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Skin sensitisation to fragrance ingredients: is there a role for household cleaning/maintenance products?

The induction of contact allergy to fragrance ingredients and the consequent risk of allergic contact dermatitis (ACD) present a human health concern that cannot be ignored. The problem arises when exposure exceeds safe levels, but the source(s) of exposure which lead to induction often remain unclear. This contrasts with the elicitation of ACD, where the eczema frequently can be traced to specific source(s) of skin exposure. Cosmetic products are often implicated, both for induction and elicitation. However, other products contain fragrance ingredients, including household cleaning products. In this paper, the risk assessment concerning the ability of these products to induce fragrance contact allergy is considered and the clinical evidence for the induction and/or elicitation of ACD is reviewed. It can be concluded that the risk of the induction of fragrance contact allergy from household cleaning products is low. Especially where more potent fragrance allergens are used in higher exposure products, the aggregated exposure from such products can augment the risk for the elicitation of ACD. This supports the need to manage this risk via the provision of information to consumers.

Key words: allergic contact dermatitis, contact allergy, detergents, fragrances, household cleaning products, quantitative risk assessment

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The world of chemistry contains a minority, but toxicologically important, category of substances, of either natural or synthetic origin, which possess the intrinsic capacity to cause sensitisation by skin contact [1, 2]. Prominent among the causative chemicals are organic molecules whose olfactory properties render them valuable as fragrances, but which also possess the capacity to induce contact allergy and to elicit allergic contact dermatitis (ACD) [3-7]. Consequently, it is essential that potential fragrance allergen hazards are identified and the risk that they present to human health is properly assessed and that that risk is adequately managed. That overall process has been the subject of review and commentary, demonstrating its evolution over a number of years [exemplified in 8-12]. However, the final proof of success is delivered via the experience from dermatological clinics and diagnostic patch testing [13].

In terms of hazard identification, predictive test methods in the guinea pig and in the mouse have been available for several decades [reviewed in 8, 14-16]. It is accepted that these methods are imperfect [17], but it is also the case that the method of first choice, the local lymph node assay (LLNA), is the only skin sensitisation assay to have been formally validated and shown to approach 90% accuracy for the prediction of human skin sensitisation hazards [18-20]. These methods demonstrate that many substances (with functional properties in a product formulation) also possess a degree of skin sensitisation hazard. Consequently, important emphasis is thrown on the aspects of risk assess-

ment and risk management in relation to (fragrance) contact allergy (induction) and allergic contact dermatitis (elicitation) [21, 22]. Regarding risk assessment, there are only two elements, measurement of the relative skin sensitising potency of an identified allergenic hazard and the integration of that information with quantitative data on skin exposure. Both of these aspects can be the subject of variation and uncertainty. For example, potency prediction from the current *in vivo* assays is a valuable source of information but is not entirely accurate [23, 24]. In addition, exposure assessment also represents an area where knowledge is improving, particularly for cosmetics [25, 26], but where there are also critical uncertainties, e.g. in the estimation of aggregated exposure from multiple sources [27, 28]. Finally, efforts on risk assessment, quite rightly, are directed towards prevention of the induction of (fragrance) allergy. However, given human heterogeneity, both in susceptibility to allergy and in patterns of product usage, the achievement of zero risk (of induction) is probably unattainable (and possibly associated with other, undesirable, consequences), which means that risk management measures to limit the risk of elicitation of allergy in those already sensitised may be required. This may require information on elicitation dose response that, currently, cannot be derived from predictive *in vivo* methods, but must be generated in clinical studies.

