Effects by inhalation of abundant fragrances in indoor air – An overview

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Abstract

Odorous compounds (odors) like fragrances may cause adverse health effects. To assess their importance by inhalation, we have reviewed how the four major abundant and common airborne fragrances (α-pinene (APN), limonene (LIM), linalool (LIL), and eugenol (EUG)) impact the perceived indoor air quality as odor annoyance, sensory irritation and sensitization in the airways. Breathing and cardiovascular effects, and work performance, and the impact in the airways of ozone-initiated gas- and particle phase reactions products have also been assessed.

Measured maximum indoor concentrations for APN, LIM and LIL are close to or above their odor thresholds, but far below their thresholds for sensory irritation in the eyes and upper airways; no information could be traced for EUG. Likewise, reported risk values for long-term effects are far above reported indoor concentrations. Human exposure studies with mixtures of APN and LIM and supported by animal inhalation models do not support sensitization of the airways at indoor levels by inhalation that include other selected fragrances. Human exposure studies, in general, indicate that reported lung function effects are likely due to the perception rather than toxic effects of the fragrances. In general, effects on the breathing rate and mood by exposure to the fragrances are inconclusive. The fragrances may increase the high-frequency heart rate variability, but aerosol exposure during cleaning activities may result in a reduction. Distractive effects influencing the work performance by fragrance/odor exposure are consistently reported, but their persistence over time is unknown. Mice inhalation studies indicate that LIM or its reaction mixture may possess anti-inflammatory properties. There is insufficient information that ozone-initiated reactions with APN or LIM at typical indoor levels cause airway effects in humans. Limited experimental information is available on long-term effects of ozone-initiated reaction products of APN and LIM at typical indoor levels.

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1. Introduction

Numerous odorous compounds (odors) are present in indoor air. For shortness, we use “odors” synonymous with “odorous compounds”, which may have a pleasant or unpleasant smell. They are emitted from several construction, consumer and cleaning products, including air fresheners, plants and flowers, food and beverages. For instance, lignol (LIL) from orange blossoms (Arey et al., 1991) and limonene (LIM) from cleaning products, meals, drinks, services, and perfumes (Guan et al., 2014). Also, secondary reactions of construction products produce many odors (Uhde and Salthammer, 2007). Dietary intake from food ingredients is an alternative route of exposure; thus, LIL and LIM are major flavoring compounds in Earl Grey tea resulting in both dietary and inhalative exposure (Orth et al., 2013; Wolkoff, 1980). Several of the most common mono-terpenes with α-pinene (APN) as the major one emitted from pine and spruce construction products (Risholm-Sundman et al., 1998) are also inhaled during forest walking, e.g. from pine wood trees, and accumulated in plasma (Sumitomo et al., 2015).

Odors may cause severe adverse health effects. Thus, diacetyl (butter flavor) has caused life threatening lung disease (bronchiolitis obliterans) (Kreiss et al., 2002); this has, however, only been observed in the general population at unusual and extreme exposures (Eigilman and Schilling, 2012). Odors may also be carcinogenic. For instance, safrole and isosafrole (IARC, 1975) and cinnamyl anthranilate (IARC, 1982) are considered animal carcinogens. Skin application of perfumes and scented candles, e.g. ter Burg et al. (2014) and Yazar et al. (2010), and Eugenol (EUG) in scented candles (Bartsch et al., 2016).

It is not possible to make generalized statements about all fragrances and their potentially associated health effects caused by inhalation. Thus, the current knowledge has been compiled about inhalative exposure to the four and most common fragrances in indoor air with the purpose to assess their impact on the IAQ and potential airway and cardiovascular effects; also, including their ozone-initiated gas-phase and surface reactions, which may be associated with airway effects (Rohr, 2013). Since there is public concern about the use of fragrances (and associated odor/scent), additional information has been compiled of fragrance/odor perception to achieve a better understanding of their potential influence on perceived IAQ, health, and work performance.

2. Method

The four fragrances, α-pinene, eugenol, limonene, linalool, were searched together with: “airway effects, asthma, distraction, IAQ, health, lung functions, odor, ozone, perception, secondary organic aerosols (SOA), sensory irritation, and performance” in PubMed, Google Scholar, and ECHA (European Chemicals Agency) covering the literature from 2005-July 2016. Additional references were added from our own research collections compiled during the last three decades. Phenomena within environmental idiopathic intolerance of fragrances/odors (MCS) will only be dealt with briefly, where considered relevant.

3. Overview of findings

3.1. Concentration of fragrances in indoor air

Table 1 summarizes reported mean and maximum concentrations of APN, LIL, LIM, and EUG common in consumer products and found in major indoor and outdoor air studies, and in emission studies of consumer products; a few other selected fragrances are included. Reported mean concentrations of APN and LIM are generally below 50 μg/m³ in homes and public buildings except for specific sources, see Sarigannis et al. (2011). For instance, a major study in German day care centers (n = 45) showed short-term mean concentrations of APN and LIM of 3 and 9 μg/m³, respectively (Schmidt et al., 2015), while the maximum short-term concentrations in European offices for APN, LIM, and LIL were, 1, 32, and 1 μg/m³, respectively (Nørgaard et al., 2014a).

Temporary activity-dependent high concentrations may occur, e.g. after spray of an air freshener or use of burning lavender oil; this is in part reflected in the reported maximum concentrations. For instance, the European EPHECT testing program of 16 product categories of selected consumer products for household use modeled maximum micro-environmental concentration in a house over 30 min; simultaneous use of insecticides, personal care products (e.g. hairstyle products, perfumes), and scented candles, e.g. Bartsch et al. (2016), Petry et al. (2014), and Trantallidi et al. (2015). The number of fragrances is about 3000 (Groot and Frosch, 1997). Four of the most common volatile organic compounds (VOCs) used in fragrances or mixtures thereof are APN, LIL, and LIM, e.g. ter Burg et al. (2014) and Yazar et al. (2010), and eugenol (EUG) in scented candles (Bartsch et al., 2016).
of a plug-in air freshener, hairstyle product, deodorant spray, and a perfume amounted to 1400 μg/m³ of LIM at an air exchange rate of 0.1 h⁻¹ that dropped to 200 μg/m³ over 24 h (Trantallidou et al., 2015). Personal high concentrations may also be expected from fragranced toys (Masuck et al., 2011), but real life concentrations caused by toys have not been reported. The majority of reported fragrances, in general, are higher than in scented candles, and burning lavender oils, which may reach levels for olfaction but below the threshold for sensory irritation (Schiffman 2004). The odor perception of a VOC will prevail above its threshold odor or it is also sensed as a sensory irritant, or both (Doty et al., 2004). This appears to be a general observation for most VOCs (Wolkoff, 2013) with sensory irritation in certain conditions (Wise et al., 2012).

