



Fragrance inhalation and adverse health effects: The question of causation

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ABSTRACT

The toxicology of fragrance materials is largely well understood. Although most are benign, a minority have the potential to cause adverse health effects, notably allergic contact dermatitis resulting from skin sensitization. As a consequence, industry guidelines have banned certain materials and strictly limited the use of others. Recently, data have been published that have been interpreted to suggest that inhalation of fragrances is associated with the occurrence of a variety of health effects, ranging from headaches to asthma attacks. In this review, the evidence basis for these assertions is examined critically and the biological basis and mechanistic plausibility for causation by fragranced products of these health effects is explored. This review concludes that respiratory effects, including irritation and allergy appear highly unlikely to occur by this route. While some sensory/psychosomatic effects are possible, this does not explain the very high rates of adverse effects reported in the recently published questionnaire studies, which this review concludes are more likely to be attributed to methodological weaknesses. Ultimately, it is concluded that adverse health effects arising from fragrance inhalation are uncommon and remain to be identified and confirmed by methodologically rigorous epidemiological investigations supported by a convincing biological and mechanistic basis.

1. Introduction

The history of the use of fragrances stretches far back into ancient times, and gives every indication that humans have long regarded preparations providing attractive odours, either to themselves, or to the general environment, as something that is very much to be desired. During the last century, such aspirations have led to a substantial modern industry producing large amounts of fragrance materials to satisfy a very wide market. Supporting this there exist both safety specialists within individual fragrance industries, as well as overarching trade bodies, of which perhaps the most important is the International Fragrance Association (IFRA) which produces guidelines whose aim is the safe production and use of fragrances, either by outright ban or via the conduct of risk assessments, which may lead to restrictions on the use of individual fragrance materials with the potential for adverse health effects (Api et al., 2015; IFRA Standards, 2015).

Despite these efforts, it is well known that a minority of fragrance materials have the ability to cause allergic reactions in the skin, expressed as allergic contact dermatitis (ACD) (e.g. Goossens, 2018; Montgomery et al., 2018). Accordingly, there is a continuing substantial effort to refine the risk assessment process, further limit exposure, and thereby markedly reduce the incidence and extent of any adverse

effects (Basketter and Safford, 2016; SCCS, 2017; IDEA project, 2018). The intrinsic allergenic potential of certain fragrance materials also has led some to question whether there may also be a risk to human health following inhalation. Whilst this risk cannot be entirely discounted, it has been argued that it is extremely low (Basketter and Kimber, 2015). More recently, however, the potential of fragrance materials to trigger a range of adverse health effects in response to inhalation exposure has been proposed (Steinemann, 2016, 2017; 2018). In one sense, this is not new, as it has long been recognised that there is the risk that certain individuals with hypersensitive airways and who are capable of responding to a wide range of non-specific triggers, may have amongst those triggers the inhalation of odoriferous chemicals (e.g. Kumar et al., 1995; See et al., 2016; Weinberg et al., 2017). Indeed, a very carefully controlled study undertaken in partnership with the fragrance industry identified a tendency for moderate asthmatics to experience symptoms when exposed to a fragrance aerosol for up to 30 min (Vethanayagam et al., 2013). Nevertheless, the ontogeny of these reactions remains unclear and is potentially indicative of a psychological connection (e.g. Jaen and Dalton, 2014). Certainly, inhalation studies in standard toxicological animal models have also demonstrated an absence of pathology, even after prolonged exposure at high dose levels (Fukayama et al., 1999). A recent review concluded "... that reported lung function

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effects are likely due to the perception rather than toxic effects of the fragrances.” (Wolkoff and Nielsen, 2017).

