

Review

Can We Make Cosmetic Contact Allergy History?

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Abstract: Chemical allergy is of considerable importance to the toxicologist, who, amongst other things, has the responsibility of identifying and characterizing the skin (and respiratory) sensitizing potential of chemicals, and estimating the risk they pose to human health. Allergic contact dermatitis (ACD) is to a large extent a preventable disease. Although quantitative risk assessment (QRA) for contact allergy can be performed, it is reasonable to ask why the burden of the skin disease ACD appears to remain stubbornly high, and in particular, that the general level of ACD to sensitizing ingredients found in cosmetics has not fallen noticeably over recent decades; some could argue that it has increased. In this review, this conundrum is addressed, considering whether and to what extent the prevalence of cosmetic allergy is truly unchanged, whether the predicted test methods and potency estimations are sufficiently precise and how proposed changes to the QRA process (*i.e.*, cumulative exposure) may ameliorate the situation. Improved and more widespread use of risk assessment, better education of risk assessors, better post-marketing surveillance and monitoring of dermatology clinic feedback to improve QRA, all together could help to “make contact allergy history”.

Keywords: cosmetics; skin sensitization; contact allergy; allergic contract dermatitis; risk assessment

1. Introduction

At the core of toxicology lies the underlying premise that it is the dose that makes the poison, the original concept being attributed to Paracelsus or Philippus Aureolus Theophrastus Bombastus von Hohenheim [1]. This is certainly the case for skin sensitizing chemicals which have the capacity to induce contact allergy in humans and thereby lead to the disease allergic contact dermatitis (ACD)—the existence of dose–response relationships and the existence of thresholds has long been recognized [2–4]. Furthermore, it is true for this toxicology endpoint that the simple paradigm “risk = hazard × exposure” must apply. It is also important to recognize that skin sensitizers vary widely in their relative potency, with the consequence that the paradigms might better be represented as “risk = hazard (potency) × exposure”. Against this background must be set the reality that *in vivo* methods for the predictive identification of skin sensitizers have been available for many decades [5,6]. These methods are rightly regarded as generally predictive of human hazard [7,8] and for approaching 20 years, the lead method, the local lymph node assay (LLNA) has also delivered information on the relative potency of identified skin sensitizers [9–13]. This information has been combined with information on human exposure in a process termed quantitative risk assessment (QRA) [14–17]. Given this background therefore it is reasonable to ask why the burden of the skin disease ACD appears to remain stubbornly high, and in particular, that the level of ACD to sensitizing ingredients found in cosmetics has not fallen noticeably over recent decades. In the material which follows, this conundrum is addressed, considering whether and to what extent the prevalence of cosmetic allergy is truly unchanged, whether the predictive test

methods and potency estimations are sufficiently precise and how proposed changes to the QRA process, in particular the estimation of aggregate exposure to sensitizing materials, has the ability to transform the situation. Finally, attention is given to the importance of monitoring the impact of improvements to risk assessment and risk management via the day-to-day assessment of contact allergy undertaken by dermatologists performing diagnostic patch testing in their clinics [18].

2. Allergic Contact Dermatitis to Cosmetic Ingredients

Other contributors to this Special Issue of the journal will provide much greater detail on the topic of those ingredients in cosmetics which are most commonly associated with the causation of contact allergy and ACD, so these will not be reiterated here. However, it is important that we exemplify how the frequency of contact allergy to a range of cosmetic ingredients has been documented over a period of many years. In addition, it is also of note that the diagnostic patch testing series used to evaluate potential cosmetic allergy, while not entirely static, has not changed over perhaps half a century of patch testing history to such a degree that it is no longer recognizable. Both of these are generally consistent with the view that contact allergy to cosmetic ingredients is a continuing problem.

