



Commentary

Quantitative risk assessment for skin sensitization: Success or failure?

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ABSTRACT

Skin sensitization is unique in the world of toxicology. There is a combination of reliable, validated predictive test methods for identification of skin sensitizing chemicals, a clearly documented and transparent approach to risk assessment, and effective feedback from dermatology clinics around the world delivering evidence of the success or failure of the hazard identification/risk assessment/management process. Recent epidemics of contact allergy, particularly to preservatives, have raised questions of whether the safety/risk assessment process is working in an optimal manner (or indeed is working at all!). This review has as its focus skin sensitization quantitative risk assessment (QRA). The core toxicological principles of QRA are reviewed, and evidence of use and misuse examined. What becomes clear is that skin sensitization QRA will only function adequately if two essential criteria are met. The first is that QRA is applied rigorously, and the second is that potential exposure to the sensitizing substance is assessed adequately. This conclusion will come as no surprise to any toxicologist who appreciates the basic premise that “risk = hazard x exposure”. Accordingly, use of skin sensitization QRA is encouraged, not least because the essential feedback from dermatology clinics can be used as a tool to refine QRA in situations where this risk assessment tool has not been properly used.

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1. Introduction

Many hundreds of chemicals have been shown to cause skin sensitization associated with allergic contact dermatitis (ACD). In common with other forms of allergy, ACD develops in two phases. In the first of these, the induction phase, skin exposure of a subject to an appropriate concentration of a contact allergen will result in specific immunological priming and the acquisition of skin sensitization (contact allergy). If the sensitized subject is exposed subsequently, at the same or a different skin site, to the same chemical allergen then the second or elicitation phase will be initiated. This is associated with the elicitation of an accelerated and more vigorous secondary immune response resulting in a local cutaneous inflammatory reaction that is described clinically as ACD (Kimber and Dearman, 1997).

There remains an important need to understand the hazards and risks associated with exposure to chemicals that have the potential to cause skin sensitization. For hazard identification there are available validated *in vivo* and *in vitro* methods. The use of these

methods to evaluate chemicals for the presence or absence of skin sensitizing potential is beyond the scope of this article and will not be explored further. The focus here is rather the assessment of the risk of skin sensitization. It is important to emphasize that it is the risk for the induction of skin sensitization (rather than the risk of eliciting a reaction in a previously sensitized subject) that is the primary purpose of the safety evaluation process. Risk can be defined most simply as the likelihood that, under a given set of circumstances, a hazard will translate into a meaningful adverse health effect.

Potency is inversely proportional to the amount of chemical required to initiate the pathway leading ultimately to an adverse event. That is, the lower the level of exposure required to induce an effect, the more potent the chemical. In the context of this article potency of a contact allergen describes the amount of chemical required to cause the acquisition of skin sensitization, and the relevant dose metric is the amount of chemical experienced per unit area of skin, e.g. $\mu\text{g}/\text{cm}^2$. An understanding of skin sensitizing potency is particularly important because it has been established that contact allergens vary by up to 5 orders of magnitude with respect to their relative skin sensitizing potency (Gerberick et al., 2005; Kern et al., 2010).

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The pattern of exposure takes into consideration the dose of chemical, the medium in which it is experienced, and the site, duration and frequency of contact. If these variables are understood it is possible, using the QRA approach, to establish whether certain conditions of exposure to a specified chemical allergen will result in the acquisition of sensitization. The QRA seeks to determine whether, and to what extent, anticipated patterns of exposure (in an occupational setting or among consumers) will be below the estimated threshold for induction of skin sensitization based on an understanding of sensitizing potency.

It is timely now to consider the value of the QRA paradigm, and the extent to which this provides a basis for accurate assessment of the risk of inducing skin sensitization. In this article the principles and practice of the QRA methodology will be considered, including the relevance of safety factors incorporated into the risk assessment process. In addition, evidence regarding the effectiveness of the QRA system will be reviewed and conclusions drawn about the general applicability of the method for evaluating risks of inducing skin sensitization.

