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Skin sensitization quantitative risk assessment: A review of underlying assumptions

David Basketter [a, *], Bob Safford [b]

[a] DABMEB Consultancy Ltd, Sharnbrook, Bedfordshire, UK
[b] B-Safe Toxicology Consulting, Rushden, Northamptonshire, UK

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ABSTRACT

Toxicological risk assessment informs exposure limits, so the potential for adverse effects to human health are minimised or avoided. For skin sensitisers, the situation is complicated by asymptomatic induction of contact allergy, a necessary prerequisite for expression of the disease allergic contact dermatitis (ACD). For fragrance skin sensitisers, the development of quantitative risk assessment (QRA) arose from the need to improve the extent to which contact allergy occurred. However, the perceived impact has been less than anticipated. Accordingly, the science and assumptions upon which QRA was founded have been scrutinised and proposals for refinement have been made. In addition, areas of uncertainty have been made explicit, e.g. inter-individual variability and the impact of concomitant disease, clarifying where numerical safety assessment factors are based on expert judgement. Also, the relatively small contribution of factors eg. age, gender, ethnic origin, vehicle matrix and skin permeability are highlighted by reference to the (now controversial) human experiments carried out in the second half of the last century. Adoption and widespread implementation of the current recommendations for QRA, taken in concert with improved assessment of aggregate exposure from multiple sources, should ensure that the frequency of contact allergy will decrease over the coming years.

1. Introduction

A substantial, divergent set of chemicals possess the intrinsic hazard of being able to induce the state of contact allergy in humans (summarised in Rietschel and Fowler, 2008; Johansen et al., 2011). Toxicologically, these chemicals are described as skin sensitizers and for decades have been identified by in vivo methods in the guinea pig or the mouse (Andersen and Maibach, 1985; Kimber and Basketter, 1992). Once an individual has become sensitized, i.e. has developed contact allergy, then given further and sufficient exposure they are inevitably at risk of the expression of the clinical disease we recognise as allergic contact dermatitis (ACD). The large majority of individuals who are exposed to skin sensitisers neither develop detectable contact allergy nor do they express allergic contact dermatitis (Krasteva et al., 2009; Basketter et al., 2011). However, with regard to fragrance ingredients, a recent epidemiological study indicates a prevalence of 0.9–4.1% of fragrance contact allergy in the European Union (Rossi et al., 2010; Naldi et al., 2014). The frequency of positive diagnostic patch tests in dermatology clinics has remained elevated, with 1 in every 7 patients positive in a recent report (Mann et al., 2014). Thus, dermal sensitization to fragrance ingredients remains a significant issue. However, the material that follows relates to all chemical skin sensitisers and not specifically to fragrance substances.

The processes associated with the risk assessment of skin sensitizing chemicals have evolved considerably in the last two decades. In part this has arisen because of the appreciation of the large variation in the intrinsic induction potency of skin contact sensitizers, covering approximately 5 orders of magnitude (Gerberick et al., 2005; Kern et al., 2010). In 2008, a proposal was made for the dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients (Api et al., 2008). The performance of the approach was then evaluated by retrospective analysis of clinical data (Api et al., 2010). It has subsequently been used to establish industry guidelines, for risk assessment and as a basis for risk management of fragrance ingredients in cosmetics and household products (Api and Vey, 2008). The existing QRA process defines an Acceptable Exposure Level (AEL) for daily consumer exposure, expressed in μg/cm^2, which is based on a weight of

* Corresponding author. DABMEB Consultancy Ltd, Sharnbrook, MK44 1PR, UK.
E-mail address: dabmebconsultancyltd@me.com (D. Basketter).

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evidence derived No Expected Sensitization Induction Level (NESIL), and to which various Sensitization Assessment Factors (SAFs) are applied. Although application of these SAFs allows for uncertainty between 1 and 1000, typically the range used is narrower, 30–300. The use of $\mu g/cm^2$ is based on the evidence that this measure represents the key metric governing the induction of skin sensitization (Kimber et al., 2008). The NESIL, derived by assessment of the weight of evidence (detailed in Api et al., 2008) represents an exposure level which, in a Human Repeat Insult Patch Test (HRIPT) should not induce skin sensitisation, and then uses this level as the point of departure for the risk assessment. The NESIL represents the highest dose that would not induce sensitization in 100 subjects under the conditions of HRIPT exposure. However, other limitations relating to the HRIPT have to be borne in mind: for example, even when it is actually carried out, there will often only be one dose tested, and the NESIL defined as this dose (assuming that the expected outcome, no evidence of skin sensitization, was observed). Thus the measured NESIL may well be lower than the actual threshold dose which just fails to induce skin sensitization. It is understood that the number of subjects in a typical HRIPT offers limited resolving power, such that use of the HRIPT for more general prediction of human safety is inappropriate (Basketter, 2009; Gefeller et al., 2013). Human heterogeneity, the great diversity of the chemicals and wide range of uses to which they are put, introduces complexity which needs to be considered within the risk assessment of potential sensitising ingredients. For this reason, SAFs are applied to the NESIL to derive an AEL that is relevant for the whole population, and encompasses all allergens and exposure situations.