The first publication discussed herein reports the results of an online survey of the adult American population, using a national random sample, representative of age, gender, and region with 1136 participants (Steinemann, 2016). The second publication reports the results of an online survey of the adult Australian population, also using a national random sample representative of age, gender, and state with 1098 participants (Steinemann, 2017). Both papers advocate the reduction of exposure to fragranced products as a means of preventing widespread adverse health effects. However, given the well recognised emotional benefits of fragrances, this can only be justified if a clear causal relationship can be established between exposure to fragrance materials and an adverse effect (Ethgen and Bruyère, 2017). The data as presented and analysed do not appear to justify such a conclusion. This paper offers a critical commentary on the Steinemann publications, examining whether the results can be regarded as robust by considering the extent to which they address the demands of a selected number of the Bradford Hill criteria, but focuses particularly on exploring whether, and to what extent, there is any biological mechanistic basis which might substantiate a fragrance reduction strategy.

1.1. Human evidence

The Steinemann surveys gather data on the types of exposures from respondent's self-reported personal use, as well as from the use by others, of a range of fragranced products, together with prevalence of self-reported health effects (including respiratory, mucosal, migraine, skin, neurological and musculoskeletal diseases) and societal impacts (Steinemann, 2016, 2017). These data were collected using a questionnaire that was reported as taking less than 15 min for completion. The conclusions drawn are that there exists both an association and a causal relationship, between exposure and reported health effects. However, it is our view that these studies suffer from a number of methodological limitations and deficiencies that mitigate against the validity of these conclusions.

The US and Australian studies have the same design; an online survey with a national sample representative of age, gender, and region/state. The details of the selection processes are not described in the publications. Both studies used the same questionnaire, and the full format of these is not provided in the publication, nor could it be found via internet searching. However, the survey methodology which is available separately (Steinemann Survey Methodology, 2016) explains that as part of the survey, the aims of the study were explained and the option given to the panel members to participate. The extent to which this information was managed to exclude the possibility of inducing bias in the respondents was not explained, and no information was provided on how any resultant confounding issues might be addressed. For example, there is nothing to suggest that a social desirability scale test (e.g., Marlow and Crowne, 1960) was used to screen participants.

The response rate in both samples is very high, therefore a non-response bias can be discounted.

A survey (cross-sectional study) measures both exposure and adverse effects simultaneously at a single point in time. These studies were performed to estimate the prevalence of the adverse effects and the prevalence of the exposure. The temporal relationship between the self-reported exposure and the occurrence of the health effect are not discussed and there is no indication that this information was collected or considered. Thus, the given prevalences are used to measure the occurrence of an adverse health effect without giving a clear moment of onset. Therefore, it is not possible to assess whether the exposure actually preceded its presumed effect on health (Wild, 2004). It is not described in the publications what, if any, instructions were given to the participants as to which period of time should be covered by the questions in the online survey. This makes it extremely difficult to determine how causation was established (Hill, 1965). This view is also

supported by the papers reporting no data on, or any related attempt to establish, a dose-response relationships (Hill, 1965) by, for example, examining levels of exposure and attempting to correlate this with occurrence and/or severity of the reported health effects. Also, as the product data are non-specific regarding individual ingredients, it is not possible to compare situations of no exposure versus exposure. It could be that the observed health effects would be found to be similar to those in a survey in which only self-reported health effects were covered.

In conclusion, it is not possible to establish an association between an exposure and a health effect with the design of this cross-sectional study, given the limitations in establishing a temporal relationship between exposure level and outcome. A cohort and/or case-control studies would be necessary to establish etiologic relationships (Gordis, 2014).

The questions used appear to be of a very general nature, e.g., ‘Which fragranced products are you exposed to, at least once a week, from your own use?’. These have significant limitations in that they tend to produce general, as opposed to specific, responses which would have the possibility to include a temporal dimension. The questions used do not appear to be sufficiently specific to measure adverse consequences reliably and in a valid way. In the case of questions related to disease, they appear to invite a response and should be considered leading (Kelly, 2003; Harvard, 2017).