Perhaps it is most appropriate to start with the last mentioned point: the standard series for diagnostic patch testing has been in place for at least four decades. The initial and the current patch testing series are displayed in Table 1. There is considerable overlap, although perhaps only a few (sequence numbers 2, 9, 11, 14, 16 and 18) are specifically relevant for cosmetics. Notably, of the additional eight in the 2015 series, 75% (sequence numbers 21, 22, 25, 26, 27 and 28) are relevant to cosmetics, which of itself is suggestive of an increasing and/or increasingly understood, rather than a decreasing, problem. At the time of writing in December 2015, the additional cosmetic series from one supplier contains a further 57 patch test allergens. Some might well argue that such a substantial list is hardly consistent with a fully successful cosmetics risk assessment process.

Table 1. Standard Series in 1974 *versus* 2015.

No.	ICDRG 1974 ¹	European Baseline Series 2015
1	Potassium dichromate	Potassium dichromate
2	<i>p</i> -Phenylenediamine	<i>p</i> -Phenylenediamine
3	Thiuram mix	Thiuram mix
4	Neomycin sulphate	Neomycin sulphate
5	Cobalt chloride	Cobalt chloride
6	None	Benzocaine
7	Nickel sulphate	Nickel sulphate
8	Clioquinol	Clioquinol
9	Colophony	Colophony
10	Paraben mix	Paraben mix
11	Black rubber mix	<i>N</i> -Isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine
12	Wool alcohols (lanolin)	Wool alcohols (lanolin)
13	Mercapto mix	Mercapto mix
14	Epoxy resin	Epoxy resin
15	Balsam of Peru (<i>Myroxylon pereirae</i>)	Balsam of Peru (<i>Myroxylon pereirae</i>)
16	Carba mix	Butyl phenolformaldehyde resin
17	Ethylenediamine HCl	Mercaptobenzothiazole
18	Formaldehyde	Formaldehyde
19	Fragrance mix I	Fragrance mix I
20	Wood tars	Sesquiterpene lactone mix
21	Naphthyl mix	Quaternium-15
22	None	2-Methoxy-6- <i>n</i> -pentyl-4-benzoquinone
23	None	Methylchloroisoithiazolinone/methylisothiazolinone (MCI/MI)
24	None	Budesonide
25	None	Tixocortol pivalate
26	None	Methyldibromo glutaronitrile (MDGN)
27	None	Fragrance mix II
28	None	Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)
29	None	Methylisothiazolinone
30	None	Textile dye mix

¹ The original numbering of the 1974 series has been modified slightly to facilitate comparison with the current 2015 series.

As noted elsewhere in this issue, fragrances, hair dyes and preservatives are the most common skin sensitizing chemicals associated with the induction of contact allergy and the causation of ACD to cosmetic products [19]. Consequently, they provide useful markers for the prevalence of cosmetic allergy, since several of these have been tested routinely over a few decades. For example, the North American Contact Dermatitis Group (NACDG) has been reporting collated diagnostic patch test results for many years [20–25]. From this can be abstracted information such as that shown in Figure 1, which displays the overall incidence of contact allergy to three preservatives, the standard fragrance mix (FM1) and the main sensitizing hair dye ingredient, *p*-phenylenediamine (PPD). Each of these five contact allergy markers, all used in cosmetics, show variation over the approximately quarter century period covered, but they do not indicate any general downward trend. It might be reasonable to expect that since the QRA approach was developed specifically to assist with the high level of fragrance allergy, then this source of contact allergy should be on the decline. However, the prevalence of contact allergy to FM1 remained about 11% \pm 2% over the testing period shown.

