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Fragrance sensitisers: Is inhalation an allergy risk?

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ABSTRACT

It is well established that some fragrance substances have the potential to cause skin sensitisation associated with the development of allergic contact dermatitis (ACD). Fragrances are invariably relatively volatile leading to the consideration that inhalation of fragrances might be a relevant route for either the induction of allergic sensitisation or the elicitation of allergic reactions. Moreover, there has been increasing recognition that allergic sensitisation of the respiratory tract can be induced by topical exposure to certain chemical allergens. Here the central question addressed is whether inhalation exposure to fragrance allergens has the potential to cause skin and/or respiratory sensitisation via the respiratory tract, or elicit allergic symptoms in those already sensitised. In addressing those questions, the underlying immunobiology of skin and respiratory sensitisation to chemicals has been reviewed briefly, and the relevant experimental and clinical evidence considered. The essential mechanistic differences between skin and respiratory allergy appear consistent with other sources of information, including the phenomenon of ACD that can arise from topical exposure to airborne allergens, but in the absence of accompanying respiratory effects. The conclusion is that, in contrast to topical exposure (including topical exposure to airborne material), inhalation of fragrance sensitisers does not represent a health risk with respect to allergy.

1. Introduction

A minority of fragrance substances have been identified as contact allergens, such that with sufficient topical exposure they are capable of inducing skin sensitisation in susceptible individuals resulting in allergic contact dermatitis (ACD) (Johansen and Lepoittevin, 2011). Clinical experience demonstrates that, collectively, these fragrance chemicals constitute one of the more common causes of ACD (Frosch et al., 2015). It is for this reason that, not only are guidelines in place directed towards the limitation of dermal exposure to sensitising fragrances (IFRA, 2015a), but also there is an ongoing intensive review of the overall fragrance skin sensitisation risk assessment process (IFRA, 2015b). However, although fragrances are very commonly applied to the skin, their purpose is to create a pleasant odour, a process that requires inhalation. Consequently, it is reasonable to consider whether there are adverse health effects that might result from inhalation exposure to sensitising fragrance substances. Related to this it is increasingly recognised that exposure to chemical respiratory allergens via the skin can support the acquisition of sensitisation of the respiratory tract (reviewed in Redlich, 2010). In this review, therefore, we consider whether the inhalation route of exposure can lead to respiratory allergy to skin sensitising fragrance substances, as well as whether that route plays any role in either the induction of contact allergy or the elicitation of ACD. Excluded from this analysis are non-allergic mechanisms, including those of a psychosomatic nature, and which might be termed fragrance sensitivity as distinct from true immunological sensitisation (Vethanayagam et al., 2013; Jaen and Dalton, 2014). Therefore, it is the purpose of this review to address the following questions:

1. Do fragrance materials, experienced either by skin contact or inhalation exposure, induce allergic sensitisation of the respiratory tract?
2. Does skin contact with, or inhalation exposure to, airborne fragrance materials induce skin sensitisation, or elicit allergic contact dermatitis?
3. Does inhalation exposure to fragrance materials elicit respiratory reactions in skin sensitised subjects?

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In addressing these questions it is important to appreciate that airborne sensitising materials can result in skin and/or inhalation exposure. In this review, the term "inhalation" is used when exposure of the respiratory tract is under consideration, whereas the term "airborne" is used when this particular route to skin exposure is being considered.

2. Do fragrance materials, experienced either by skin contact or inhalation exposure, induce allergic sensitisation of the respiratory tract?

Consideration of respiratory allergy induced by chemicals requires that certain key terms are defined accurately. For the purpose of this article allergy is defined as the adverse health effects that result from the stimulation of an adaptive immune response. Consistent with this, allergy to chemicals is immunologically driven and develops in two phases. In the first (induction) phase, sensitisation of the respiratory tract is acquired via immunological priming to the inducing chemical allergen. In the second (elicitation) phase, inhalation exposure of the sensitised subject to the same chemical allergen may elicit an inflammatory reaction in the respiratory tract that can manifest as asthma (Boverhof et al., 2008; Kimber et al., 2011, 2014). In this context it is important to appreciate that extrinsic asthma can be triggered not only by exposure to chemical or protein allergens, but also by non-immunological mechanisms (asthmagens) (Kimber et al., 2001; Health and Safety Executive [HSE], 2001 and 2014). In this review, attention will focus exclusively on allergic asthma; that is when asthma is a manifestation of the elicitation of an allergic reaction in a subject with sensitisation of the respiratory tract.

