. 1, where RR is the risk ratio, $C_i$ is the 15-minute average concentration of the substance in the breathing zone of the modelled exposure, and OEL$_i$ is the OEL (or DNEL) for substance $i$.

$$RR = \frac{C_i}{OEL_i}$$

1) Asthma-related endpoint DNELs

- Asthma-related substances identified by harmonised classification and QSAR: DNEL is identified in ECHA
- All other substances: DNEL is identified in ECHA

For the DNEL it is noted if the most sensitive endpoint is respiratory irritation (no DNELs set on respiratory sensitisation)

2) General toxicity exposure limit

- All substances:
  1) Only OEL present: use OEL
  2) Only DNEL present: use DNEL (chronic multiplied by a factor 2 to acute)
  3) Both OEL and DNEL present: lowest selected of local vs. systemic effect
- Only chronic DNEL present: then OEL is used
- Both acute OEL and acute DNEL present: use lowest value

Fig. 2. Overview of the process of evaluating the asthma-induction potential of substances in spray products for car cabin detailing. The DNEL extracted from ECHA is the DNEL for workers.
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**RR** = \( \sum_{i=1}^{n} \frac{C_i}{OEL_i} \) (1)

### 3. Results

The data relating to substance classifications, product composition, and comparison of exposure concentrations with exposure limits can be found in the Excel data library included as Supplemental Materials File S2, and a description of the content of each worksheet in the Excel data library is found in Supplemental Materials File S1.

#### 3.1. Hazard characterisation at the substance level

The 71 products identified from 12 manufacturers contained 122 unique substances. The distribution of substances belonging to different hazard groups is illustrated in Fig. 3 (and presented in tabulated form in Supplemental Materials File 2, Table S7).

##### 3.1.1. Respiratory sensitisation

Seven substances were positive in the QSAR model for respiratory sensitisation (monoethanolamine, bronopol, glycerol, methyl salicylate, benzoic acid, sodium benzoate, and ammonium benzoate) (substance details provided in Supplemental Materials Table S9). None had a harmonised classification for this endpoint and no DNELs were identified to be set on this endpoint.

##### 3.1.2. Respiratory irritation

Four substances had a harmonised classification of respiratory irritation (bronopol, 2-phenoxyethanol, 2-methoxypropanol, and butan-1-ol) (Supplemental Materials Table S9). There was no QSAR model on this endpoint. Ammonia and 2-aminoethanol are also assigned an H335 statement (respiratory irritation) if the concentration is > 5% in a product (ammonia was <1% in 10 products, and 2-aminoethanol was 0.55% in one product).

Concerning occupational exposure limits, DNELs were identified set on respiratory irritation as the sensitive endpoint for 18 substances: isopropyl acetate, cyclohexane, morpholine, 2,2'-oxydiethanol, 2-butoxyethanol, dodcan-1-ol, tetradecanol, n-butyl acetate, sodium hydroxide, ammonia (aqueous solution or anhydrous), ethyl acetate, ammonium benzoate, 2-methyl-2 H-isothiazol-3-one, bronopol, sodium benzoate, naphtha (petroleum), benzoic acid, butan-1-ol, (the DNELs are provided in the Excel File Supplemental Materials File S2).

##### 3.1.3. Supporting endpoints of skin effects

A substantial skin-sensitising potential was noted in the products (Fig. 3) (The identity of substances affecting skin can be found in the Excel File Supplemental Materials File S2).

#### 3.2. Hazard characterisation at the product level

Fig. 4 shows the number of products that contain one or more substances that may pose a risk of asthma induction in terms of respiratory irritation and respiratory sensitisation and the supportive endpoints of allergic contact dermatitis, skin sensitisation, and skin irritation. The respiratory endpoints are activated in fewer products than are the supportive dermal endpoints.