In terms of other confounding factors, the Steinemann papers do not address how these have been adjusted for, or even indicate that they have been considered. For example, some 18 different triggers, including odours (fragrance and foul), have been listed as triggers for episodic migraine sufferers, with stress and sleep deprivation identified as the most significant at 57.7% and 55.1%, respectively from 1099 headache days (Jeong-Wook et al., 2016). The papers do not address how significant confounders such as these have been adjusted for in arriving at the reported results. This is particularly important as the paper claims that 10.0% of those surveyed reported migraine associated with exposure to fragrance products. This compares with the total of 11.1% diagnosed in general practice in Australia (Stark et al., 2007).

Based on the above methodological review and the limitations identified therein, the studies as reported, do not justify the conclusion that there is a causal link between the self-reported exposures and the similarly self-reported health effects. That said, a review of the studies also does not allow a link to be excluded. The likelihood of causation must depend, following the Bradford Hill criteria, on examining biological plausibility. These considerations follow below.

1.2. Respiratory allergy and irritation

As described above, there have been suggestions in the literature that inhalation of fragrance materials can be associated with a wide range of health effects, including respiratory problems, but also adverse effects involving other organ systems (Steinemann, 2016, 2018). In exploring the biological and mechanistic plausibility for these assertions it is relevant to consider the possibility that certain fragrance materials have the potential to induce respiratory allergy and asthma, or exacerbate respiratory reactions in those that have pre-existing respiratory disease.

However, before proceeding with this aspect, it is appropriate to mention that other mechanisms such as narcosis have not been excluded. Rather, it has been concluded that the airborne exposure levels associated with fragrance chemicals are substantially below those levels that would be associated with toxicities such as solvent narcosis. This topic has been reviewed extensively in a recent work prepared for the European Chemicals Agency (ECHA, 2017). For example, exposure limits for toluene are generally in the 100 mg/m³ range, whereas fragrance chemical exposure is orders of magnitude lower. Even in the provocative exposure study in allergic individuals (discussed later in this paper), the highest airborne concentration was 1 mg/m³ and was noted by the authors to be an atypically high level (Schnuch et al.,

2010). In reality, exposure levels are normally more than an order of magnitude lower (Wolkoff and Nielsen, 2017). As an example, it is suggested that limonene, a commonly used fragrance will not produce any sensory (let alone physical) irritation in a mouse model at an airborne concentration of < 100 ppm (Larsen et al., 2000). Now although there will likely be some interspecies difference, this would still require an airborne concentration at least 2 orders of magnitude higher than those identified above as likely worst case scenarios. Indeed, more generally, the possibility that respiratory irritation will arise, even from indoor concentrations, appears to be highly unlikely. The airborne levels encountered have been reported to be far below those required to produce airway irritation (Wolkoff and Nielsen, 2017). This is unsurprising, as some 99% of fragrance material (inhalation) exposure falls below the most conservative threshold of toxicological concern (Carthew et al., 2009). Furthermore, since 2010, the Research Institute for Fragrance Materials, Inc. (RIFM) in partnership with Creme Global (<https://www.cremeglobal.com/>) has been developing a model to estimate the aggregate exposure to fragrance ingredients resulting from the use of multiple consumer products. The Creme RIFM Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) is based on the declared habits and practices data from over 40,000 panelists across Europe and The United States of America. The aggregate exposure to fragrance materials from the combined oral, dermal and inhalation routes of exposure is very low.

Given the data and the examples summarised above, it is likely that respiratory irritant reactions to inhaled fragrance materials – certainly at the airborne concentrations normally encountered – are going to be, at most, very uncommon.

1.3. Chemical respiratory allergy: definitions, mechanisms and uncertainties

In this section, the ability of fragrance materials to induce allergic sensitization of the respiratory tract will be considered.

Allergy is best defined as the adverse health effects that may result from the stimulation of a specific (adaptive) immune response. Allergy characteristically develops in two phases. In the first phase (induction phase) exposure of a susceptible subject, via a relevant route, to a sufficient amount of the inducing allergen, causes sensitization (a heightened level of immune responsiveness to that allergen). If subsequently the now sensitized subject encounters the same allergen, then an accelerated and more aggressive secondary immune response will be induced resulting in the elicitation of an allergic (inflammatory) reaction. This is the second, or elicitation, phase (Kimber et al., 2011).