3.2. Odor and sensory irritation thresholds

Table 2 shows thresholds for acute (odor or sensory irritation) and long-term effects and how they have been derived. The four fragrances have odor thresholds in the order of ng/m³ to μg/m³; thus, low concentrations may alter the perceived air quality markedly by the use of personal care and consumer products. For comparison, it is relevant to notice how the odor threshold values have been obtained. The odor threshold for LIM is P₀₅₀ (the concentration where 50% of test panel can detect the odor) that was determined under clean background conditions, while the other reported values for LIM and APN are represented by P₁₀₀ values. A P₀₅₀ threshold value would be expected to be about 3 to 5 times lower than the P₀₅₀ threshold; for LIM, this would be between 2 and 4 ppb (11–22 μg/m³) according to Cain et al. (2007). Much lower odor thresholds are expected for oxygenated terpene compounds like linalool, e.g. a few μg/m³ (Elsharif et al., 2015). It has been debated whether EUG is a VOC causing only “pure olfaction” or it may blunt sensory irritation in certain conditions (Wise et al., 2012).

The threshold for sensory irritation of APN, 3-carene, LIL and LIM are 2 to 3-fold higher than their corresponding odor thresholds. This appears to be a general observation for most VOCs (Wolkoff, 2013) with few exceptions, e.g. methyl isothiocyanate (Cain et al., 2010). The sensory irritation thresholds (no-observed-effect-adverse effect-levels) for APN, 3-carene and LIM are derived from RD₅₀ values (the concentration causing 50% reduction of the breathing rate in mice) according to Kuwabara et al. (2007) algorithm and from controlled human exposure studies by using an assessment factor of five for the lowest-observed-adverse-effect-level of reported irritation, according to Nielsen et al. (2007b). Clearly, such thresholds have uncertainties reflected in the methodology, but they are the best available data. Thus, the value for LIL, based on squeeze bottle exposure, would be expected to be overestimated, since sensory irritation, in general, is characterized by latency before steady-state has been reached, thus resulting in a lower threshold upon extended exposure duration, cf. Claeson and Lind (2016), Cain et al. (2010) and Wise et al. (2009).

The reported maximum concentrations in Table 1 are one–two orders below their thresholds for sensory irritation to cause trigeminal simulation. Sensory irritation by simultaneous exposure to an indoor

Table 1

Examples of selected mean/maximum fragrance (CAS number) concentrations (μg/m³) in indoor environments and outdoors, and after air freshener spray events.

<table>
<thead>
<tr>
<th>Buildings</th>
<th>Sampling time, h</th>
<th>α-Pinene 80-56-8</th>
<th>Limonene 5989-54-8</th>
<th>Linalool 78-70-6</th>
<th>Dihydromyrcenol 18479-58-8</th>
<th>Eugenol 97-53-0</th>
<th>Geraniol 106-24-1</th>
<th>α-Terpineol 98-55-5</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offices</td>
<td>168</td>
<td>3/4</td>
<td>9/176</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Geiss et al. (2011)</td>
</tr>
<tr>
<td>104</td>
<td>6/68</td>
<td>19/81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mandin et al. (2017)</td>
</tr>
<tr>
<td>Offices</td>
<td>2</td>
<td>0.1/1.2</td>
<td>2.5/32</td>
<td>0.1/0.6</td>
<td>0.1/0.4</td>
<td>0.2/1.4</td>
<td>0.1/0.3</td>
<td></td>
<td>Næegaard et al. (2014a)</td>
</tr>
<tr>
<td>Daycare</td>
<td>2</td>
<td>0.5/0.7</td>
<td>7/13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salonen et al. (2009)</td>
</tr>
<tr>
<td>BO³</td>
<td>0.33</td>
<td>3/31</td>
<td>9/490</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schmidt et al. (2015)</td>
</tr>
<tr>
<td>3</td>
<td>2–6/9</td>
<td>500–1541</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Su et al. (2007)</td>
</tr>
<tr>
<td>Homes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF/CP⁵</td>
<td>168</td>
<td>15/241</td>
<td>29/493</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Geiss et al. (2011)</td>
</tr>
<tr>
<td>AF/CP⁵</td>
<td>672</td>
<td>32/854</td>
<td>28/642</td>
<td>20–32</td>
<td>600–1000</td>
<td></td>
<td></td>
<td></td>
<td>Lamas et al. (2010b)</td>
</tr>
<tr>
<td>BO³</td>
<td>7</td>
<td>3/10</td>
<td>31/1400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lamas et al. (2010a)</td>
</tr>
<tr>
<td>Personal sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rösch et al. (2014)</td>
</tr>
<tr>
<td>Offices</td>
<td>-22³</td>
<td>8/59</td>
<td>26/277</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glas et al. (2015)</td>
</tr>
<tr>
<td>Emission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Geiss et al. (2011)</td>
</tr>
<tr>
<td>Spray event</td>
<td>0.5 min</td>
<td>347</td>
<td>339</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rogers et al. (2005)</td>
</tr>
<tr>
<td>Air freshener</td>
<td>110 min</td>
<td>29</td>
<td>20/10</td>
<td>160</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>Rogers et al. (2005)</td>
</tr>
<tr>
<td>Outdoor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Singer et al. (2006)</td>
</tr>
<tr>
<td>Orange grove</td>
<td>168</td>
<td>0.1/1.5</td>
<td>0.3/2</td>
<td>&lt;1–3</td>
<td>1–17</td>
<td></td>
<td></td>
<td></td>
<td>Geiss et al. (2011)</td>
</tr>
</tbody>
</table>

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Table 1: Examples of selected mean/maximum fragrance (CAS number) concentrations (μg/m³) in indoor environments and outdoors, and after air freshener spray events.

