

Review Article

Proactive surveillance of contact allergies: an important component of the risk management strategy for skin sensitizers

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Risk assessment serves to ensure that dermal exposure to skin sensitizers does not result in the acquisition of allergic skin disease. Traditionally, the approach adopted was one of comparative analysis, involving benchmarking against other allergens of known potency. More recently, efforts have been made to embrace a quantitative risk assessment (QRA) approach. However, the accuracy of any risk assessment is reflected in the extent to which it meets the fundamental objective stated above. Thus, clinical experience is of key importance. There exists the possibility for the originators of risk assessments relating to chemicals that possess skin-sensitizing potential to work directly with the clinical community to proactively obtain this experience through specific surveillance programmes. This forms the focus of this review article. The current status of the QRA approach is considered initially. A recently published example of one such surveillance programme that was undertaken as a collaborative initiative between industry and the clinical community is then reviewed. Finally, a possible strategy for the future is presented, in which it is suggested that surveillance strategies might be deployed in certain situations as an adjunct to the initial risk assessment. It is hoped that such a framework might further improve the efficacy of future approaches to skin sensitization risk assessment.

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Risk assessments serve to ensure that human exposure to skin sensitizers is carefully managed in accordance with their sensitizing potency. Over the years, much effort has been devoted to refine methods capable of informing this latter parameter. For example, the development of the mouse local lymph node assay (LLNA) has made it possible to identify skin-sensitizing hazard and to quantify relative potency to a greater extent than was ever previously possible with predictive methods such as the guinea-pig maximization test (1). Taken together with accurate information regarding predicted exposure, such data can be used in the context of risk assessments that serve to prevent the acquisition of allergic skin disease.

Traditionally, the risk assessment approach adopted was one of comparative analysis, involving benchmarking against other allergens of known potency that are used in similar product types. More recently, efforts have been made to consolidate this with a quantitative risk assessment (QRA) (2).

QRA for Skin Sensitization

Central to the QRA is the derivation of a no expected sensitization induction level (NESIL), which represents the threshold (expressed in terms of dose per unit area) for the induction of sensitization in a human experimental exposure model such as the human repeat insult patch test (HRIPT). The demonstrated correlation between EC₃ values (the concentration of test material required to give a threefold increase in lymph node cell proliferation when compared with a concurrent vehicle-treated control) in the LLNA and thresholds for the induction of sensitization in the HRIPT has made it possible to predict a NESIL using LLNA data (3), although a confirmatory HRIPT may be appropriate to demonstrate that the predicted concentration is indeed below the threshold for the induction of sensitization. This NESIL is then translated into an acceptable exposure level (AEL) by dividing it by the product of 3 sensitization assessment factors (SAFs), the scientific rationale for which has been discussed previously

(4). These seek to represent semiquantitatively sources of uncertainty that must be considered when relating data obtained in a controlled manner in the human experimental exposure model to consumer use of the material in a particular product type. The 3 SAFs applied represent uncertainties associated with the following: (i) interindividual variability (the intended consumer population will probably exhibit much greater diversity than the limited study population in respect to variables that contribute to the acquisition of sensitization – a standard value of 10 is applied here), (ii) matrix differences (the vehicle system used to deliver the test material in product use may be different from that which was used in the human study – a value between 1 and 10 is applied here, based upon expert judgement), and (iii) exposure considerations (the site of exposure through product use may be considered more susceptible than the skin of the upper arm often used in the HRIPT – a value between 1 and 10 is applied here, based upon expert judgement). The product of these 3 factors can range from 10 to 1000.

Thus, the AEL (also expressed in terms of dose per unit area) should represent a conservative estimate of the concentration of a material that could be incorporated in a given product type without inducing sensitization. This value can then be compared with the actual consumer exposure level (CEL) to the material from product use (also expressed in terms of dose per unit area). In order to avoid skin sensitization, CEL should be lower than AEL.