#### 3.3. Risk assessment

We found two of 71 products to have a risk ratio > 1 based on the level of sodium benzoate, positive in the QSAR for respiratory sensitisation (Fig. 5) and based on its DNEL set on respiratory irritation. The products were two aerosol spray can-formulated vinyl treatments with risk ratios of 4.8 and 12 (from the same manufacturer). Two other products had risk ratios of 0.69 and 0.73, based on 2-methyl-2 H-isothiazol-3-one and its OEL/DNEL set on respiratory irritation (trigger sprays for textile treatment and glass cleaning, respectively). Of all the products, the one that contains the largest amount of sensitising

![Substance categories](image1.png)

![Substance categories](image2.png)

Fig. 3. The number of substances within categories based on function and type of hazard. ‘Total hazardous substances’ is the total of all hazard categories. ‘Total substances in products’ refers to the total number of substances in the category. Distillates, propellants, and surfactants can be seen in the insert and have no hazardous substances based on respiratory or skin effects. Base refers to substances that are added to change the pH.
We used CAD to perform a risk assessment of spray products for car cabin detailing. First, we made a hazard characterisation identifying substances based on QSAR prediction is the vinyl treatment product with product number 6.2, which contains 7.5% glycerol, but as the substance does not have an OEL/DNEL, the risk ratio was zero. Apart from the above-mentioned products, the risk ratios of the spray products are well below 1 (Fig. 5).

DNELs are not set on respiratory sensitisation as stated in Chapter R.8 of the ECHA guidance on information requirements and chemical safety assessment: ‘since there are currently no available methods to determine the thresholds and to establish DNEL for respiratory hypersensitivity, only qualitative risk assessment for this endpoint can be performed’ (ECHA, 2012); and accordingly this endpoint does not contribute to the risk ratio. Thus, the products that contain substances that are positive in the QSAR model for respiratory sensitisation can only be qualitatively risk assessed. There were nine such products, two of which already had a risk ratio of 2 and a vinyl treatment product had a risk ratio of 0.88 indicating an asthma-induction potential of ammonium benzoate or benzoic acid. However, there is some knowledge from structurally similar substances not found in the car cabin detailing products. In one study of methyl salicylate, a respiratory local lymph node assay (LLNA) was developed. Male mice were exposed by inhalation to various substances including methyl salicylate, which was negative for LLNA stimulation indices but which induced histopathological lesions in the upper respiratory tract (Arts et al., 2008). In a subsequent inhalation study, methyl salicylate did show proliferation in the LLNA (De Jong et al., 2009). In an earlier study, Arts et al. found that methyl salicylate did not affect IgE levels after challenge in rats by the dermal pathway and subsequent inhalation; the study looked at whether this immunoglobulin is associated with immediate-type specific airway reactivity which substances had a harmonised classification or positive QSAR prediction for the asthma-related endpoints of respiratory sensitisation or respiratory irritation. Second, we performed a risk assessment using mainly DNELs from ECHA.

4. Discussion

We used CAD to perform a risk assessment of spray products for car cabin detailing. First, we made a hazard characterisation identifying substances which already had a risk ratio of 2 and a vinyl treatment product had a risk ratio of 0.88 indicating an asthma-induction potential of ammonium benzoate or benzoic acid. However, there is some knowledge from structurally similar substances not found in the car cabin detailing products. In one study of methyl salicylate, a respiratory local lymph node assay (LLNA) was developed. Male mice were exposed by inhalation to various substances including methyl salicylate, which was negative for LLNA stimulation indices but which induced histopathological lesions in the upper respiratory tract (Arts et al., 2008). In a subsequent inhalation study, methyl salicylate did show proliferation in the LLNA (De Jong et al., 2009). In an earlier study, Arts et al. found that methyl salicylate did not affect IgE levels after challenge in rats by the dermal pathway and subsequent inhalation; the study looked at whether this immunoglobulin is associated with immediate-type specific airway reactivity which substances had a harmonised classification or positive QSAR prediction for the asthma-related endpoints of respiratory sensitisation or respiratory irritation. Second, we performed a risk assessment using mainly DNELs from ECHA.