2. Elements of QRA

Based upon the familiar tenet of toxicology that ‘the dose makes the poison’ a guiding principle is that risk is the product of hazard and exposure. However, until approximately the end of the last century risk assessment for skin sensitization had been conducted rather differently (reviewed in [Basketter et al., 1996](#)). That changed with the availability of a robust method for assessing accurately the skin sensitizing potency of contact allergens ([Basketter et al., 2007](#)). That approach was based on evaluation of dose-response relationships in the validated mouse test, the local lymph node assay (LLNA) ([Kimber and Basketter, 1997](#)). It was found that estimates of skin sensitizing potency as measured using the LLNA, correlated closely with clinical assessments of potency by practicing dermatologists, and the results of the Human Repeated Insult Patch Test (HRIPT) (e.g. [Gerberick et al., 2001a,b](#); [Basketter and McFadden, 2012](#); [Api et al., 2015](#)). Despite the inevitable variability associated with biological assays such as the LLNA (e.g. [Hoffmann, 2015](#)), the ability to measure with confidence relative skin sensitization potency, and the assurance that such measurements are relevant to humans, permitted the adoption of a classical approach to risk assessment for skin sensitizing chemicals that incorporated the following features:

1. A no effect level is derived from the predictive toxicology work
2. Appropriate safety factors are used to adjust the no effect level
3. The adjusted level is compared with the human exposure level

For the purposes of skin sensitization QRA, the no effect level derived from the toxicology assessment has been given a specific term - no expected sensitization induction level (NESIL) - where it is important to remember that this value is based on a weight of evidence approach using all available data followed by confirmatory HRIPT to establish the NESIL, and is not directly relevant to the end user. It is important to note that HRIPT testing is not an option for some regions. In such cases, small consumer studies may be employed to gain confirmation of the risk assessment before larger scale marketing of the ingredient evaluated.

In the original manifestation of QRA, three safety factors, termed Sensitization Assessment Factors (SAFs) were applied to the NESIL: a factor of 10 for human variability; a factor of between one and 10 to accommodate the uncertainty associated with differing exposure matrices; a factor also between one and 10 to accommodate other possible exposure conditions or characteristics not included in the actual exposure assessment for the end-user. Comprehensive

details of this first iteration of skin sensitization QRA were published several years ago ([Robinson et al., 2000](#); [Gerberick et al., 2001a,b](#); [Griem et al., 2003](#); [Felter et al., 2002, 2003](#); [Api et al., 2008](#); [Api and Vey, 2008](#)).

One essential element of skin sensitization risk assessment is that it is intended only to address the induction of skin sensitization (commonly termed contact allergy in humans). The sole intention is therefore to prevent induction. Where contact allergy has already been induced, then an entirely different process is necessary to establish safe exposure limits, and that is not a part of this commentary paper - which is not to say that defining safe exposure limits for the elicitation of contact allergy, i.e. allergic contact dermatitis, is unimportant, it is, but it is not part of QRA.

3. Highlights of QRA

In response to critical commentary concerning the original QRA approach, for example by the European Union Scientific Committee for Consumer Products (SCCS) (http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_135.pdf), the scientific principles underpinning this risk assessment method have been again subjected to detailed review ([Basketter and Safford, 2016](#)). The review resulted in proposals for some changes to the safety assessment factors as well as providing support for the inclusion of aggregated exposure assessment for the end user. Collectively those changes have resulted in a revised and updated QRA process.

3.1. Skin sensitization QRA in action

As already mentioned, the underlying principles of skin sensitization QRA are entirely congruent with the general principles and practice of toxicology. Furthermore, the aim of the risk assessment process is always to avoid the induction of skin sensitization in humans. Consequently, it is necessary to examine not only whether QRA follows standard toxicology principles, but also whether there is evidence that it is operationally effective. Several publications have exemplified the use of QRA, including for transition metal allergens ([Basketter et al., 2003](#)), for many preservative chemicals ([Basketter et al., 2008, 2010](#)) as well as for a number of fragrance sensitizers ([Gerberick et al., 2001a,b](#); [Corea et al., 2006](#); [Api and Vey, 2008](#); [Basketter et al., 2015](#)). All these examples have followed the original version of QRA and demonstrate, via retrospective analysis, that its rigorous application should lead to levels of exposure that are below those required for the acquisition of skin sensitization. Skin sensitization QRA has also been applied in the same manner to a substantial number of frequent sensitizers, leading to extensive revision of industry guidelines ([Api and Vey, 2008](#)). Nevertheless, there is good evidence that the frequency of contact allergy at least to fragrances and preservatives has not declined significantly, judging by clinical data up to the end of 2015 ([Basketter et al., 2015](#); [Basketter and Corsini, 2016](#); [Schwensen et al., 2015, 2016](#)). Of course, making an impact on the frequency of contact allergy in humans where there is a substantial existing population of individuals that are already sensitized is challenging, just as is any such demonstration of effects at an epidemiological level. What has caused particular disappointment though is that the introduction into the marketplace of a new preservative, methylisothiazolinone, has led to substantial epidemic of contact allergy ([Schwensen et al., 2015, 2016](#)). These matters have certainly been a key driver for the critical examination of the whole skin sensitization QRA process.