In this present work, attention has been directed towards fragrance exposure associated with the use of a variety of household products, including fabric washing, dish-

washing, hard surface cleaning and domestic maintenance, including air care. Existing examples of (quantitative) risk assessment for induction have been reviewed; new induction risk assessments are examined for other product types, using selected fragrance chemicals that are commonly found in the household product portfolio. How these assessments contribute to an aggregated view of exposure to individual fragrances also is considered. Lastly, existing understanding of elicitation dose response is reviewed, focusing on the extent to which household cleaning products may participate to the current morbidity of fragrance ACD. It should be noted that it is not the intention of this review to include occupational exposures but it is recognised that these can be of relevance clinically and must be considered in any holistic risk assessment.

Household cleaning products

Cleaning products for the home, often based on a combination of surfactants, oxidising agents and/or acids/alkalis, represent a diverse range of formulations with widely varying patterns of use. For many, skin contact is limited in duration and often may involve a diluted form of the product, whereas for some use may be frequent and might require the wearing of appropriate skin protection, not least to avoid the development of irritant contact dermatitis. In addition, various products may be used in combination, resulting in the potential for aggregated exposure with commonly used fragrance chemicals. Of course, it is not possible to generate a standard household cleaning product use (and therefore skin exposure) scenario, but in this section potential exposures are considered and defined so that risk assessments for the induction of contact allergy and elicitation of ACD can be completed.

Of course, exposure also depends on the levels and variety of sensitising fragrance chemicals that are used. The industry employs the following default, typical worst case, assumptions for three broad categories: household care and laundry products contain 1% fragrance; some continuous action air fresheners contain up to 50% or occasionally even higher (unpublished data). It is worth noting that there are a few highly concentrated detergents and fabric softeners where the fragrance concentration may be somewhat higher than 1%, occasionally up to approximately 3%. Individual components of a fragrance rarely exceed 10% of the fragrance compound, leading to a maximum concentration of an individual fragrance chemical of 0.3%. Some years ago, an analytical survey of the fragrance in household products indicated which substances were likely to be the most common (limonene and linalool) and showed that individual substance concentration only occasionally exceeded 0.1% [29]. The results of a more recent qualitative survey of 291 Italian household products were consistent with the earlier data [30]. Where a fragrance classified as sensitising to the skin is present in the product between 0.1% up to 1.0%, European chemicals legislation requires specific on-pack warning labels [31-33]. Were the substance to be present at 1% or above in the product, then the full labelling requirement for a skin sensitiser would be applied to the product [31-33]. In addition, specifically for 26 fragrance chemicals identified as potential sensitisers, the Detergents regulation requires mention of their presence on the labels of products

where their individual concentration is 0.01% or greater [32], by analogy to the requirements from the Cosmetics Regulations [34]. For several years, this has also assisted physicians to identify particular contactants and to determine the likely relevance of a positive diagnostic patch test.

Based on the above, the foundation of the assessment of the risk from product use is the actual skin exposure to individual sensitising fragrance substances which occurs, including the potential for exposure via the undiluted product or from secondary exposures, e.g. to fragrance residues on laundered fabrics.

Risk assessment for the induction of contact allergy

Prevention of the induction of contact allergy by skin sensitising chemicals is the principal focus of toxicological risk assessment for this category of products. If this is completed correctly, then the target of primary prevention will have been achieved. In the past, the risk assessment would generally have consisted of a comparative evaluation of potentially sensitising ingredients, perhaps followed by a human experimental study [9, 10]. However, in recent years, the approach to risk assessment for skin sensitisation has evolved to incorporate the type of practice used more widely in toxicology [11, 35-37]. It has been termed quantitative risk assessment (QRA) [11]. Now, whereas many practical examples of skin sensitisation QRA for fragrances and preservatives have involved personal care products [e.g. 11, 38-42], there have also been two publications which have detailed the application of QRA to household cleaning products, notably associated with fabric washing/conditioning [21, 43]. These latter works considered fragrance sensitisers as well as the transition metal allergens, nickel, chrome and cobalt, and identified safe exposure levels. The outcome of the work was consistent with what is expected more widely from fragrance allergy QRA, although it has to be recognised that some time may still be required for convincing evidence of the success of the application of QRA to be obtained [44].