4.1. Asthma hazard characterisation at the substance level

4.1.1. Data from the peer-reviewed literature on substances that are positive for respiratory sensitisation in QSAR

Salicylic acid-like substances. Sodium benzoate was responsible for the risk ratio being > 1 in two of the products. We previously reviewed two old studies with some indication of an association between sodium benzoate and asthma (Hadrup et al., 2022). We identified no studies indicating an asthma-induction potential of ammonium benzoate or benzoic acid. However, there is some knowledge from structurally similar substances not found in the car cabin detailing products. In one study of methyl salicylate, a respiratory local lymph node assay (LLNA) was developed. Male mice were exposed by inhalation to various substances including methyl salicylate, which was negative for LLNA stimulation indices but which induced histopathological lesions in the upper respiratory tract (Arts et al., 2008). In a subsequent inhalation study, methyl salicylate did show proliferation in the LLNA (De Jong et al., 2009). In an earlier study, Arts et al. found that methyl salicylate did not affect IgE levels after challenge in rats by the dermal pathway and subsequent inhalation; the study looked at whether this immunoglobulin is associated with immediate-type specific airway reactivity which substances had a harmonised classification or positive QSAR prediction for the asthma-related endpoints of respiratory sensitisation or respiratory irritation. Second, we performed a risk assessment using mainly DNELs from ECHA.

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after inhalation challenge (Arts et al., 1998). Salicylic acid, which is also positive in the QSAR model for human respiratory sensitisation but not found in the products in the current work, has been associated with asthma induction or exacerbation after oral exposure (Botey et al., 1988; Sanak, 2000; Vally, 2002). Oral challenge studies with aspirin causing decreased FEV₁ have been reported (Micheletto et al., 2006; Weber et al., 1979). The above-described cases occurred after oral exposure.

Overall, there is some evidence in the peer-reviewed literature both in humans and animals supporting that sodium benzoate has a potential for asthma induction. This is supported by QSAR, as well as the fact that a DNEL on this substance has been set on irritation to the respiratory tract.

4.1.2. Monoethanolamine, glycerol and bronopol

When guinea pigs were exposed by inhalation to an aerosol of 0.1 mL/kg of 3.3% monoethanolamine solution, increased bronchoconstriction was seen as a change in airway opening pressure in anaesthetised ventilated animals (Kamijo et al., 2009). Concerning glycerol, knowledge of this compound’s asthma-induction potential was absent, and there was no DNEL or OEL on this substance. Bronopol had no data on respiratory irritation or sensitisation. Overall, data on the asthma-induction potential of these three substances were few or absent.

4.1.3. Data from the peer-reviewed literature on substances that have a harmonised classification of ‘may cause respiratory irritation (H335)’

Concerning 2-phenoxethanol, peer-reviewed research articles with in vivo knowledge of its asthma-induction potential were absent. In one in vitro study, the irritancy of 2-phenoxethanol was evaluated along with other biocides in an airway model as well as a human epidermis model and found to be a non-irritant (Hwang et al., 2021). A repeated dose inhalation study in rabbits on 2-methoxypropanol-1 looking at maternal and foetal toxicity reported no asthma-related endpoints (Hellwig, 1994). Concerning butan-1-ol, the literature on this substance and asthma induction is very limited. One study investigated the association between VOCs reported to be associated with dampness and microbial growth and lung function in 159 adults from Reykjavik, Uppsala, and Tartu. The association between 1-butanol and lower FEV₁ had a P value of 0.046 in males, while several other VOCs were more significantly associated with lower FEV₁ (Wang et al., 2023). Overall, there is a lack of data in the literature on the asthma-induction potential of these three substances.