Notes:
- a Burning of lavender oil in offices or homes; range of measured concentrations.
- b Use of air freshener, cleaning products, etc.; range of measured concentrations.
- c Personal sampling during working hours for one week.
- d Personal sampling during working hours for three days.
- e Five second spray release of air freshener (5 g) simulating normal consumer use in residential exposure room (58 m³ and 0.6 h⁻¹) taken at two time intervals.
- f Plug-in air freshener in 50 m³ (0.54 h⁻¹) climate chamber.
- g Sampled in Valencia orange grove (1 l air sample); result of two measurements.

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mixture of the fragrances would not be predicted to cause sensory irritation by assuming addition of their effects (Nielsen et al., 2007b); even for maximum reported concentrations, see fragrances measured in European offices (Nergaard et al., 2014).

As for odor thresholds (Dalton and Jaén, 2010), thresholds for sensory irritation do not differ significantly among mild to moderate asthmatics (and MCS patients) and healthy controls as shown for fragrance mixtures and ammonia, e.g. Opiekun et al. (2003) and Petрова et al. (2008), respectively.

3.2.2. Long-term health effects

Long-term based thresholds (guides) have been derived; such thresholds comprise all types of toxicological effects. For instance, direct-no-effect-levels have been suggested for risk assessment of scented candle emissions, based on two-week inhalation studies in rats, see Petry et al. (2014). The German Committee on Indoor Guide Values has derived guide values 1. These values include an assessment factor of 2 for children, although no support is available, e.g. Petry et al. (2014) and Ginsberg et al. (2010). The EU-LCI (lowest concentration of interest) working group has derived values for APN, LIM and 3-carene; the values are specific for health assessment of construction product emissions after 28 days. Their derivation follows the classic approach for deriving air quality guidelines applying assessment factors according to ECHA. ECHA has also derived some long-term (systemic effect) thresholds for the general population.

Reported mean concentrations in homes and public buildings of the key fragrances are far below their derived long-term thresholds, see Tables 1 and 2. Indoor air mixtures of the fragrances are not predicted to cause systemic effects based on long-term thresholds and assuming additivity; this is considered valid irrespective of different health-endpoints as basis for the threshold derivations.

3.2.3. Emotional effects of fragrance perception (odors)

Attitude, beliefs, expectations, familiarity, mood, and “manipulation” may influence the acceptance, intensity, and perceived pleasantness of fragrances/odors and associated health risk in a complex manner (Bogaerts et al., 2010; Jaén and Dalton, 2014; Janssens and Ritz, 2013; Krusemark et al., 2013; Smeets and Dalton, 2005); this may be attenuated or accentuated depending on context (Johnson, 2011). Although, the odor perception is not a measure of exposure (Greenberg et al., 2013), it may evoke emotions about health (Knasko, 1992), happiness/disgust (Glass et al., 2014), and fear of exacerbation of asthma (Jaén and Dalton, 2014; De Peuter et al., 2005); initiation of stress reactions among people susceptible to certain odors may also occur (Schiffman and Williams, 2005).

Fear or warning about the exposure that results in the odor may have a strong impact on the perception among asthmatics (Baldwin et al., 1999; Winters et al., 2003; Janssens et al., 2011), and so does risk communication about the exposure of the odor (Jaén and Dalton, 2014). Thus, positive information may have a beneficial effect on the odor perception (and possibly reporting of sensory irritation) in subjects with high negative affectivity in comparison with normal subjects and vice versa; the studies, however, were carried out at occupational levels, see Jaén and Dalton (2014) and Opiekun et al. (2003). Information about the risk has also been shown to modulate the inflammatory airway response (Jaén and Dalton, 2014). It has also been shown that perception of a fragrance (environmental agent/perfume) as an asthma trigger or suggestive thereof may elicit the perception of asthma symptoms but also lead to an increase in bronchoconstriction (Janssens and Ritz, 2013). Further, psychological triggers (e.g. depressed mood, being angry) may be important in the reporting of asthma symptoms, but not the lung function (Ritz et al., 2014).

In summary, reported mean concentrations of APN, EUG, LIL, and LIM, are in the lower μg/m³ range, 2 to 3-fold below their thresholds for sensory irritation, but at or above their odor thresholds. The derived thresholds available for long-term exposure of EUG, LIL, and LIM are also far above reported mean concentrations. The individual acceptance of a fragrance or mixture of fragrances (odor) depends on several personal and external factors, which may alter over time; furthermore, suggestions or negative information about the fragrance(s) may exacerbate reporting of asthma symptoms. Unfortunately, a majority of the studies...
have been carried out close to occupational levels, thus hampering extrapolation of effects to low indoor air levels without a validated model. Clearly, there is a research gap regarding exposure studies at more indoor realistic levels.

3.3. Fragrance inhalation and airway effects

Twenty-six common fragrances have been classified as skin allergens (skin sensitizers) and they are regulated in the EU accordingly in consumer, personal care products, toys, and detergents (cleaning products) by the Directives 2003/15/EC, 2009/48/EC, and Regulation 648/2004/EC, see, e.g. Schnuch et al. (2007) and Masuck et al. (2011). Some fragrances are weak skin sensitizers, while their oxidation products like hydroperoxides are potent sensitizers, e.g. LIM hydroperoxide (Karlberg et al., 1994). The situation, however, is different by inhalation of fragrances emitted from products creating either gas-phase or spray generated aerosol phases.

3.3.1. Airway versus skin sensitization

The essential differences between skin sensitization by contact and airway sensitization or allergy from inhalation are well established at the cellular and cytokine level causing different immune responses. Skin contact of some fragrances may cause skin allergy (allergic contact dermatitis), which is characterized by a delayed skin reaction. This is an immunological skin inflammation associated with T helper (Th2)-1-type response (lymphocytes). In contrast, inhalation of proteins and some low molecular chemicals (e.g. acid anhydrides) may cause asthma, which is another type of immunological reaction; this is preferentially orchestrated by Th2-type lymphocyte response by chemical sensitization in the airways (Basketter and Kimber, 2015; Howarth, 1998).

Non-volatile cleaning agents, like anionic and non-ionic surfactants, which may be inhaled as aerosols, are not considered to possess allergy promoting (adjuvant) effects. However, quaternary ammonium compounds (inhaled as aerosol or by skin contact) have caused sensitization in humans in occupational settings (NIELSEN et al., 2007a; Nurmatov et al., 2015; Vandenplas et al., 2014a). Contrarily, inhalation of skin sensitizers like volatile fragrances among non-skin-sensitized subjects is not considered a route of “health risk with respect to allergy” (Basketter and Kimber, 2015). According to a review of occupational airway sensitizers, no fragrance has been identified (van Kampen et al., 2000).