The published risk assessments for fragrance allergens in household products concerned the risk of the induction of allergy from exposure to laundered fabrics [43]. The work concluded that the exposure levels were typically 2-3 orders of magnitude below the maximum safe level, an outcome consistent with industry experience of the absence of consumer complaints. A similar conclusion had been reached previously with transition metal allergens in household products, not only from laundered clothing, but also considering the conduct of hand laundry [11].

One of the fragrance ingredients commonly encountered in household products is citral, which imparts the sharp lemon/citrus aroma: "the cleaning power of lemons". It was found at up to approximately 0.1% in 25% of household products examined [29]. In the language of QRA, citral has a NESIL of 1400 $\mu\text{g}/\text{cm}^2$ [11], which in practice means that if one were to conduct a human repeated insult patch test (HRIPT) at this dose level, no induction of sensitisation would occur in a panel size of 100 subjects [11]. To make this figure more relevant to real life exposures, uncertainty

factors are applied, effectively reducing the NESIL by 1-3 orders of magnitude. To avoid a complex debate on the details of these uncertainty factors, for the purpose of this review, the highest possible value, 1000, has been used, a value generally higher than that deployed for a wide range of products, including cosmetics intended for direct contact with the skin [11]. Use of this very conservative factor would lead to an acceptable exposure level (AEL) of $1.4 \mu\text{g}/\text{cm}^2$. Considering direct skin contact from hand laundry and using the same exposure parameters as previously published [21], citral can be compared with chromium, which has a NESIL of $1 \mu\text{g}/\text{cm}^2$. Previous calculations for chromium demonstrated a large margin of safety in respect of its presence in a product at 1 ppm; simple arithmetic suggests therefore that citral, a substance with a more than 1000 fold higher NESIL, could be expected to be similarly safe if present in a product at 1000 ppm. In this context, it is worth noting that, in reality, the industry standard guidelines currently suggest a pragmatic limit for citral which is rather higher than this figure, as would be expected from use of a more typical safety factor [45].

Other commonly used household products comprise trigger sprays and wipes generally used for cleaning hard surfaces (kitchens, toilets, bathrooms) and air fresheners. These have been selected as examples of household products for which direct skin contact with the undiluted product is very likely to occur. That said, taking realistic examples is then instructive: the highest level found in one company for a trigger spray was 0.0152% citral in the final product. Then, using independent views of probable exposure, including a retention of 1% of the applied dose of product [46, 47], 16.2 g product use, and assuming all of this is deposited on the non-dominant hand with a ventral surface area of 215 cm^2 , leads to a dose per unit area of $0.113 \mu\text{g}/\text{cm}^2$. This is more than an order of magnitude below the AEL, even with a dozen uses (effectively using about two-thirds of a standard size of container!) the dose would only just begin to approach the AEL. Similarly, an instant action air freshener aerosol product composed of 0.05% citral, at a 1.5 g/sec spray rate, sprayed for 3 seconds twice a day, results in 9 g of product used per day and $4500 \mu\text{g}$ of citral discharged. If sprayed in a bathroom over a floor surface area of 4 m^2 , this results in a dose per unit area of $0.1125 \mu\text{g}/\text{cm}^2$. Even if we assume the entire product is transferred from the floor onto the skin and all of this penetrates through the skin, the consumer exposure level of citral in an air freshener product results in a 12-fold difference (i.e. lower) when compared with the AEL for citral. An instant action air freshener product is modelled here as it is expected to result in the highest level of exposure when compared to all other air freshener products. A similar type of calculation can be performed for the use of citral in a surface wipe. The highest level found in this product type in one company was 0.308% in the final product. Using the independent exposure parameters already published [46] leads to hand skin exposure of $0.067 \mu\text{g}/\text{cm}^2$, which compared to the AEL of $1.4 \mu\text{g}/\text{cm}^2$ is a safe level by some considerable margin. Use of 20 wipes in succession would accumulate the exposure to approach the AEL, assuming that successive wipes failed to remove any citral previously deposited on the skin.