3.2. How is QRA best used?

Risk assessment in skin sensitization is founded on general

principles of toxicology, including most importantly dose-response relationships and exposure. The specific principles of QRA for skin sensitization have been defined clearly above and are designed to inform limits of exposure such that the potential for adverse effects is minimised or avoided (Robinson et al., 2000; Gerberick et al., 2001a,b; Griem et al., 2003; Api et al., 2008, 2010; Basketter and Safford, 2016). Years of experience have informed us that understanding the nature of consumer or occupational exposure to a new substance alone, or in a formulated product, together with knowledge of the material's allergenic potency, allows the development of risk assessments that protect individuals from developing contact allergy. As stated above, the risk assessment can be challenging if there exist a substantial population of individuals already sensitized to the ingredient and the exposure levels to elicit a response in these individuals is not understood well. Naturally, the robustness and reliability of risk assessments is dependent upon the quality of information available regarding patterns and extent of exposure and sensitizing potency. If that information is of low quality then of course it is possible that the risk assessment will be flawed with the opportunity for adverse health effects. However, if the input data are sound then experience indicates that the risk assessment will provide a reliable mechanism for protecting human health.

In practice, the first component for QRA for skin sensitization is the identification of the sensitizing potency of a given chemical defined via a no effect level considering relevant animal and human data in a weight-of-evidence (WoE) approach. This approach is referred to as the WoE NESIL. Experience has shown that contact allergens vary by 5 orders of magnitude with respect to their relative skin sensitizing potency (Gerberick et al., 2005; Kern et al., 2010), and therefore accurate information about potency is a critical element of an effective risk assessment. The LLNA has served us well for this purpose. However, it is sometimes necessary in characterizing potency to adopt a WoE approach that may incorporate data deriving from other animal models and/or (when available) human data (for instance taken from Human Repeat Insult Patch Tests; HRIPT). Although SAFs are used to account for any uncertainty in the risk assessment, having reliable potency data is critical for conducting a robust QRA. It is important to ensure that the experimental data being used are from well-conducted and well-controlled studies so that a reliable NESIL can be derived.

Once the best possible information is experimentally determined, or extracted from the literature, to establish a NESIL, it is essential to use expert judgment in addressing areas of uncertainty, specifically choosing numerical SAFs for deriving an acceptable exposure level (AEL). The NESIL identifies a level of exposure that should not permit the acquisition of skin sensitization.

For fragrance skin sensitization QRA, there has been a great deal of work done to help in identifying the best SAFs (Api et al., 2008; Api and Vey, 2008). Basketter and Safford (2016) have more recently performed a thorough review of SAFs to improve our understanding of them and their use for skin sensitization QRA. In setting the values of the SAFs, it is necessary to consider those aspects that may influence the degree of sensitization, and also to consider how these aspects differ between the experimental situation and consumer exposure to various product types. SAFs take into account uncertainties when extrapolating from the WoE NESIL underlying test conditions to the actual product in-use exposure conditions. Usually, they cover areas of uncertainty by values from 1 to 10 for: (a) inter-individual variability, accounting for susceptibility differences caused, among others, by age, sex, race, genetic factors and compromised skin, (b) product matrix, i.e., other components causing skin irritation or enhanced skin penetration, and (c) product use patterns, accounting for factors affecting human exposure, such as use frequency, occlusion and dermal integrity.

These SAFs have been applied e.g. in QRAs for nickel, chromium and cobalt as well as for preservatives and fragrance ingredients (Gerberick et al., 2001a,b; Basketter et al., 2003, 2008; Api et al., 2008).