3.4. Health effect exposure studies

3.4.1. Human studies

Studies have demonstrated that other reactions not considered to be associated with the toxicity of the fragrance(s) may occur among asthmatics. For instance, in one study, non-asthmatics (n = 217) and asthmatics (n = 89 mild and n = 75 moderate) were exposed randomly and blinded for 30 min to either of two spray products, a commonly

Healthy non-asthmatics (n = 12), mild asthmatics (n = 12), and moderate asthmatics (n = 8) were exposed randomly for 15 or 30 min in a climate chamber (9 m³) to an aerosolized product with nine fragrances or without (saline); exposures were at least two weeks apart. Symptoms measured by use of a visual-analogue-scale (VAS) scale (extremely unpleasant to extremely pleasant) generally declined post-application within 45 min, except for nasal symptoms that remained severe for 165 min among the moderate asthmatics; the moderate asthmatics also showed the greatest severity in symptoms (e.g. eye and chest). Significant lung function (FEV1, FVC) differences were not observed between exposed and saline-exposed subjects, but a non-significant trend in inflammation was observed in the lower airways in the moderate asthmatics. The authors concluded that no significant clinical effects after exposure were observed; nevertheless, they hypothesized a risk of developing nasal and skin symptoms and inflammatory response in the airways among the moderate asthmatics “sensitized” to specific fragrances, but at levels most likely well below (no data reported) the threshold for sensory irritation. Thus, asthma severity may play a role in sensitivity to aerosol products emitting fragrances (Vethanayagam et al., 2013). It is noted that the study was unblinded, had a small sample size, severe asthmatics were excluded, and no exposure concentration was reported.

Chest tightness and wheezing was reported in 21% of asthmatics (n = 29) compared with healthy non-asthmatics (n = 13) after being exposed to perfume sticks. A significant decline of lung functions (FEV1) was observed in severe asthmatics in comparison with mild asthmatics; decrease in FEV1 after the challenge was 36%, 17%, and 8% in the severe, moderate and mild asthmatics, respectively (Kumar et al., 1995). The study was neither randomized nor blind, and the exposure concentration unknown. Much smaller declines in FEV1 were observed in a fourth study with 15 asthmatics exposed for 20 min to top-six perfumes with maximum decline out of 38 perfumes (McCants et al., 2000). Eleven of the 15 subjects (73%) showed mean maximum 5.1% decline to one or more perfumes. An assessment of this study is hampered by insufficient information about the overall test protocol.

In two controlled human exposure studies, lung functions (FEV1, FVC) and FeNO (exhaled nitrogen dioxide) were unchanged in healthy subjects exposed for two hours to clean air or a mixture of terpenes dominated by APN (2–6 mg/m³), aldehydes, acetic and hexanoic acids (total VOC = 9–13 mg/m³) emitted from oriented-strand boards (n = 24) and pinewood (n = 15), respectively (Gminski et al., 2011b; Gminski et al., 2011a). The perceived odor intensity increased during the exposure, but sensory irritation in the eyes (change in eye blink frequency) and upper airways remained unchanged up to 13 mg/m³ total VOC in comparison to sham air exposure. In similarly studies, no acute change in lung functions was observed during workshifts in joinery shops with maximal APN concentrations of 150 mg/m³ (Erikkson et al., 1997), in agreement with two-hour exposure studies with 450 mg/m³ APN (Falk et al., 1990) and 10 mg/m³ LIM (Falk-Filipsson et al., 1993); furthermore, irritating eye symptoms were absent at 450 mg/m³ for both terpenes.

Skin sensitized patients were exposed to 1 mg/m³ in controlled conditions for one hour to two fragrance skin allergens (used in personal care products) either ISO-group (isoeugenol) (n = 11) or HICC-group (hydroxyisohexyl-3-cyclohexene carboxaldehyde; Lyral®) (n = 10), respectively; geraniol was used as control at the same concentration (Schnuch et al., 2010). Patients, who also had a history of allergic asthma, six out of eleven and four out of ten, respectively, to ISO and HICC, were protected against skin exposure during the exposure period. Base-line values of FEV1 prior to exposure were comparable in the groups and the lung function was unchanged during and after the exposures, but with a trend towards an increase of a bronchial hyper-response in both groups. FeNO was insignificantly affected between baseline before and after the exposures; the ISO-group, however, showed a significant decrease against the baseline level after 72 h. Inflammatory markers
in blood (eosinophils, CRP and mast cell tryptase) also remained unchanged. Significant changes were not observed in bronchial hyper-responsiveness when evaluated after each of the different exposure conditions, but a non-significant trend towards an increase was observed after exposure in the ISO-group. Two ISO patients reported skin symptoms after the exposure despite skin contact protection; further, some patients reported airway symptoms that were unrelated to exposure and objective measures. It should be noted that the exposure concentration is 2 to 3-fold higher than reported indoor air values (Lamas et al., 2010b). Thus, FeNO and the inflammatory markers are not necessarily indicative of asthma (Schnuch et al., 2010). This, the inhalative exposure might trigger skin reactions, despite skin exposure protection. Re-exposure to a lower more realistic level of ISO did not result in any response. Overall, the study showed few statistical significant findings and realistic low level exposure showed no association between skin sensitivity and inhalation of ISO.

A Canadian questionnaire and spirometry study of participants (n = 5604) indicated that use of at least one personal care product in the past 3 months was associated with a small adverse effect on lung functions (FEV1, FVC, and FEV1/FVC). The most commonly reported products are fragrances and scented body products. Among women an interquartile increase in use of eye makeup, hairstyle products, and scented body products was associated with a 3% decrease in FEV1 (Dales et al., 2013). For men, only hairstyle products were associated with 2% reduction in lung functions, and fragrances were negatively related to FVC. Among men and women, hairstyle products were associated with 2% reduction in all lung functions (p < 0.05). The greatest effect was 4% decrease in FVC associated with interquartile increase of use of body scented products. The study suffers from lack of randomization, potential selection bias of products, and no information about the use of aerosol products, which are known to be associated with adverse airway effects, e.g. Quirce and Barranco (2010). The time delay between home interview and testing at the lung clinic might further weaken the significance of the observed, but small, reductions.