The example presented above has been given because citral is relatively widely used in the product category under consideration, plus it is not as weakly sensitising in pre-

dictive tests as many of the other fragrances frequently used in household cleaning products [11, 29, 30, 37]. The most common fragrance ingredients in household products, limonene and linalool [29] have NESIL values approximately 10 fold higher (i.e. less sensitising) than citral. The consequence is that QRA calculations also indicate that even the highest use levels of these materials (1%) are very unlikely to lead to the induction of contact allergy. In this respect, it has also to be acknowledged that some fragrance allergens, including the two just mentioned, may be susceptible to air oxidation, with the consequent production of additional sensitising species, such as hydroperoxides [reviewed in 47-49]. Where this is known to be the case, appropriate use of antioxidant strategies in the formulation in combination with a substantial safety margin may be necessary to ensure product safety.

It is important to keep in mind two factors which will impact on the above. Firstly, the possibility of exposure to a specific fragrance allergen accumulating as a consequence of aggregate exposure from multiple products has not been addressed. Clearly, it is reasonable to assume that an individual may carry out laundry tasks, dishwashing and hard surface cleaning in combination (although such products may not necessarily use the same fragrances). The individual may well also use a skin moisturiser, although again, the fragrance may well differ. Secondly, the overall uncertainty factor applied in the calculations was 1000, whereas in reality, a value of 100 seems more likely to be chosen for household cleaning products, a view based on the practice already published for a wider range of product types [11, 21, 23, 37-40]. It is the opinion of the author(s) that these opposing factors (i.e. a very conservative uncertainty factor *versus* the potential for an increased risk from aggregated exposures) are likely to cancel each other out but proof of this can ultimately only be derived from an examination of the clinical evidence, which is discussed below.

Clinical evidence (induction)

The diagnosis of ACD involves combining information from the clinical history of a patient and the results of patch testing with suspect skin sensitisers [reviewed in 50]. However, although it is relatively common for a dermatologist to be able to identify the skin sensitisers - and the products(s) - involved in the elicitation of the current eczema, it is much less likely that the original inducing exposure source(s) can be determined. The likelihood that this can be done is generally highest for occupational ACD and it is probably lowest where the causative allergen is used in a wide range of products, such as is the normal situation with fragrance sensitisers. Consequently, properly documented evidence that skin sensitising chemicals, including fragrances, present in household cleaning products have been responsible for the primary induction of contact allergy, is extremely rare. This rarity could of course arise from a low level of suspicion in the investigative dermatology community but, of itself, that would also speak in favour of household cleaning products not being a primary cause of the induction of fragrance contact allergy. However, at least historically, a level of suspicion of the involvement

of household products in the causation of allergic contact dermatitis has existed [e.g. 21, 51, 52]

Two primary sources were inspected regarding the availability of clinical evidence of the induction of fragrance allergy by household cleaning products: standard textbooks on the subject of contact dermatitis and a wider published literature search via PubMed. Regarding the former, the encyclopaedic work of Dr Etain Cronin, published over three decades ago, mentions occasional incidences of fragrance allergy from two detergents, the main agent responsible being benzyl salicylate [53, 54]. Interestingly, this was the fragrance allergen found at the lowest frequency in a product survey [29]. The more recent standard texts were published in 2008 and 2011 [55, 56]. The earlier of these two publications suggests that perfumes play no significant role in hand dermatitis, certainly in respect of the primary induction of contact allergy [55]. In the most recent textbook, there is a comment concerning detergent products which indicates that it is the additives, rather than the surfactant agents, which should be suspected, although it notes that the frequency of contact allergy to this type of product is apparently often overestimated, a remark based on an extensive US survey concerning allergic contact dermatitis to detergents, which found only a single case that could be explained by fragrance allergy [57].