It is sometimes assumed that sensitisation of the respiratory tract to chemical allergens will be acquired only as the result of inhalation exposure. However, although there is no doubt that sensitisation can be induced via this route, there is a growing appreciation that topical exposure to chemical respiratory allergens can also support the acquisition of sensitisation of the respiratory tract. That is, skin contact with such allergens can stimulate the quality of immune response required for effective sensitisation of the airways. Evidence for this derives from both studies conducted with experimental animals and from clinical experience (Karol et al., 1981; Botham et al., 1989; Rattray et al., 1994; Kimber and Dearman, 2002; Tarlo and Malo, 2006; Bello et al., 2007; Redlich and Herrick, 2008; Redlich, 2010). It is necessary, therefore, to consider both skin contact and inhalation as relevant routes of exposure when exploring the potential of chemicals to cause allergic sensitisation of the respiratory tract.

Compared with contact allergens, of which a few thousand have been identified (De groot, 2008), far fewer chemicals have been implicated as having the potential to cause sensitisation of the respiratory tract, the number being no more than 80 (Kimber and Dearman, 1997; Bakerly et al., 2008; Health and Safety Executive, 2001; Baur, 2013; Baur and Bakehe, 2014). Among the most commonly reported causes of allergic occupational asthma are the diisocyanates, acid anhydrides, certain reactive dyes and chloroplatinate salts (Baur, 2013; Baur and Bakehe, 2014). There are, in addition, a comparatively small number of other chemicals that have also been identified as confirmed or presumed respiratory allergens. These include, for example, carmine, chloramine T, ethylenediamine, piperazine, plicatic acid and glutaraldehyde (Health and Safety Executive, 2001, 2014). A search of the literature for "non-occupational allergic asthma" returned only 19 hits, none of which involved chemical respiratory allergy, suggesting that outside of the occupational setting, allergic asthma to chemical respiratory sensitisers is very rare.

The important point is that not all chemicals that have some potential to cause sensitisation *per se* are able to induce respiratory allergy. That is, there are a very large number of chemicals that are recognised to have some potential to cause skin sensitisation and allergic contact dermatitis that have never been implicated as respiratory allergens. At least for volatile chemicals, this is not attributable to lack of appropriate exposure for the development of respiratory sensitisation, but is rather a reflection of the fact that chemical allergens are associated with different forms of allergic disease because they vary with respect to the type of sensitisation that will be induced. That is, contact allergen induces different types of immune response that are associated with different forms of allergic sensitisation Those different forms of sensitisation translate into the elicitation of different forms of allergic disease (skin allergy [allergic contact dermatitis], or respiratory allergy associated with occupational asthma) (Kimber and Dearman, 2002, 2005).

The question of why chemical allergens behave differently, and are associated with different forms of allergic disease, is intriguing. The answer is provided by the fact that contact allergens and chemical respiratory allergens preferentially induce qualitatively different immune responses. It is now clear that the adaptive immune system is able to tailor responses to meet different types of challenge. This potential to mount qualitatively diverse immune responses is facilitated by the functional heterogeneity of subpopulations of T lymphocytes. There is a growing consensus that a common characteristic of chemical respiratory allergens is that they drive the selective development of type 2 T cell responses. Thus, it has been found in a variety of rodent studies that contact allergens elicit in mice selective type 1 $CD4^+$ and $CD8^+$ T cell responses, whereas chemical respiratory allergens provoke preferential type 2 responses. Moreover, it appears that such selectivity is independent of the route of exposure (Kimber and Dearman, 1995, 1998; Vento et al., 1996; Vandebriel et al., 2000; Van Och et al., 2002; Dearman et al., 2005; De Jong et al., 2009).

There is increasing evidence that in humans also chemical allergens of different classes selectively induce qualitatively discrete immune responses. That is chemical allergens of different types (contact and respiratory chemical allergens) appear to induce in humans similar to those that are induced in rodents (Sastre et al., 2003; Newell et al., 2013; Ouyang et al., 2013; Kimber et al., 2014a). The consequence is that, although these different types of chemical allergens share the ability to elicit immune activation and T lymphocyte responses, the nature of those responses are qualitatively distinct resulting in the acquisition of discrete forms of allergic sensitisation. The unifying immunologic characteristic of chemical respiratory allergens is that they provoke selective type 2 T cell responses that favour allergic sensitisation of the respiratory tract (Kimber et al., 2014b; c). Moreover, that potential to produce the quality of immune response required for respiratory sensitisation appears to be independent of the route of exposure (skin or respiratory tract) (Dearman et al., 2013).

Against this background the question being addressed here is whether fragrance materials, and particularly those known to cause skin sensitisation, have the potential to induce allergic sensitisation of the respiratory tract (consequent upon either skin contact or inhalation exposure). From a mechanistic perspective the issue is whether fragrance materials have the potential to induce the quality of immune response required for respiratory sensitisation.

Before considering specific reports available in the literature, it is relevant to refer to various surveys and compendia that list the chemicals that are commonly associated with respiratory allergy. In a book first published in 1993 (*Asthma in the Workplace)* there was included a compendium listing the major inducers of occupational asthma (both proteins and chemicals). No fragrance materials were included in those lists (Chan-Yeung and Malo, 1993). Another