Measurements of lung functions (FEV1, FVC, and PEF) in workers (n = 60) occupationally exposed in 10 UK fragrance companies and in controls (n = 52; office staff) did not show significant effects (Dix, 2013). However, the outcome should be considered cautiously due to the low response rates, 33 and 24%, respectively, and different gender distributions in the groups.

Apparently, there may be independent risk factors as also found in population-based studies on allergic diseases, e.g. Elberling et al. (2005b). For instance, in a population-based study (n = 1052) contact sensitization to a fragrance mixture in women did not influence FEV1 and FVC values; however, an increased risk of association with bronchial hyper-responsiveness was identified, but not in men (Schnabel et al., 2010). The Schnuch et al. (2010) study illustrates how high fragrance exposure, considerably higher than its odor threshold, may pose a risk of skin symptoms among patients that are skin sensitized to specific fragrances. Furthermore, airway symptoms were reported by single patients, but without changes in their lung functions. Learned symptoms, learned cues or past experiences (Bogaerts et al., 2010; Van den Bergh et al., 2002), negative affectivity (Put et al., 2004; Van Diest et al., 2005), and distress and life events (Jaén and Dalton, 2014; Skovbjerg et al., 2012; Zachariae et al., 2001) may influence the outcome among the patients that suffer from skin sensitivity or from idiopathic environmental intolerance (Berg et al., 2011; Elberling et al., 2004), but it is unclear how.

3.4.2. Animal studies

Acute studies in a mice inhalation model showed that APN and LIM caused sensory irritation at high concentrations (Nielsen et al., 2005; Larsen et al., 2000); extrapolation to irritation in humans is shown in Table 2, which also includes 3-carene. Furthermore, sensitization of the airways has not been observed in animals. Thus, it was concluded that LIM, LIL and iso-EUG were “highly unlikely” to induce “respiratory sensitization” by the respiratory local lymph node assay (ter Burg et al., 2014). In a third model, no change was identified in the total serum immunoglobulin E (IgE) by topical exposure to isoEUG and EUG in mice and guinea pigs, in contrast to well-known airway allergens like trimellitic anhydride and diphenylmethane disocyanate (Hilton et al., 1996; Basketter and Kimber, 2015).

3.4.3. In-vitro study

The exposure of human A549 lung epithelial cells in the Vitrocell® system to 1800 and 600 mg/m3 APN and 3-carene, respectively, for 1 h did not induce cytotoxic nor genotoxic effects (Gminski et al., 2010).

In summary, human exposure studies do not provide convincing evidence of adverse lung function effects nor sensitization despite claims about adverse effects in eyes and airways among asthmatics and healthy subjects exposed to fragrances by inhalation; this is further supported by animal inhalation models for APN and LIM, and an in-vitro study for APN. Thus, it is tempting to speculate that the reported effects in humans are ascribed to the odor perception of the fragrance(s) itself. Furthermore, moderate skin sensitized patients might develop airway responses and skin symptoms by inhalation of specific fragrances at relatively high concentrations, but no clear data is available to allow for extrapolation to indoor exposure levels of low molecular weight compounds (Basketter and Kimber, 2015; Redlich, 2010). There is a research gap about indoor air levels of inhaled fragrances, and how positive, neutral and negative information may influence the outcome among skin sensitized patients, asthmatics and odor sensitive people in comparison with normal subjects, cf. Baldwin et al. (1999).

3.5. Effects on breathing, cardiovascular system, and work performance

It is relevant to be able to assess the indoor air health perspective using fragrances, apart from the aesthetics and altered perception of the IAQ; for instance, how they may influence breathing rate, cardiovascular effects, and work performance, topics of general interest regarding odors (Rohilman et al., 2008) and recently a topic of increasing priority in the indoor air science community.

3.5.1. Effects on breathing

Certain fragrances may alter the breathing rate, e.g. due to emotional memory of the odor, and thereby positively influence relaxation, while other odors may result in excitation (Dayawansa et al., 2003). Some fragrances, pentylic acetate and menthone, have shown no effect in contrast to unpleasant odors like ammonia and hydrogen sulfide, which significantly reduced the breathing rate (Danuser et al., 2003).

The perception of pleasant odors, e.g. rose (fragrance), may significantly increase the tidal volume; however, not the breathing rate as found in studies above (Kleemann et al., 2009). Autobiographical memories of an odor (e.g. perfume) may trigger pleasant emotional memories that increase tidal volume and reduce breathing rate more than a control situation, as shown in a study with 23 subjects (Masaoka et al., 2012a, 2012b). However, for how long such effects will last by repeated odor experiences is uncertain (Dalton and Jaén, 2010).

3.5.2. Cardiovascular effects of fragrances

Pleasantness/unpleasantness of fragrances influences the heart rate and heart rate variability, see (Glass et al., 2014). Thus, the high frequency heart-rate variability (reflecting parasympathetic nervous activity) was decreased about 4% in healthy women (n = 22) exposed (double-blind) to a reaction mixture of LIM and ozone for 3 h in a controlled climate chamber (22 m³). The mixture had (initial/residual) mean concentrations (μg/m³) of LIM (900/80) and ozone (80/10) composing both gaseous products and SOA with a mean concentration of 80 μg/m³ (Hagerman et al., 2014). The initial and residual concentration of LIM was substantially higher than commonly found in indoor environments, but it was too low to cause sensory irritation (Wolkoff et al., 2012). The residual LIM concentration is twice its P90 odor threshold. The odor
perception of LJM and its reaction products has been intense and possibly unpleasant for some of the subjects, which may have influenced the parasympathetic activity; however, inhalation of the SOA may also have been causative. Contrary, the exposure to pure APN or LIM, respectively, resulted in 47% and 26% enhancement of the high frequency heart-rate variability (Ikei et al., 2016; Joung et al., 2014). Similar enhancements were observed for exposure to candles (25%) (aerosol concentration 200 μg/m³) (Hagerman et al., 2014), and fresh rose flowers (19%) relative to a control situation (Igarashi et al., 2014). This indicates a positive influence on the parasympathetic activity, possibly due to positive recognition or familiarity of the candle, fragrance or rose flower odors, and in agreement with Glass et al. (2014). Increase of the high frequency heart-rate variability was also observed by a 10-min face-mask exposure of healthy subjects (n = 26) to Cedrol, a sesquiterpene alcohol fragrance derived from cedar wood oil and among subjects (n = 8) with a predilection for Jasmine tea odor, but not among those with antipathy for the tea (Inoue et al., 2003). Furthermore, reduction of the heart rate and the low frequency heart-rate variability, reflecting lower sympathetic nervous activity, was observed for Cedrol (Dayawansa et al., 2003), while for those disliking the Jasmine tea odor an increase was seen at high odor intensity, indicative that intensity and preference of odors/fragrances may play an important role (Pichon et al., 2015).