The online database PubMed was searched using combinations of the following terms: skin sensitization, contact allergy, allergic contact dermatitis, detergents, household cleaning and laundry. The results were inspected to remove material not relevant to the present review. Typically this was achieved by adding the term “fragrance” to the search. Thus for example a search with “skin sensitization” and “detergents” produced 10 hits; addition of the term “fragrance” reduced this to 0 (zero) hits. Contact allergy and detergents yielded 274 hits, reduced to just 21 by addition of the search term “fragrance”. Of these 21, only perhaps a quarter were relevant, of which some have already been referenced in this review [29, 53] or will be mentioned in the section that follows on the elicitation of ACD. Other search combinations gave only a few hits, e.g. “allergic contact dermatitis + household cleaning + fragrance” produced two hits, one the survey of Italian products already mentioned [30] together with an important publication on oxidised limonene [58]. This latter work identifies an issue for which a detailed discussion is beyond the scope of the present review. However, the production of more potently sensitising species by air oxidation from what are seen in their native form as weakly sensitising fragrance ingredients, such as limonene, geraniol and linalool [58-60], is an aspect of risk assessment which should not be overlooked. The fact that the quantitative risk assessment detailed earlier indicates a substantial margin of safety means that, even where oxidation does lead to the production of a more potently sensitizing chemistry, the low concentration/exposure that occurs will render the induction of contact allergy from this product type most improbable.

Clinical evidence (elicitation)

In contrast to the situation with the induction of contact allergy, it is much more likely that the sources of (fragrance) allergen exposure that are associated with the expression of

ACD can be identified. Of course, with widely used allergens, there may be many sources, which complicates the analysis. Having offered that caveat, the examination of the dermatological literature presented in the preceding section already demonstrates that there is little documentation indicative of an important role for fragrances in the expression of ACD in individuals who are already sensitised.

The most important skin site at risk of the elicitation of ACD in relation to household cleaning products is the hands, and this has been recognised in various reviews [61, 62]. The particular risk for this skin site arises from the multiple sources of exposure and the real possibility of concomitant cumulative irritant dermatitis. Despite this, clinical evidence of a problem is largely lacking. Consistent with this has been the outcome of clinical studies involving groups of individuals proven to be sensitised to specific fragrance chemicals, specifically hydroxycitronellal and hydroxyisohexyl cyclohexene carboxaldehyde (HICC) [63, 64]. In this work, the repeated immersion, over a 4 week period, of hand skin into solutions containing up to 250 ppm of the specific fragrance allergen in the presence of an anionic surfactant irritant failed to elicit any evidence of an allergic skin reaction.

In a separate investigation, the importance of fragrance residues on laundered fabric was investigated [65]. This clinical study involved 36 patients allergic to either isoeugenol or HICC, both recognised as relatively potent fragrance allergens of considerable clinical importance. Even under 48 hours of occlusion, fabric which was impregnated with either of these allergens at more than ten times the expected maximum level found on laundered clothing, failed to produce any evidence of an allergic skin reaction in these sensitised individuals.

The experimental data gives credence to the view expressed earlier, that the elicitation of fragrance allergy from exposure to household cleaning products, although possible, appears in practice to be relatively uncommon [56, 57]. Elicitation responses have been reported in association with occupational exposure, although again, these appear to be uncommon [66]. In addition, there have been very rare reports of airborne contact dermatitis to fragrance allergens in highly sensitised individuals [reviewed in 67][67]. This is consistent with the perspective that fragrance chemicals are intended to become airborne but are typically selected on the basis that low concentrations activate human olfactory senses.