The second component of the QRA process is the quantification of the actual consumer exposure to the chemical of interest (Consumer Exposure Level, CEL, expressed as dose per unit area). Thus, the successful development of a sound QRA depends on an accurate identification of the sensitization potency under hazard assessment conditions as well as a detailed knowledge of the consumer exposure under in use conditions (Gerberick et al., 2001a,b; Griem et al., 2003; Basketter et al., 2002, 2005). Determining consumer exposures with accuracy can, however, be very challenging, and getting them wrong may have important consequences for QRA with potentially unfavorable outcomes. Recently, Goebel et al. (2010) used an adaptation of a skin penetration model to refine the way the consumer exposure to a hair dye ingredient is evaluated. The approach is designed to determine the relevant levels of actual exposure in the context of skin sensitization to hair dyes and is referred to as the measured exposure level (MEL). As the applied hair dye formulation is washed off the skin surface after 30 min by removing the surface excess whereas the experimental measurements continue for 24 h, the MEL represents the actual dose theoretically available for allergy induction under hair dyeing conditions, i.e. the amounts on/in the skin surface (i.e. stratum corneum (SC)) and the bioavailable amounts (i.e. living skin and system). In a subsequent paper (Goebel et al., 2012), the authors introduced a direct comparison of the NESIL with the MEL as a simplified approach that allows an appropriate estimation of the potential skin sensitization risk associated with hair colorants. This concept has been applied here to the common hair dye ingredients para-phenylenediamine (PPD) and resorcinol as proof of concept exercises to determine whether this simplified approach is appropriate for such products. Just as important as it is for determining a robust NESIL, it is critical that any experimental exposure data used are obtained from well-controlled and reproducible experiments. Going forward it will be critical to determine aggregate dermal exposures when conducting QRA for skin sensitization. This is especially true when evaluating materials where consumers can be exposed to the same ingredient in multiple products such as fragrances (Nijkamp et al., 2015; Safford et al., 2015).

3.3. How do we know QRA works?

The only way to know with any certainty whether if a skin sensitization QRA for a new ingredient has been successful, and has not resulted in consumers developing ACD, is to put in place and review carefully a rigorous post-market surveillance program (Gerberick and Robinson, 2000; Api et al., 2008). The skin sensitization risk assessment process does not, and must not, end with the decision to market the product. Until data can be obtained from consumers to substantiate the risk assessment it is only a theoretical exercise.

Cosmetovigilance programs can be very helpful in signalling problems in the marketplace when new materials are introduced, or existing chemical ingredient limits are changed. Of course, programs established by industry need to be designed such as to ensure that all relevant information (including the product type, usage and reported adverse events etc) is captured that could identify whether there an emerging problem in the marketplace. The SCCS has indicated in a draft opinion that cosmetovigilance programs have limitations, including their lack of sensitivity for detecting some problems in the marketplace (SCCS/1557/15). There is no doubt there can be limitations in data deriving from such programs, but that does not diminish at all the importance of

having in place robust surveillance programs.

Another approach that can be used to obtain relevant skin sensitization data among consumers is the conduct of diagnostic patch test surveys with relevant controls, and the use of questionnaires about skin effects among consumers who have used the product compared with control subjects (non-users) matched for age, gender, and other relevant factors. These data are useful not only for confirming the validity of the risk assessment, but also for the early detection of potential problems. A post-market monitoring program provides both ongoing reassurance of product safety, as well as providing additional benchmark data for comparison with other ingredient and product initiatives that follow. In situations where there will be new materials introduced at high usage levels it may be appropriate to establish specific diagnostic patch testing programs within dermatology clinics in the regions to monitor the prevalence of ACD. From a very general perspective, the purpose of conducting skin sensitization risk assessments is to prevent disease (in this case ACD). If a high incidence of cases of ACD is found in the population then it is clear that measures need to be taken to remove or modify exposures to the offending material in the interest of public health to prevent disease.

4. Summary

Fundamentally practicing toxicologists follow a simple paradigm: risk = hazard x exposure. Of course, the reality is rather more complex, and for skin sensitization not only is the hazard identified, but it is quantified in terms of relative potency that can be thought of as a hazard characterization. This information is then combined with an assessment of pattern and levels of exposure to determine whether there is a likely to be a risk to human health. Probably unique to skin sensitization among other end points in toxicology, a steady stream of feedback comes from dermatology clinics around the world concerning the acquisition of contact allergy to skin sensitizing substances. Such clinical feedback, along with exposure understanding, provides toxicologists with invaluable information on the legitimacy or otherwise of assumptions that have been made in developing a risk assessment. In principle the QRA approach should work for occupational assessments, the key factor being the need to understand fully the exposure that will occur in this setting.

Naturally, just as with computer systems, skin sensitization QRA can suffer from the “rubbish in, rubbish out” phenomenon. Moreover, a QRA can be conducted perfectly, but if the risks identified as a result of the assessment are not managed effectively, then dermatology feedback does not apply to the QRA itself. Thus, the essential requirements for the avoidance of future epidemics of contact allergy are that the QRA methodology is used rigorously, begins to incorporate aggregate exposure to the particular sensitizer under examination, and that it is adapted, if and when necessary, based on feedback from human experience gathered by the dermatology community. Finally, although not intrinsic to the QRA itself, it will be important to ensure that the whole process is able to accommodate the replacement of *in vivo* methods with the new non-animal alternatives.

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Transparency document

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