Household cleaning activities with fragrance containing detergents or use of incense were also associated with reduced heart-rate variability, especially among elderly women using scented spray products frequently (Huang et al., 2014; Metha et al., 2012). However, the observed effect was proposed to be associated with PM2.5 levels that were observed for exposure to candles (25%) (aerosol concentration 200 μg/m³) (Hagerman et al., 2014); other confounding could be by psychosocial conditions (e.g. anxiety, stress), and lack of physical activity on a weekly basis as suggested by Metha et al. (2012); furthermore, an effect of perceived unpleasantness of the scented products may have occurred.

3.5.3. Work performance effects

Slower reaction time was observed for low-frequency words in lexical decision performance among naïve subjects (n = 28) during exposure to an air freshener (3.2 mg/m³ total VOCs); the authors suggest mental distressful stimuli impairs the task performance (Gaygen and Hedge, 2009). Lower work performance (e.g. more errors) was also observed in exposure studies to a smelly carpet and office equipment, respectively (Wargocki et al., 1999; Bakó-Biró et al., 2004), and to unpleasant odors (Danuser et al., 2003). This is further supported by a study with healthy subjects (n = 86) carrying out spatial memory performance during exposure to a pleasant odor (LIM), unpleasant odor (machine oil), and sham air as control. The exposure to the unpleasant odor was generally associated with poorer performance compared to LIM or sham air, as stated by the authors: “This finding extends those of other studies, which have demonstrated poorer spatial and visuospatial performance during exposure to negative olfactory and non-olfactory emotional stimuli” (Martin and Chaudry, 2014). This agrees with the observed influence of ambient odors, which included the fragrance phenyl ethyl alcohol, slowing down the “visual attentional capture” (Michael et al., 2005). This is further supported by a recent controlled study of healthy subjects (n = 48) exposed for 4 h to the unpleasant odor of propionic acid at 0.3 and 10 ppm (30 mg/m³) level (about 1 to 3-fold above its odor threshold). No neurobehavioral effects on working performance in four out of six visual tasks were found, but statistical significance was shown for reaction time and response inhibition, and with an increase of errors going from 0.3 to 10 ppm (Pacharr et al., 2016).

It is important to note that the impact of odors on cognitive operations is complex (Heuberger and Ilmberger, 2010; Johnson, 2011; Rohilman et al., 2008). It depends on many personal factors including context, experimental design, gender, and psychological factors (Ilmberger et al., 2001; Jaén and Dalton, 2014; Martin and Chaudry, 2014); including the subjective rating (e.g. arousal, intensity, pleasantness, stress) of the fragrances (Heuberger and Ilmberger, 2010). It is possible that the odors may act through different mechanisms, e.g. “cross-modal integration of visual, olfactory, and trigeminal information” (Michael et al., 2005; Millot et al., 2002).

In summary, experience, annoyance and pleasantness may affect the breathing rate in a positive or negative manner. Studies have shown that fragrances generally increase the high frequency heart-rate variability, in part influenced by the preference (likeliness) of the odor. Odor annoyance and possibly chemosensory distraction deteriorated the work performance in many studies, but for how long is uncertain. Therefore, effects on performance are inconclusive (Johnson, 2011; Hoenen et al., 2016). Pleasantsness of the odor may have a positive effect on mood in a less demanding task as indicated for LIM (Hoenen et al., 2016), cf. Knasko (1995). The exposure to aerosols rather than fragrances during cleaning activities appears to induce a reduction in the heart-rate variability, thus, hampering a clear conclusion about the impact of fragrances in cleaning products.

3.6. Sensory irritation and airway effects among professional and domestic cleaners

Several epidemiological studies have shown associations between the use of cleaning products and adverse airway effects, in particular asthma (Zock et al., 2010). Evidence of a deleterious role of cleaning products mostly comes from studies on risk factors of work-related asthma, but an adverse effect of home-cleaning exposure has also been observed, e.g. Folletti et al. (2014) and Sircusca et al. (2013). One group of constituents, fragrances or mixtures thereof, that are common constituents in cleaning products (Nazaroff and Weschler, 2004), have been considered as potentially causative that includes their ozone-initiated reaction products, see below. The epidemiological literature, however, has identified strong associations with the use of spray products and airway effects, rather than fragrances (Quirce and Barranco, 2010; Zock et al., 2010).

With a few exceptions (e.g. acid anhydrides, isocyanates) indoor VOCs, in general, are not considered to cause asthma and asthma-like symptoms, exacerbate asthma, or sensitize the airways by inhalation at low levels (Becher et al., 1996; Nurmatov et al., 2015; Nielsen et al., 2007a). On the other hand, it has been suggested that fragrances and other cleaning chemicals are strong sensory irritants and several studies have proposed irritative-induced exacerbation by inhalation of sensory irritants, e.g. Vandenplas et al. (2014b). Established thresholds for sensory irritation of common fragrances, however, are 2 to 3-fold higher than concentrations encountered in indoor air, see Table 2. However, repeated exposure to activity-related temporary peak concentrations is likely, see Bello et al. (2010).

Information, however, about exposure to more aggressive cleaning chemicals is limited, except for a few chemicals like bleach (hypochlorite) (Quirce and Barranco, 2010). It has been hypothesized that repeated exposure to sensory irritants sub-threshold levels could cause development of or exacerbate asthma with special focus on formaldehyde (Dumas and Le Moul, 2016). However, an adjuvant effect of formaldehyde or as an allergen is not supported (Wolkoff and Nielson, 2010). Furthermore, 10-day repeated exposure of mice to LIM did not cause an increase in inflammation in bronchial lavage (Wolkoff et al., 2012).