Here the question addressed is whether certain fragrance materials have the ability to cause sensitization of the respiratory tract such that following subsequent inhalation exposure to the same inducing chemical a respiratory allergic reaction will be provoked. This reaction being commonly characterized by rhinitis or asthma (Bernstein et al., 1993; Mapp et al., 2005).

Compared with the most common manifestation of chemical allergy (skin sensitization resulting in ACD) a relatively small number of low molecular weight chemicals (probably less than 80) have been shown conclusively to be respiratory allergens in humans. Certain classes of chemicals are commonly associated with sensitization of the respiratory tract, and these include: diisocyanates, acid anhydrides, chloroplatinate salts and reactive dyes (Baur, 2013; Baur and Bakehe, 2014).

Chemical respiratory allergy remains an area of some controversy, largely due to uncertainties about the relevant immunological and biochemical events through which sensitization of the respiratory tract is acquired. A detailed review of chemical respiratory allergy and the challenges it poses is beyond the scope of this article. However, there is available a number of review articles that address these issues (Kimber and Dearman, 2005; Tarlo and Malo, 2006; Holsapple et al., 2006; Isola et al., 2008; Boverhof et al., 2008; Kimber et al., 2011; Cochrane et al., 2015; North et al., 2016; Vincent et al., 2017a).

Do fragrance materials cause allergic sensitization of the respiratory

tract? Human evidence.

It is against this background that we here consider whether adverse health effects reported to be associated with inhalation exposure to fragrance materials might be attributable to respiratory allergic reactions in subjects previously sensitized (by either skin contact or inhalation). A similar analysis has been published previously (Basketter and Kimber, 2015), and some of the information contained within that article is also summarised here.

There is little evidence to suggest that fragrance materials have the ability to induce sensitization of the respiratory tract and respiratory allergy in humans. Published lists of chemicals associated with occupational respiratory allergy/occupational asthma do not contain fragrance materials. A detailed list of chemicals implicated in cases of work-related asthma was compiled by Chan-Yeung and Malo (1993) and this contains no fragrance materials.

Data are also available from the UK Surveillance of Work Related and Occupational Respiratory Disease (SWORD) that registers agents that have been shown to cause occupational asthma during specific reporting periods. During the period spanning 1989–2001, no fragrance materials were identified as causative agents (McDonald et al., 2000, 2005). In another survey, the UK Health and Safety Executive (HSE) reported that during the calendar year 2013 there had been 177 new cases of occupational asthma none of which was attributed to fragrance materials (HSE, 2014). Although these analyses reveal that no specific fragrance materials have been implicated as causative agents in confirmed cases of occupational asthma, it must be acknowledged that a general category of ‘cleaning products’ is included among causative agents in such surveys, but without specific chemicals being identified (see later).

Another piece of evidence that fragrance materials lack the potential to induce allergic sensitization of the respiratory tract is provided in a study of lung function among those working in the fragrance industry. A cross-sectional study was conducted in which workers exposed to fragrances (working in production and allied functions) were compared with a non-exposed control group working in administrative functions. No differences in lung function between the exposed and non-exposed populations were found (Dix, 2013).

Taken together, the evidence available from human studies indicates that as a class, fragrance materials lack the potential to cause allergic sensitization of respiratory tract, despite the fact that some are known to cause skin sensitization. It is appropriate now to consider whether the same conclusion can be drawn from data available from studies performed in experimental animals. However, before reviewing the results of such studies, it is necessary to provide a brief commentary on the current state-of-the-art of experimental approaches to predicting the respiratory sensitizing potential of chemicals.

Do fragrance materials cause allergic sensitization of the respiratory tract? Evidence from experimental animal studies.