4.1.4. The contribution of knowledge of skin sensitising and skin irritant potentials

We found that a substantial number of substances (and corresponding products) had skin sensitising or irritating potential, which were included as supportive endpoints as there is an overlap between substances that are skin and respiratory sensitisers (Arts et al., 2008; Burge et al., 2012; Roach et al., 2020; Tsui et al., 2020), as there is between substances that cause skin irritation and airway irritation as reviewed in Hadrup et al. (2022). This means that there may be a larger potential for asthma induction than what we see by only looking at the specific respiratory endpoints. Thus, more airway studies on these substances could be warranted.

4.2. Hazard identification compared to substance categories and product types

Notably, the substance groups of distillates, propellants, and surfactants contained no substances with identified hazards in respiratory or skin endpoints (Fig. 3). Distillates and surfactants often had a CAS or EC number covering a complex mixture (UVCB). We note that QSAR models cannot screen the complex mixtures by their overall CAS number; and that only 4 of 14 distillate UVCBs in the current database had a harmonised classification. Gathering more information on surfactants and distillates would require identifying the constituents of the UVCBs or searching for further knowledge on the particular mixture.

Most critical risk ratios were driven by preservatives in the products with respiratory sensitisation and/or irritation potential (i.e., sodium benzoate and 2-methyl-2-H-isothiazol-3-one). This may reflect that these substances have toxic potency to target microorganisms in order to be effective preservatives. Perfumes have a large potential for skin effects, but these are not essential for the products’ effectiveness and could be eliminated in a safe-by-design process. It is notable that out of the 122 substances, 37 were perfumes, meaning that there is a wide range of perfumes used in the industry; several products contained multiple perfumes. At the product category level, it seems there is no clear picture that some product types have a larger asthma-induction potential than others (Fig. 4).

4.3. Risk assessment using the risk ratio

We found two of 71 products with a risk ratio > 1 based on the levels of sodium benzoate and positive in the QSAR for respiratory sensitisation. Two other products had risk ratios of 0.69 and 0.73, respectively, based on 2-methyl-2-H-isothiazol-3-one and its DNEL set on respiratory irritation. Yet, in general, the risk ratios of the spray products were well below 1 (Fig. 5). We note that glycerol had a high concentration (7.5%) in one product and has a respiratory sensitisation potential by QSAR.

However, as glycerol does not have a DNEL or OEL, a risk ratio could not be determined; and the fact that glycerol occurs naturally in the body as the structural backbone of lipid molecules (Gull and Pasek, 2021) opposes that it has a sensitisation potential. As stated by ECHA, there are currently no available methods to determine the thresholds and to establish DNEL for respiratory hypersensitivity, and only qualitative risk assessment for this endpoint can be performed (ECHA, 2012). Thus, none of the DNELs used in risk assessment were based on respiratory sensitisation, but rather on respiratory irritation – the other pathway of asthma induction. Notably, none of the products contained substances that had a harmonised classification of respiratory sensitisation. Nonetheless, the mere presence of a potential respiratory sensitizer, as identified by QSAR, raises a flag that there is a risk of asthma induction of the product. This pertains to seven additional products (detailed in Supplemental Materials Table S13).

Although the focus of this work was to look at asthma endpoints, we also screened using DNELs/OELs of all other endpoints. We found that two products had risk ratios of 0.88 and 2, respectively, based on non-asthma endpoints (Supplemental Materials File S2 Table S12). This indicates only limited extra toxicity in the products caused by non-asthma endpoints. Notably, other lung endpoints are not accounted for with the asthma endpoints and we have previously shown that effects of spray products on the lung surfactant can cause acute lung toxicity – especially products intended for impregnation of different surfaces (Sørlø et al., 2022; Sørlø et al., 2018). We also note that a CAD-based risk assessment typically considers all endpoints and does not focus on one endpoint alone – as we have done for asthma in the current work.