The current approach to skin sensitization quantitative risk assessment (QRA) has been fully detailed elsewhere, including documentation of the underlying assumptions used in deriving the SAFs (Gerberick et al., 2001; Felter et al., 2002, 2003; Api et al., 2008). Since those publications, a significant new body of scientific, clinical and consumer use data has become available that permits verification and possible revision of parts of the assessment process proposed in 2008. A number of reviews have appeared (e.g. Friedmann and Pickard, 2010; Thyssen et al., 2012) that provide more detail on some aspects that we touch on here. However, the present paper endeavours to summarise available data in the context of sensitising fragrance ingredients used in consumer products, although the principles outlined hereafter could be extended assessing the risk of dermal sensitization due to other allergenic materials and in other exposure scenarios. Proposals made in this paper reflect the current state of knowledge, but are not represented as the ultimate definitive risk assessment procedure. It can be anticipated that further advances in knowledge will lead to additional improvements of this procedure. It is also recognised that while the aim of QRA is the prevention of induction of allergy, it is probably impossible to achieve this in the whole population and in all feasible exposure scenarios.

Finally, it is essential to be aware that this review does not address such aspects as the reliability of in vivo, in vitro or in silico predictions (e.g. as detailed in Thyssen et al., 2012). Neither, since the goal is to avoid the induction of contact allergy, does it consider matters concerning the elicitation of allergic contact dermatitis, except where these specifically enlighten our understanding of the variables associated with the induction of contact allergy, thus facilitating the conduct of a thorough risk assessment.

2. Background and definitions

Skin sensitizer: a chemical which possesses the intrinsic toxicological property (i.e. hazard) that with sufficient skin exposure in humans it can cause the induction of skin sensitization/contact allergy.

Contact allergy: the asymptomatic condition which an individual has when they are sensitized to a specific chemical, and which can be detected by a diagnostic patch test.

Diagnostic patch test: a clinical procedure designed to reveal whether an individual has contact allergy and who is then susceptible to the development of allergic contact dermatitis upon subsequent exposure to the allergen.

Allergic contact dermatitis (ACD): the eczema elicited following sufficient skin exposure in an individual who has contact allergy.

Frequency/prevalence: these and related terms endeavour to follow their standard usage in epidemiology.

Irritant contact dermatitis: an eczema clinically very similar to ACD, but of non-immunologic origin.

Hazard identification/characterisation: these terms refer specifically and exclusively to the elucidation of the intrinsic skin sensitizing properties of chemicals.

Risk assessment/characterisation: this term refers to the process by which skin sensitization hazard information is combined with exposure data to determine the likelihood of an exposure resulting in the induction of contact allergy and is thus the risk quotient of the induction of contact allergy and the exposure (both in $\mu g/cm^2$).

Risk management: this refers to the actions taken to control exposure to a skin sensitizer where the risk assessment indicates that the development of contact allergy would otherwise be likely to occur.

Atopic: a genetic disposition to develop an allergic reaction (allergic rhinitis, asthma, or atopic dermatitis) associated with elevated levels of IgE to an environmental antigen and especially one inhaled or ingested. (Note that this allergy mechanism is wholly different from that associated with the development of contact allergy.)

The primary aim of safety assessment must be to avoid the induction of contact allergy by skin sensitizers and it is to this end that the quantitative risk assessment approach discussed herein is directed. In some cases, it may also be necessary to identify safe exposure levels for sensitized individuals and ensure the implementation of adequate risk management control. This latter aspect falls outside the scope of this current review, which is directed wholly to that part of the risk assessment whose aim is to establish levels of exposure which are anticipated not to cause the primary induction of contact allergy. More important has been the development of a risk assessment strategy whose aim is to predict maximum safe exposure levels (with respect to the induction of contact allergy) using a transparent quantitative approach (Api et al., 2008).

In the QRA process previously published (Api et al., 2008) three SAFs were applied:

1. The Inter-individual SAF was applied to account for biological variability between individuals in the population at risk.
2. The Matrix SAF was applied to account for the influence of product formulation.
3. The Use SAF was applied to account for differences in normal use of the product, taking into account body areas of skin to which the product is applied and the frequency and duration of product use.

Normally, no inter-species factor is required since the NESIL is predicated on confirmatory studies in humans, or is based on an extrapolation from an in vivo murine threshold which can directly be used to predict the human NESIL (Griem et al., 2003; Basketter et al., 2005; Api et al., 2008; Safford, 2008; Safford et al., 2011, 2015; Api et al., 2014). Where there is specific knowledge of an