There are a number of published examples in the literature in which this QRA approach has been deployed. Gerberick et al. (5) considered the use of cinnamic aldehyde in 2 hypothetical product use scenarios. This analysis suggested that a leave-on eau de toilette product containing 1000 p.p.m. cinnamic aldehyde would present an unacceptable risk of induction of skin sensitization. By contrast, the use of cinnamic aldehyde at the same levels in a rinse-off shampoo product was considered to pose an acceptable risk of induction of sensitization. Corea et al. (6) also deployed the QRA approach in the context of fragrance allergy. This study suggested that the risk of inducing sensitization to fragrance materials via exposure to washed fabrics is extremely low. More recently, Basketter et al. (7) performed retrospective QRA analysis on 4 preservatives (formaldehyde, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), imidazolidinyl urea, and 3-iodo-2-propynyl butyl carbamate) in 5 product types (shampoo, face cream, non-aerosol deodorant, body lotion, and lipstick) and demonstrated that, for certain preservative/product type combina-

tions, actual exposure through product use was greater than the ideal level (i.e. $CEL > AEL$). This outcome was considered consistent with the clinical picture (8). It is important to keep in mind that the above examples represent hypothetical or retrospective uses of QRA, and the efficacy of this approach will also require assessment of its use prospectively to establish AELs for new materials shown to be skin sensitizers or for known skin sensitizers deployed in new product types.

New risk assessment approaches such as this serve to illustrate, in a quantitative way, the relationship between an AEL for a material with skin-sensitizing potential and the actual level of the material delivered through product use (CEL). The objective being to ensure that CEL is lower than AEL. They also seek to provide a more accurate and transparent assessment of the risk associated with skin-sensitizing chemicals (9). Nevertheless, as the ultimate goal of risk assessment is to prevent the acquisition of allergic skin disease, its efficacy or otherwise can only be obtained through clinical experience. Historically, often there has been a passive reliance on the clinical community to obtain and publish this experience. However, there are examples where the originator of the risk assessment and the clinical community have engaged in collaborative initiatives to obtain and publish this knowledge. One such example is reviewed below.

Proactive Surveillance: Polyhexamethylene Biguanide

While proactive surveillance was deployed as part of the complex risk management programme associated with MCI/MI (10–13), the focus of this article is the use of one such strategy to support a very focussed risk assessment. This relates to polyhexamethylene biguanide hydrochloride (PHMB), a cationic polymer mixture that has been used for many years as a water disinfectant in the treatment of swimming pools (14). Annex VI of the European Cosmetics Directive 76/768/EEC lists PHMB as a preservative option, with a maximum allowed use concentration of 0.3% (15). Data from predictive testing showed that PHMB is a weak skin sensitizer (16), and an initial risk assessment indicated that the use of this antimicrobial at lower levels (<0.2%) could be extended to include underarm deodorants. To consolidate the specific risk assessment supporting the use of PHMB in this product type, a strategy also was deployed to monitor the ongoing frequency of PHMB sensitization and to determine whether the use of PHMB in underarm deodorants could be identified as a likely causal exposure in any sensitized individuals. The

first data relating to the frequency of PHMB sensitization were generated in 1998 by St. John's Institute of Dermatology (London, UK) (17) and a larger multicentre study conducted by the Information Network of Departments of Dermatology (IVDK; Göttingen, Germany) (18–20). As the PHMB risk assessment was relevant for both these geographical locations (i.e. both were exposed populations), these studies provided a baseline frequency of PHMB sensitization before its significant use in the scenario supported by the risk assessment in question. In the initial St. John's study (17), only 2 patients ($n = 374$) were found to exhibit positive patch test reactions to PHMB 2.5% aq. Similarly, the larger study conducted by the IVDK (18) identified only 6 patients ($n = 1554$) with positive patch test reactions to PHMB 2.5% aq. This initial series of data suggested that the baseline frequency of PHMB sensitization was very low, both in the UK and in Germany (0.5% and 0.4% for St. John's and IVDK, respectively). The significant majority of reactions were weak, and relevance was only considered likely in a single patient (a hospital cleaner who used a disinfectant containing PHMB). These data suggested that PHMB may not be a relevant contact allergen (18).