Risk assessment for the elicitation of allergic contact dermatitis

Toxicological risk assessment for known skin sensitisers quite rightly places its focus on primary prevention of the induction of contact allergy (see above). However, where it is known that a substantial number of individuals already exist who are already sensitised, then it is appropriate to consider whether household cleaning products present a significant risk regarding the elicitation of ACD. In contrast to induction (see above), there is no standard predictive approach to the identification of a safe exposure level, nor can this be predicted from a knowledge of the relative potency for the induction of skin sensitisation [68]. Conse-

quently, risk assessment in this area has to be based largely on an understanding of the elicitation dose response characteristics for common contact allergens. Optimally, clinical studies of the type already mentioned in the preceding section can establish acceptable levels for individual fragrance components [63, 64, 66]. Unfortunately, until there is a broadly agreed protocol for such work, studies will remain of variable type and quality. In practice, they are likely only to be undertaken where there is a clear need to do more than accept an "administrative" limit, based on experience with other contact allergens, such as applied in current regulations [e.g. 33].

An example of the application of this risk assessment approach can be found in a publication which considered acceptably safe levels of nickel, chromium and cobalt in consumer products [21]. In this case, which included frequently used products intended for prolonged contact with the skin, and even for highly sensitised individuals with damaged/irritated skin, it was argued that a product level of 5 ppm would be expected to protect the overwhelming majority of those exposed and 1 ppm would essentially protect 100%. Of course, it is important to note that this related to adventitious content of these three transition metal contact allergens, not to their deliberate addition to the products. Adoption of this very stringent target for these important, strongly sensitising agents was based on the evidence of elicitation dose response studies, particularly for nickel, the single most frequent cause of allergy at that time [69]. Where detailed elicitation dose response studies do not exist (the situation for most allergens), the pragmatic view has been to inform consumers about the content of specific fragrance allergens when exceeding a limit of 100 ppm in association with products that normally have short term contact with the skin. An example of this is represented by the Detergents Regulation [32] and by the closely related requirement of the EU legislation concerning cosmetic products [34].

Conclusions

A number of fragrance ingredients represent an important cause of contact allergy in consumers [1-7]. Among these is a chemical with the INCI name hydroxyisohexylcyclohexene carboxaldehyde, but this has not been discussed in detail here because its use in household products is very low (approx. 5% of products sampled, compared to citral in 11%) [70]. It is relatively uncommon that the specific uses of products are directly implicated as the cause of the induction of sensitisation. This means that any use of fragrance in products needs to be considered carefully, in terms both of the risk of induction of contact allergy and also regarding the possibility of the elicitation of ACD in individuals who are already sensitised. In this paper, the clinical evidence for both the induction of contact allergy and the elicitation of ACD associated with non-occupational skin exposure to household cleaning and air freshener products has been reviewed. There is very little evidence that these products induce contact allergy. Furthermore, although there is some level of suspicion amongst many dermatologists that these products are capable of eliciting ACD, published evidence to this effect is largely lacking. This is despite the potential confounding factor that existing eczema has the potential

to predispose to ACD [71]. Support for this perspective also arises from a recently published German survey in which just 22 cases of confirmed allergic reaction were found to be associated with 6 years of sales involving a total of almost 10^{10} product units amongst a population of about 80 million individuals [72]. Also consistent with these conclusions is that the risk assessment for the induction of fragrance allergy from household cleaning products indicates that they should be safe in use, as demonstrated in this paper. Added to this is the evidence that the typical levels of incorporation of individual fragrance ingredients is sufficiently low that, at least for short term (rinse off) exposure, the likelihood of the elicitation of ACD is very limited. However, notwithstanding this generally positive conclusion, the frequency of contact allergy to fragrance, at least in the adult European population, is such that careful consideration must be given to each risk assessment, information on fragrance allergen presence above defined thresholds be provided to consumers and account taken of the possibility of the erosion of safety margins for individual products via aggregated exposure deriving from multiple product use, including the occupational use of products or in other sectors, such as cosmetics. Finally, feedback from dermatology clinic testing can be critical in identifying occasions where predictive toxicology may have underestimated the potential human risks [73]. ■

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