In summary, fragrances are abundant and common in cleaning products, the exposure by inhalation is not considered to cause sensory irritation effects or sensitization. It has been hypothesized that loss of the skin barrier function could initiate allergen sensitization via the skin as a critical step (Redlich, 2010). For example, 3-carene skin-sensitized guinea pigs induced an increase in bronchial reactivity in isolated lungs after inhalation of the terpene (1900 mg/m³) in comparison to lungs from non-sensitized animals (Lästibom et al., 2003). Unprotected skin may be impaired by repeated use of aggressive cleaning products, e.g. with alkaline properties, hypochlorite or contact with water, which
may facilitate access of allergens and immunological sensitization and cause adverse airway effects (Redlich, 2010). Clearly, alternative mechanistic hypotheses should be developed and tested for further understanding of the reported airway effects among cleaners, e.g. increased or modified susceptibility from early life exposure to maternal smoking, severe infection, maternal age > 35 years, and winter month delivery (Svanes et al., 2015).

4. Ozone-initiated gas-phase reactions

Ozone-initiated reactions with APN, EUG, LIL, and LIM produce a host of products, both gaseous, inter alia formaldehyde, and ultrafine particles (SOA), e.g. Atkinson and Arey (2003) and Huang et al. (2012). A few human exposure studies have been carried out with ozone and APN or LIM, see below, while many rodent inhalation experiments have studied upper and lower airway effects (Rohr, 2013). For a study about cardiovascular effects, see Section 3.5.2.

4.1. Human exposure studies

Young women (n = 130) were exposed to a typical indoor VOC mixture with 23 VOCs (TVOC = 26 mg/m³), including APN (0.9 mg/m³) and LIM (0.7 mg/m³), for 140 min in a controlled climate chamber (25 m³, 1.8 h⁻¹). The mixture was used as such or mixed with ozone to a residual concentration of 0.04 ppm (0.08 mg/m³), and 0.04 mg/m³ formaldehyde. No sign of inflammatory effects in nasal lavage was seen, i.e. no increase of polymorphonuclear cells, total protein, IL-6 and IL-8 (Laumbach et al., 2005). The symptom rating was marginal and not statistically significant with or without ozone (Fiedler et al., 2005). Similarly, bronchoalveolar lavage in mice exposed repeatedly to ozone-initiated LIM oxidation products for 10 days did not exhibit signs of inflammation (Wolkoff et al., 2012).

Young non-asthmatic subjects (n = 33) and mild asthmatics (n = 38) were exposed blindly to a steady-state reaction mixture of max 37 ppb ozone (max 74 μg/m³) and 36 ppb LIM (200 μg/m³) for 3 h in a climate chamber (240 m³, 1 h⁻¹, recirculation 7 h⁻¹) (Fadeyi et al., 2015). The asthmatic subjects reported a lower perceived, but marginal, nose and throat sensory irritation than the non-asthmatics. The rating was < 15 on a continuous intensity scale from 0 to 100 with 20 = slight irritation. The difference between the non-asthmatics and asthmatic subjects is compatible with recent studies with naïve and sensitized mice exposed to formaldehyde or a reaction mixture of ozone and LIM (Larsen et al., 2013; Hansen et al., 2016); the excess mucus in the airways of asthmatics and in sensitized animals has been proposed to have a scrubbing (protective) effect of the airways. Furthermore, no significant difference was observed for sensory irritation in the eyes that was rated < 13 on the intensity scale; this is compatible with an expected formaldehyde concentration < 40 ppb (1:1 reaction), which is significantly lower than the threshold for sensory irritation in the eyes (Mueller et al., 2013; Wolkoff and Nielsen, 2010). However, a stress marker (α-amylase) in saliva increased significantly in both the normal and asthmatic subjects after the exposure, but significantly more among the asthmatics, but it is not clear whether the increase was caused by the odor perception, the experimental set-up, or the reaction products.

4.2. In-vivo and in-vitro exposure studies

Secondary organic aerosols are also formed in ozone/terpene reactions; for instance, orange peeling (Langer et al., 2008; Vartiainen et al., 2006) and use of fragrance emitting cleaning products (Nørgaard et al., 2014b; Wainman et al., 2000) produce SOA. Generally, neither in vitro nor in vivo studies of ozone-initiated reactions have the gas-phase reaction products been separated from the SOA phase. This was investigated in a mice bioassay by denuding the ozone/LIM-initiated gas-phase reaction products from the SOA. The denuding showed that the SOA contributed minimally to sensory effects or caused airflow limitation (Wolkoff et al., 2008). In another study, F344 rats and ApoE −/− mice were exposed for seven days to denuded APN-SOA (200 μg/m³) derived from UV radiation of a mixture of nitrogen dioxide (± sulfur dioxide) and APN (McDonald et al., 2010). Pulmonary inflammation was not observed in either mice or rats and the authors suggested the gaseous products to be of concern rather than the SOA. Thus, the biological response was mild, also the cardiovascular-related effects. In general, denuded SOA generated from 1670 μg/m³ APN and 1000 μg/m³ ozone did not show clear pulmonary or systemic responses in rats (Godleski et al., 2011) or in vivo oxidative stress (Lemos et al., 2011), see Rohr (2013) and Rohr and McDonald (2016). The only significant finding was a minor increase of the breathing rate (Diaz et al., 2011).

Repeated exposure to an ozone/LIM-initiated reaction mixture with the generation of formaldehyde did not elevate the sensory irritation or developed airflow limitation or inflammation in the airways in mice. Based on the study, it was concluded that ozone < 200 μg/m³ (0.1 ppm) would be safe, even in combination with high LIM concentrations (Wolkoff et al., 2012).

Human bronchial epithelial cells (BEAS-2b) showed minor elevation of IL-8, among several inflammatory markers, to the exposure of magnetic nanoparticles coated with SOA generated from APN or terpinolene, but not to the SOA or the nanoparticles alone, or clean air (Jang et al., 2006). Further, the exposure of human lung epithelial cells (A549) to ozone-initiated non-denuded reaction mixtures with α-terpineol or LIM did not show biological effects at levels mimicking indoor air (Anderson et al., 2010, 2013). Thus, the overall effects of SOA, which included release of inflammatory markers in rodents or human lung cells from ozone-initiated terpene reactions, appeared not to be significant for those investigated; furthermore, the results are difficult to extrapolate to real life conditions.