In order to obtain proactively the corroborative clinical data to consolidate the initial risk assessment, a subsequent multicentre study was initiated in 2005 with the IVDK (21). In this most recent study ($n = 1974$), only 9 patients (0.5%) were found to exhibit positive patch test reactions to PHMB 2.5% aq. Again, the majority of positive reactions were weak. Thus, when considered together, the data generated since 1998 (summarized in Table 1) suggest that the frequency of sensitization to PHMB has remained low and stable despite the use of PHMB in underarm deodorants. Furthermore, no evidence of axillary dermatitis was presented among the PHMB-positive patients, and occupational exposures were considered the most probable cause of sensitization (21). This data

set was considered to represent a valuable corroborative supplement to the original risk assessment.

Proactive Surveillance: A Potentially Important Future Component of the Risk Management Process?

This example represents one of the published studies in which industry and the clinical community have worked together formally to proactively generate sensitization prevalence data to support a very focussed risk assessment. While the value of any such study is dependent upon judicious data interpretation and subsequent decision making, it is suggested that such a collaborative approach can represent an important adjunct to the initial risk assessment. Of course, such a proposal must in no way obviate the requirement for the highest standards of accuracy from the initial risk assessment and, as discussed previously, there are ongoing efforts to advance this area (2, 4–7). Rather, the intention is to suggest that by integrating risk assessment with proactive surveillance in certain situations, it becomes possible to obtain (or otherwise) the necessary corroborative clinical experience in a controlled and expeditious manner. Figure 1 shows a schema for a possible approach for integrating risk assessment with proactive surveillance. The key stages are described as follows:

- (A) Hazard (potency) data. The risk assessment requires data relating to the relative skin-sensitizing potency of the material in question. At present, this is typically obtained initially in the LLNA (1) in the form of an EC3 value. The EC3 value can be used to predict a NESIL, expressed in terms of dose per unit area (3). As discussed previously, a confirmatory HRIPT may be considered appropriate to demonstrate that the predicted concentration is indeed below the threshold for the induction of sensitization. The NESIL forms the basis of the QRA.
- (B) Existing clinical data. If the substance in question is already in use and there exists evidence of sensitization in a consumer or occupational setting, this must also contribute to the risk assessment. Consideration should be given to the likely causal exposure historically and how this compares to the exposure being considered.
- (C) Exposure data. Anticipated exposure to the material from product use is considered. For QRA, this is calculated and expressed in terms of dose per unit area.

Table 1. Proactive surveillance of sensitization to PHMB. Summarizing the outcome of studies undertaken since 1998. Data taken from references McFadden et al. (17), Schnuch et al. (18), and Schnuch et al. (21)

	Positive patch test reactions to 2.5% PHMB		
	St. John's, 1998	IVDK, 1998	IVDK, 2005
Population size, n	374	1554	1974
Total positive	2	6	9
% Positive	0.5	0.4	0.5

IVDK, Information Network of Departments of Dermatology; PHMB, polyhexamethylene biguanide hydrochloride.

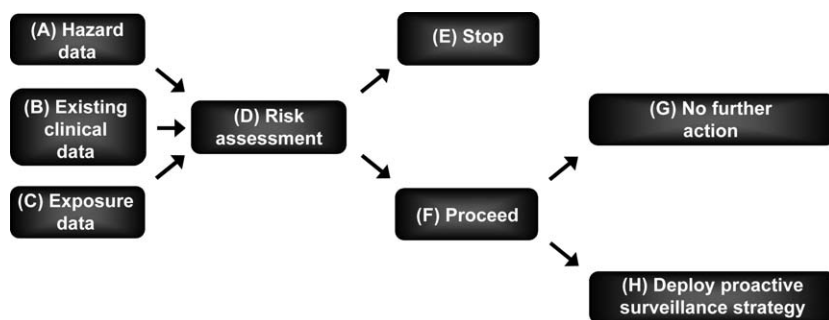


Fig. 1. Schematic showing how proactive surveillance of contact allergies may be integrated as a strategy to support risk assessment.