Although there is now a growing consensus that a specific subset of T lymphocytes [T helper 2 (Th2) cells] play a pivotal role in the induction of respiratory sensitization to chemicals (reviewed in: Kimber et al., 2014a; b; Kimber et al., 2018), there has in the past been considerable uncertainty about the immunological mechanisms that are responsible for respiratory sensitization, and in particular the role of IgE antibody (Kimber and Dearman, 2002; Kimber et al., 2018). There can be no doubt that this has impeded the development and acceptance of methods for hazard identification and characterization of chemical respiratory allergens. Thus, despite a considerable investment in research, and a variety of suggested approaches (for instance: Griffiths-Johnson and Karol, 1991; Sarlo and Clark, 1992; Hilton et al., 1996a; Dearman and Kimber, 2001; Enoch et al., 2012; Forreryd et al., 2015), there are currently no validated, or even widely recognised, methods available for toxicological evaluation.

Despite this lack of validated methods it is appropriate to question whether there is available experimental evidence that fragrance materials have any potential to cause allergic sensitization of the respiratory

tract. This is a relevant question to ask because it is clear that some fragrance materials have an ability to cause skin sensitization and ACD, and therefore have some intrinsic allergenic potential (Johansen and Lepoittevin, 2011; Frosch et al., 2015).

The available data are very limited, but information is available for isoeugenol, a fragrance with known skin sensitizing potential. This chemical has been evaluated in a method known as cytokine fingerprinting that seeks to distinguish between skin sensitizing chemicals and those that have the potential to cause sensitization of the respiratory tract (Dearman and Kimber, 1999, 2001; Dearman et al., 2003). This method is predicated on an understanding that different classes of chemical allergen (those that induce skin sensitization and those that induce sensitization of the respiratory tract) elicit in mice different types of immune response characterized by discrete cytokine expression profiles (Dearman et al., 1997; Kimber et al., 2011). Employing this approach, it was found that isoeugenol induced in mice a cytokine profile consistent with skin sensitizers, and different from that which characterizes respiratory allergens (Dearman et al., 1997).

Isoeugenol has also been tested in another experimental system in which chemical respiratory allergens are identified as a function of their ability to stimulate an increase in the total serum concentration of IgE immunoglobulin (a serum marker of respiratory sensitization potential) (Hilton et al., 1996a). It was found that, in common with skin sensitizing chemicals, isoeugenol (and eugenol, another fragrance material that is known to have a weak potential to cause skin sensitization) failed to induce an increase in IgE. This result is consistent with the evidence from cytokine profiling and indicates that isoeugenol (and eugenol) fail to elicit in mice the quality of immune response associated with respiratory allergy (Hilton et al., 1996b).

Finally, and consistent with that conclusion, studies reported by Ter Burg et al. (2014) found, using a mouse model, that isoeugenol (and other fragrance materials contained in air fresheners) do not pose a risk of respiratory allergy.

The failure of isoeugenol to cause allergic sensitization of the respiratory tract in studies using experimental animal models is supported by a study reported by Schnuch et al. (2010). In that investigation, the authors sought to examine whether patients with skin sensitization to isoeugenol displayed respiratory symptoms when exposed by inhalation to the same chemical. No significant changes in lung function were reported. The same failure to elicit changes in lung function was recorded when patients with skin sensitization to hydroxyisohexyl-3-carboxaldehyde received inhalation challenge with the same chemical (Schnuch et al., 2010).

Clearly, other fragrance materials have not been subject to the same level of scrutiny as isoeugenol. However, this chemical is probably representative of other fragrance allergens in that, despite some potential to cause skin sensitization and ACD, there is no evidence to suggest that they have the ability to induce sensitization of the respiratory tract. Indeed, even in patients that have skin sensitization (to isoeugenol at least) there is no concomitant sensitization of the respiratory tract.

1.4. Conclusions: fragrances and respiratory sensitization

The data available from clinical experience, and from investigations in humans and experimental animals, regarding the respiratory sensitizing properties of fragrances are somewhat limited. Nevertheless, collectively the information reviewed here indicates that, although some fragrance materials display the potential to cause skin sensitization, they lack the ability to induce allergic sensitization of the respiratory tract. The conclusion drawn, therefore, is that adverse effects attributed to fragrance materials are unlikely to be attributable to the induction of respiratory sensitization (however acquired) and the subsequent elicitation of respiratory allergic or asthmatic reactions to specific fragrances.