The employer needs to control the toxicological risk. The priority is, according to the hierarchy of controls, to first eliminate the toxic substances. If that is not possible then the next step is to substitute the most toxic substances with less problematic compounds in a safe-by-design process (NIOSH, 2023). A further step is the use of technical solutions to minimise exposure by e.g., the use of ventilation, followed by the step of applying administrative controls i.e., changing how people work. Finally, the application of personal protective equipment can be invoked as a last resort. In fact, the instructions on many of the products in the current work recommend the use of ventilation (46 products) or respiratory protective equipment (18). Other recommended personal protection equipment were gloves (59) and glasses (46) (Supplemental Materials Fig. S4). The distributors of the three products with a risk ratio > 1 recommend the use of personal protection equipment or enhanced ventilation in cases where the occupational limits are exceeded.
4.4. Limitations of the study

The substances in this article were all identified based on information in the safety data sheets and thus depend on the quality of these and on choices made by the manufacturer on which substances to report. Ideally, a risk assessment would be based on complete knowledge of the composition of a product, either from a recipe or from testing a product by chemical analysis, as was done in the risk assessment by the Danish Environmental Protection Agency (Tønning et al., 2009). Another source of uncertainty is the applied exposure model, which assumes complete mixing of the substances between the two zones. In real life, there could be more localised concentrations in some areas, especially considering that larger droplets settle faster than small ones. This phenomenon was not taken into account in the model in which the airborne concentration only decreases due to ventilation. The model also did not include a source term and, therefore, cannot evaluate the importance of evaporation from surfaces covered in the detailing product. Nonetheless, estimating the evaporation from interior surfaces would be difficult, as it would require information on parameters such as vapour pressures and air movement above the surface. Finally, we set the airborne fraction to 5% and 10% for trigger sprays and aerosol spray cans, respectively, and this is also based on the assumption. If we had chosen other values, they could affect the risk ratios of the products. Although the exposure model may have uncertainties that could affect whether the calculated risk ratios are place above or below 1, we note that changing the parameters of the model would not change the ranking between products. Also, we note that we used the average of the concentration interval of a substance and not the highest bound. The latter could have been employed as a worst-case scenario. Finally, the method to calculate the combined risk ratio is based on dose addition (Hadrup et al., 2013), meaning that the risk of synergy or potentiation is not taken into account (Hadrup, 2014; Kortenkamp, 2007), and there is thus a risk of unexpected high toxicities at human-relevant dose levels (Hadrup et al., 2016; Hadrup et al., 2020).

5. Conclusion

We made a risk assessment of spray products for interior car detailing. The risk assessment was based on information on chemical hazards from EU harmonised classifications and QSAR predictions, a two-box exposure model and occupational exposure limits. Seven substances were positive in the QSAR model for respiratory sensitisation (monoethanolamine, bronop, glycerol, methyl salicylate, benzoic acid, ammonium benzoate and sodium benzoate), while four had a harmonised classification for respiratory irritation (bronop, 2-phenoxethanol, 2-methoxypropanol, and butan-1-ol). We found two vinyl treatment products to have a risk ratio higher than 1 based on the concentration of sodium benzoate. Two products had risk ratios of 0.69 and 0.73, respectively, based on 2-methyl-2H-isothiazol-3-one and its acute DNEL set on respiratory irritation. In conclusion, 10 substances that may pose a risk for asthma induction were identified in the products. Two of the 71 products had a risk ratio higher than 1 based on respiratory irritation, meaning they may pose an asthma-induction risk under the modelled exposure scenario. Notably, this was caused by the preservative agent in the product rather than the active ingredients. In addition to the products identified based on respiratory irritation, care has to be taken concerning the seven additional products that contain a potential respiratory sensitisier as a quantitative risk assessment cannot be done based on this endpoint. Safe-by-design processes could be employed to limit the asthma-induction potentials of the products.

CRediT authorship contribution statement

Kasper Mikkelsen: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. Jorid B. Søeli: Writing – review & editing, Supervision, Funding acquisition. Marie Frederiksen: Writing – review & editing, Supervision, Funding acquisition. Niels Hadrup: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Niels Hadrup reports financial support was provided by The Danish Working Environment Research Fund and from the Danish Government.

Data Availability

The data is included in the Supplemental Materials.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tox.2023.153612.

References