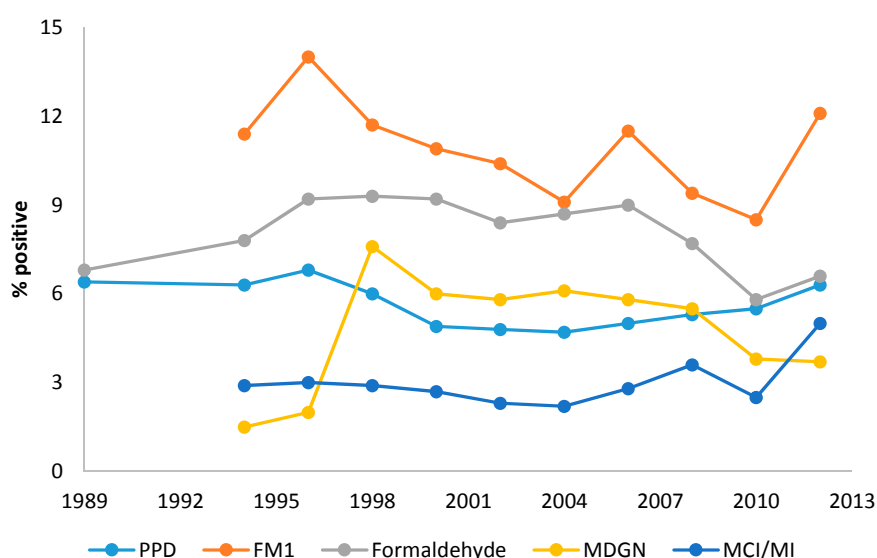


Figure 1. Contact allergy to markers of cosmetic allergy over the 25 years in the USA.

The experience from North America can readily be reproduced using dermatology clinic data from Europe. For example, a 17 year study in the UK showed a steady rate of approximately 8% \pm 2% positive to FM1 for the period up to 1996 [26]. Similarly, over a 21 year period, until 2011, a frequency of 9.1% positive to FM1 was reported from Belgium [27]. These latter authors further demonstrated that for most of the eight ingredients of FM1, despite some fluctuations, displayed no significant downward trend. Lastly, the latest results from the German group report a modest increase in the prevalence of contact allergy to FM1, with a rise to 9.6% positive [28]. Other regions of the world report even higher prevalence values, for example in Thailand a steady rate of just over 17% positive to FM1 was reported over a 10 year period to 2008 [29].

3. Hazard Identification and Characterization

In vivo methods for the predictive hazard identification of skin sensitizing chemicals have been available for decades [5,6]. Large databases of results have been published [30–33]. This body of work demonstrated that the great majority of all except the weakest human skin sensitizers could be identified, suggesting that their potential for causing adverse human health effects could be assessed and managed. However, in response to animal welfare (and other methodological) concerns, the murine LLNA was developed and this also permitted the relative potency of skin sensitizers to be measured as the EC3 value [9]. This was seen as a critical step forward in terms of hazard

characterization [11]. Obviously, this would not be a meaningful advance if relative potency in the mouse did not reflect the situation in humans. Fortunately, a series of comparative studies provided reassurance in this respect [12,13,34–37]; most recently, a series of approximately 130 substances have been characterized according to their relative human potency using, only human data, to provide an essential basis for comparative studies [38]. Despite this work, there remains a degree of uncertainty: the LLNA potency predictions are a valuable indicator, but like any aspect of predictive toxicology, they are not perfect. For example, some salicylates were over-predicted, whereas an aldehyde was under-predicted [13]. Furthermore, even a cursory examination of published correlations between LLNA EC3 values and skin sensitization thresholds in the human repeated insult patch test (HRIPT) indicates that despite a clear relationship, the “error bars” are wide (e.g., [37]). Of course, much of this uncertainty mainly derives from the poor quality of the human, not the toxicological, data.