Limonee may act as a scavenger for ozone and reactive oxygen species (inflammatory mediators); for instance, as a local scavenger in the airways. Thus, studies have demonstrated an anti-inflammatory prophylactic effect of LIM alone using rodent inhalation models of allergic inflammation (Bibi et al., 2015; Hansen et al., 2013; Hirota et al., 2012; Keinan et al., 2005) and the ozone/LIM system (Hansen et al., 2016). Anti-inflammatory effects in lungs have also been suggested for LIL (Huo et al., 2013).

4.3. Emission and field studies

4-Oxopentanal, a common ozone-initiated reaction product of LIM and other fragrances (e.g. geraniol, LIL, and skin oils), has been shown to be a bronchoconstrictor with a derived human reference value of 30 ppb (123 μg/m³) (Wolkoff et al., 2013). Measurements of this compound in a simulated user scenario under controlled conditions with a plug-in air fresher and in European offices, respectively, resulted in maximum (background adjusted) 24% and 15% of the reference value (Nørgaard et al., 2014a, 2014b).

According to derived reference values for key oxidation products only special cases with high ozone and LIM levels may result in concentrations of formaldehyde, acrolein and 4-oxopentanal sufficient to cause concern about acute effects in eyes and airways (Wolkoff et al., 2008, 2013). Measured concentrations of the oxidation products, including formaldehyde, are too low to result in sensory irritation in European offices (Nørgaard et al., 2014a) and aircraft (Wolkoff et al., 2016). Some of the reactions products, e.g. organic radicals have not been measured in real-life conditions, but their concentrations are expected to be low, e.g. (Chen and Hopke, 2010).

In summary, ozone-initiated terpene/fragrance, like LIM, reactions produce a complex mixture, sometimes with formaldehyde as a major product. Based on both human and rodent exposure studies and established human reference values for some of the major oxygenated reaction products, it is concluded that induction of sensory irritation would require concentration of ozone > 100 ppb at high LIM

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concentrations (Wolkoff et al., 2012). Further, measured levels in offices of key oxidation products are too low to cause sensory irritation and airflow limitation. Furthermore, several rodent studies indicate that some fragrances, EUG, LIL and LIM, may have scavenging effects towards reactive oxygen species and possess anti-inflammatory properties.

5. Discussion and conclusion

Odors from flowers, construction and consumer products, food, and personal care products (e.g. perfumes), ubiquitous in indoor environments, have been attributed to elevated symptom reporting, especially among people with asthma, allergic rhinitis and dermatitis in population studies, e.g. Claeson et al. (2016), Eriksson et al. (1987), Elberling et al. (2005a), and Shim and Williams (1986). The generally large number of identified and not necessarily listed fragrances in consumer products, e.g. Steine mann et al. (2011), has visualized the health and environmental concern and controversies over their use, amplifying their “witch-hunt” (Bridges, 1999; Steine mann, 2017).

The indoor air concentrations of the most common fragrances APN, EUG, LIL and LIM are 2 to 3-fold below their thresholds for sensory irritation in the eyes and airways, but close or above their threshold for odor detection. Thus, they may influence the perceived IAQ, in addition to numerous other indoor VOCs with low odor thresholds that are emitted from construction products, e.g. aldehydes and acids from wooden-based materials, e.g. Gminski et al. (2011a). Temporary higher concentrations of fragrances may occur during cleaning and spray activities in small rooms with low air exchange rates, but the concentrations are likely below thresholds for sensory irritation and levels causing lung function effects, and in agreement with Heinrich (2011). Thus, these fragrances should not be considered to cause sensory irritation. Furthermore, reported indoor concentrations are also 1 to 2-fold lower than derived thresholds for long-term health effects. Other mechanistic routes should be pursued or specific focus on compounds with sensitizing properties should be searched for to assess the reported effects among cleaning workers.

Human exposure studies to a realistic set-up with reaction mixture of ozone and LIM or VOC mixture with LIM/APN, that inter alia produces the sensory irritant formaldehyde, and other products, including SOA, did not show significant effects in the airways and eyes (Fadeye et al., 2015; Fiedler et al., 2005; Laumbach et al., 2005). This agrees with the conclusion that concentrations > 200 μg/m³ ozone at high LIM concentrations would be necessary to expect sensory airway and eye effects (Wolkoff et al., 2012). Furthermore, asthmatics may be less sensitive to water soluble sensory irritants in the airways than normal subjects due to increase of mucus production, which was further supported by an exposure study of sensitized mice.

The human exposure studies point to olfactory-associated effects, e.g. reported skin symptoms among skin sensitized patients, rather than a toxic effect by inhalation of the fragrances, and with no indication of sensitization. This is further supported by mice inhalation studies. However, suggestion or negative information about a fragrance (odor) may exacerbate asthma symptoms and possibly increase bronchoconstriction among asthmatics, and sometimes result in skin reactions among skin sensitized people. Thus, "P. Dalton advises that alarmist messages, that may increase anxiety, etc., should be avoided" in Senger (2011).

Fragrances (odors) appear to have mental distressing effects that deteriorate the visual work performance in certain conditions; however, the issue is complex to allow for generalization due to inter alia personal attitudes and previous experience. We are unaware of fragrances at indoor levels causing severe effects in the eyes and airways as known for some food flavors like diacetyl causing bronchiolitis obliterans (Kreiss et al., 2002).

Our conclusions about the four common indoor air fragrances cannot be expanded to other inhalable fragrances. Clearly, there is a research need to study airway effects and potential sensitization, not only for EUG and LIL, but a selected number of common fragrances or mixtures thereof to be in a stronger position to draw conclusions about their inhalative exposure and effects, also after extended exposure periods. Such studies should be carried out at indoor realistic levels, ideally blinded, either by oral exposure or by masking. Based on current knowledge, however, their mean indoor air concentrations, generally, would be expected to be in the ng/m³ to low μg/m³ regime, but temporarily higher acute concentrations may occur in the presence of specific sources, activities, or low air exchange rates. Furthermore, secondary emissions associated with cleaning activities, e.g. the resuspension of particles and ozone-initiated SOA should also be considered. In the meanwhile, there is a strong need to inform the general population about how low exposure to perceived fragrances/odors, despite their levels are 1 to 3-fold below the regime of toxicological effects, may trigger psychological reactions of which some can be mitigated.

Conflict of interest

The authors declare no competing financial interest.

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