- (D) Risk assessment. Data from A, B, and C contribute to the risk assessment. This will involve the QRA and comparative benchmark considerations.
- (E) Stop decision. The risk assessment is unfavourable and suggests an unacceptable risk of sensitization.
- (F) Proceed decision. The risk assessment is favourable, and the risk of sensitization is thus considered minimal. There may also exist rare situations in which a decision is eventually made to proceed even when the initial risk assessment is unfavourable. It is an unfortunate fact that there often exists overlap between the levels of materials (such as certain preservatives) that are required for efficacy and those capable of potentially causing skin sensitization. It is thus possible that similar conflicts between levels required for efficacy versus those considered to be below the threshold for the induction of sensitization will present themselves again in the future. In such situations, risk/benefit considerations may follow. These considerations are extremely complex and influenced by myriad factors, many of them political. It is not the intention of this article to progress that debate.
- (G) No further action. It is anticipated that in the vast majority of cases, it may be prudent to proceed without further action (for example, when predicted exposure to the material is substantially lower than that considered acceptable).
- (H) Deploy proactive surveillance strategy. In rare cases, further proactive initiatives may be deployed in collaboration with the clinical community (for example, when there does not exist a substantive between the predicted exposure to the material and that considered acceptable). This could take the form of a multicentre surveillance programme to confirm that the use of the material considered in the original risk assessment has not caused allergic contact

dermatitis. If it is suspected that there may already exist rare cases of sensitization to the material as a result of significantly higher exposures in the past, it may be prudent to establish initial baseline data and to follow this up for comparison some years after launch.

Proactive Surveillance: Key Considerations

If such a proactive surveillance strategy is thought appropriate, what are the key considerations in terms of design? Many distinguished experts have previously defined those criteria that should be considered when designing multicentre studies to determine and/or compare the prevalence of sensitization to a given chemical. The key areas are highlighted below, and the reader is referred to the original articles for a more detailed commentary (13, 22–26).

- (1) Patch test concentration. An appropriate patch test concentration should be defined and adopted by the participating clinics. This should allow as far as possible the separation between genuine allergic skin reactions and irritant responses. The potential for active sensitization during the patch test procedure also should be considered, especially given the large numbers of patients who may be assessed as part of such a multicentre study.
- (2) Rechallenge. Confirmation for an initial positive patch test is often followed by rechallenge in which the test material is reapplied.
- (3) Relevance. Emphasis is placed upon sensitizations that are relevant to the presenting dermatitis. Although not performed in the context of the PHMB example described previously (21), this often involves provocative use tests. Individual patient history should also be considered.
- (4) Study size. An accurate assessment of sensitization prevalence requires a sufficiently

large population size. If the objective ultimately is to compare prevalence data, efforts should be made to ensure that comparable population sizes underpin each study.

- (5) Study period. Such studies are typically required to progress for 6 months or more. It has been reported that a short study period of only a few months 'does not permit extrapolation because it does not exclude the vagaries of referral, natural and random peaks and troughs, seasonal differences, and other artefacts' (25).
- (6) Entry criteria and test population. When seeking to compare prevalence data, it is important to ensure that the characteristics of each test population are similar. To quote from Aberer and Holub (26), 'testing any eczema patient in a skin clinic cannot be compared to testing patients with facial dermatitis in a patch test clinic; data from a rural area may differ from those from heavily industrialized areas'.

Collectively, the above considerations seek to ensure that data relating to clinically relevant sensitization are obtained using a defined test system in a sufficient and uniformly defined test population. Undoubtedly, the extent to which certain of these principles will need to be adopted will probably depend upon the complexity of the hypothesis being tested. Nevertheless, it is prudent to consult the relevant literature (13, 22–26), much of which was published as a result of the controversy associated with reconciling the observed variations in MCI/MI sensitization prevalence in the late 1980s and early 1990s.

Concluding Remarks

Risk assessment serves to prevent the acquisition of allergic skin disease. Progress continues to be made in the area of skin sensitization risk assessment, and the current status of the QRA approach has been reviewed herein. Nevertheless, the accuracy of risk assessment is ultimately reflected in clinical experience. There are published examples where industry has proactively engaged with the clinical community to obtain this experience in the form of large multicentre studies to assess the frequency of sensitization to specific materials. Here, one such example has been reviewed in which corroborative support was obtained for a very specific risk assessment relating to the use of PHMB at low levels in an underarm deodorant. It is hoped that this example demonstrates the potential value in adopting such approaches for specific

scenarios. Finally, a proposal has been presented as to how such strategies might be integrated with risk assessment in the future.

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