The new reality for cosmetic ingredients and products is that the potential for skin sensitization must be determined without the use of animal methods. It is for this reason that several non-animal methods have been developed, validated and now appear either in OECD Guidelines or are progressing towards that endpoint (reviewed in [39]). It is not necessary here to review the detail of these methods, or how they may be used in combination to identify skin sensitization hazards as that has been reported and discussed extensively elsewhere [40–46]. What is clear from this is that two points emerge. Firstly, a degree of consensus is building that adoption of the majority conclusion from a combination of up to three *in vitro* assays representing the first three key events of the skin sensitization adverse outcome pathway is sufficient for hazard identification [43]. Secondly, it is recognized that this approach does not inform on the relative potency of skin sensitizers, such that an alternative strategy is required, around which there is a discussion of possibilities, but no degree of consensus has been reached, and today it is hardly possible to say if one strategy is better than the other. Examples of the latter can be found in several publications [43–47]. Potency might be estimated through Quantitative Mechanistic Modeling or alternatively through the application of Bayesian statistical approaches, the latter having given promising results for the prediction of four sensitizer potency classes, but not yet to predict a complete dose–response profile or EC3 values which remains a challenge [44,46]. Most of these efforts have been focused on the prediction of LLNA potency classes, since that is where the largest datasets of relative potency information can be found. However, the ultimate goal is prediction of relative potency in humans, not the mouse, so calibration of any approach really should be directed towards human data, such as that published recently [38]. In that work, six human potency categories were detailed. For practical purposes, each of these could (and should) be associated with a default NESIL value (the induction threshold adopted as the starting point for skin sensitization QRA). By focusing non-animal approaches on the prediction of a human potency category, much of the uncertainty associated with LLNA EC3 values and the extrapolation from mouse to humans could be eliminated. Further work is necessary, which is likely to require a better understanding of the driving forces responsible for *in vivo* potency before an effective *in vitro* strategy can be put in place [48].

4. Risk Assessment/Management

Current mechanistic understanding of allergy is such that it can be assumed that the development of sensitization (and also the elicitation phase) is a threshold phenomenon at both the individual and the population level. Prevention of sensitization in naive individuals, rather than elicitation in already sensitized persons, is a more suitable and health protective health endpoint. For those who are already allergic, allergen avoidance, assisted by proper product labeling is the only certain way to prevent the expression of allergic skin reactions.

The challenge is to identify levels of exposure below which sensitization will not be acquired. It has already been noted that the development of skin sensitization QRA offers the best method for determining human safety, that argument being based on a combination of long-standing and well founded toxicology approaches and supported by a substantial body of scientific understanding [14–16]. Evidence concerning the validity of this strategy has been presented [49]; many publications document

its application (e.g., [38,50–53]); situations where outbreaks of ACD have occurred further serve to demonstrate that failure to use QRA, or at least to use it properly, leads to problems (e.g., [54–56]). In addition, scrutiny of QRA and its scientific basis has continued, leading to proposals for refinement of the approach [57,58]. In the second half of 2015, this led to an updated version of QRA (termed QRA2.0) being presented to the European Commission for independent review.

Notwithstanding the above, the aim of risk assessment and risk management is to limit human exposure to skin sensitizing substances such that the induction of contact allergy is either eliminated, or reduced to an acceptable level. Where contact allergy in a population has not been controlled, then the aim shifts to limitation of the likelihood of the elicitation of ACD (e.g., [59,60]). Consequently, perhaps the real success embedded in QRA2.0 is the incorporation of aggregated exposure, a key contrast with the original QRA in which only the use of a skin sensitizer in single product situations was evaluated.

5. Summary

Ultimately, the real proof that skin sensitization QRA works can be derived only from human experience. In turn, that experience comes from not from the absence of evidence (e.g., cosmetovigilance), but from the active assessment of contact allergy [18,61]. Currently, and as detailed at the beginning of this article, that assessment shows that cosmetic allergy is significant in degree and is not falling (see Figure 1). QRA may well work in theory and the addition of aggregate exposure in QRA2.0 will improve matters, but formal assessment can only be meaningful if its use is widespread and consistent. The most probable area for that activity is fragrance allergy, where exposure from cosmetics dominates and the industry develops QRA-based guidelines, which are adopted and applied globally. This will also require a better training of risk assessors to make cosmetic contact allergy truly a subject of historical, rather than current, interest.

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