1.5. Household cleaning products, fragrance materials and asthma: respiratory irritation

In the preceding section the conclusion reached is that there is no evidence that fragrance materials have the potential to cause *de novo* sensitization of the respiratory tract. Further, as already mentioned above, airborne exposure levels to fragrance substances are relatively low, typically in the low $\mu\text{g}/\text{m}^3$, concentrations which will not produce irritancy in the respiratory tract (Wolkoff and Nielsen, 2017). It is, however, appropriate to consider one other potential route to an adverse health effect and that is the reported ability of some inhaled materials to exacerbate respiratory reactions in susceptible individuals, including those with pre-existing asthma (Maier et al., 2014).

For many years, there has been a particular interest in the possible influence of household cleaning products in manifestations of asthma in susceptible subjects (Zock et al., 2001; Karjalainen et al., 2002., Medina-Ramon et al., 2003, 2005; Rumchev et al., 2004; Evans et al., 2008; Siracusa et al., 2013; Folletti et al., 2017). Of course, such cleaning products contain a variety of materials including preservatives, disinfectants, perfumes, chlorine-releasing compounds and volatile organic chemicals, and it is not usually possible to link particular components with asthmatic reactions, or to identify causal relationships (Vincent et al., 2017b). Although there is no reason to believe that fragrances are the most common or most important contributors in cases of work-related asthma (Siracusa et al., 2013), they may play a part (Weinberg et al., 2017).

The ability of certain components of household cleaning products to induce or exacerbate respiratory reactions in those with asthma, or otherwise susceptible individuals, is almost certainly attributable to airway irritation (Folletti et al., 2017), rather than allergic sensitization (as discussed above). For that reason, it is probable that adverse effects will be strictly dependent upon the level of exposure, and the inherent susceptibility of the exposed subject (importantly those with pre-existing asthma), and it is unlikely that low level exposure will have any impact on the majority of individuals. It has been proposed that in susceptible subjects, adverse reactions to high levels of perfume exposure may be triggered by the local release of histamine; a potent vasoactive mediator (Elberling et al., 2007).

It is also relevant, with regards to fragrance materials, that the experience of smelling an odour – and the perception of risk – might affect airway physiology and promote adverse reactions (Jaen and Dalton, 2014). Such a type of problem was eloquently demonstrated in the assessment of a patient with suspected hypersensitivity to glutaraldehyde (a known respiratory allergen), but who proved, on careful evaluation to have entirely non-specific symptoms (Stenton et al., 1994).

In summary, it is possible that inhalation exposure of those with asthma, or otherwise susceptible individuals, to fragrance materials (and/or other components of domestic cleaning products) might trigger or exacerbate an asthmatic reaction. If such occurs then it is likely to be due to an irritant reaction requiring relatively high level exposure to the causative agent, coupled with increased sensitivity/susceptibility of the exposed subject. It is therefore unlikely that this will be a common type of response to fragrance exposure, not least due to the low airborne concentration. It appears improbable that this would explain the symptoms that have been associated with low level exposure to fragrance materials in the absence of contributory factors.

2. Conclusions

There is no doubt that airborne exposure to fragrance materials occurs widely, albeit at low concentrations – a key feature of (commercially) successful fragrance is that it stimulates olfactory receptors at low concentration. In addition, it must be acknowledged that some individuals link olfactory triggers with adverse effects, including respiratory responses. However, there appears to be no causative

explanation in terms of allergy or irritation, suggesting that any mechanism is perhaps neurological/psychological. Consequently, it is the view of these authors that it is unhelpful to confound, perhaps compound, consumer fears by unwarranted conclusions drawn from questionnaire studies with the methodological weaknesses discussed above. Given the limitations that have been identified, it is difficult to support the conclusion that more than 1 in 3 adults fear for their health when they detect pleasant fragrance. Rather, we suspect, they normally find it to be a positive experience.

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