

Review

Allergic contact dermatitis

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Abstract

Allergic contact dermatitis (ACD) is a common occupational and environmental health issue. In common with other forms of allergy the disease progresses in two stages; an initial phase during which sensitization is acquired, followed later (after subsequent exposure to the same chemical allergen) by elicitation of a cutaneous inflammatory reaction. The development of skin sensitization is associated with, and requires, the activation and clonal expansion of allergen responsive T lymphocytes and it is these cells that orchestrate the cutaneous allergic reaction. In recent years, much has been learned of the characteristics of immune responses to skin sensitizing chemicals and of the roles played by dendritic cells, cytokines and chemokines. Some of the more interesting cellular and molecular mechanisms are reviewed briefly in this article. A more detailed appreciation of responses induced by chemical allergens has in turn facilitated the design of novel approaches to the toxicological evaluation of skin sensitization. Real progress has been made, not only in the development of improved methods for hazard identification and characterization, but also in the application of new paradigms for risk assessment. The newer methods now available and the opportunities that exist for further advances are considered. Finally, progress has been made in the characterization of skin sensitization in humans and in the clinical management of ACD. This article seeks to consider skin sensitization and ACD in holistic fashion, bridging experimental observations with clinical disease and basic mechanisms with practical toxicology. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

A working definition of immunotoxicology is the study of adverse health effects that may result from the interaction of xenobiotics with the immune system. In this context allergic contact dermatitis (ACD) can be regarded as being the most frequent manifestation of immunotoxicity in humans; it is a common occupational and environmental health issue and

many hundreds of chemicals have been shown to cause skin sensitization (1). In common with other forms of allergy, ACD develops in two phases which are defined operationally as induction and elicitation. Induction of skin sensitization is initiated following topical exposure of a susceptible subject to amounts of the chemical allergen sufficient to induce a cutaneous immune response of the necessary vigor. This immunological priming results in sensitization and if the now sensitized individual is exposed subsequently, at the same or a different skin site, to the inducing chemical allergen then a more vigorous secondary

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immune response will be provoked at the point of contact. This in turn initiates the cutaneous inflammatory reaction that is defined clinically as ACD.

Here we consider the following aspects of ACD: the immunological mechanisms of skin sensitization and contact hypersensitivity, toxicological evaluation in the context of hazard identification and risk assessment and clinical aspects of the disease.

2. Mechanisms of skin sensitization and allergic contact dermatitis

Contact allergy is considered to be a form of delayed type hypersensitivity. The induction of sensitization and the elicitation of allergic contact reactions are dependent upon, and are orchestrated by, T lymphocytes. The cellular and molecular mechanisms that initiate and regulate T lymphocyte responses to the inducing chemical allergen have recently been considered in detail elsewhere [1–5] and a similarly exhaustive survey of the relevant immunological processes is beyond the scope of this article. The intention instead is to highlight some features of special interest in the context of a brief overview of the sensitization and elicitation processes.

2.1. The chemical allergen

Chemical allergens are haptens and as such are unable themselves to stimulate directly an adaptive immune response. Consequently, immunogenicity must be acquired by stable association with protein and the formation of hapten–protein conjugates [6]. It is assumed that in many instances it is the hapten–protein conjugate that is recognized and processed for subsequent presentation to the immune system in a manner analogous to the processing of foreign protein [7]. However, this may not always be the case and it is possible that hapten will also bind directly to peptides associated with major histocompatibility gene products. In either event, it is clear that for sensitization to proceed a chemical must be inherently protein-reactive or must be metabolized to a protein-reactive species. Indeed, constitutive or inducible protein reactivity forms the basis for many approaches to definition of structure–activity relationships in skin sensitization.

2.2. Allergen exposure, processing and transport

For a cutaneous immune response to be induced, the chemical allergen must gain access to the viable epidermis. In practice, this requires that the chemical has the physico-chemical properties necessary for passage across the *stratum corneum*. Once entry into the viable epidermis has been achieved, and protein adducts have been formed, there is a need for antigen processing. This is primarily the responsibility of epidermal Langerhans cells (LC), although other cutaneous (dermal) dendritic cells (DC) may also contribute. In the skin LC act as sentinels of the adaptive immune system; their functions being to recognize and internalize antigen encountered in the skin and to transport it, via afferent lymphatics, to regional lymph nodes. During migration from the skin, LC are induced to differentiate from antigen processing cells to mature immunostimulatory DC that are able to present antigen effectively to responsive T lymphocytes in draining lymph nodes [8–10]. The processes of migration and maturation are initiated and regulated by epidermal cytokines, and the directed movement of LC from the skin and their subsequent localization within draining nodes is facilitated further by changes in chemokine receptor expression and specific chemokine receptor–ligand interactions [9,10]. The epidermal cytokines that play mandatory roles in LC mobilization are tumor necrosis factor α (TNF- α) and interleukin (IL) 1 β (IL-1 β) [10,11] and more recently it has been demonstrated the stimulation of LC migration in response to skin sensitization also requires IL-18 [12]. There is, in addition, some evidence that other epidermal cytokines, such as IL-10, may provide counter regulation serving to inhibit, or at least moderate, LC migration [13].

For the effective transport of allergen and the acquisition of sensitization it is necessary that sufficient quantity of chemical is experienced in the skin and that the appropriate epidermal cytokines are induced or upregulated. The amount of antigen needed to cause allergic sensitization will clearly be dependent on intrinsic potency. However, irrespective of relative potency, a critical determinant of the effectiveness of sensitisation is the concentration of chemical per unit area of skin [14]. The interpretation is that there exists a threshold (in terms of the amount of allergen per unit area of skin) for the expression of

clinically relevant contact sensitization and that below this level the effectiveness of the immunogenic signal is compromised. Notwithstanding the dose of chemical per unit of skin, the efficiency with which the allergen is handled and transported by LC will be to a large extent determined by the local availability of the necessary cytokines. One view is that a certain degree of local trauma (with a consequential induction or upregulation of proinflammatory cytokines) may facilitate, or be required for, the optimal genesis of skin sensitization [10,15]. This would of course be consistent with the 'danger' hypothesis proposed by Matzinger [16], wherein a certain degree of tissue damage or disruption is required for the normal development of immune responsiveness. Even if, at some levels of exposure, certain allergens are able, through a combination of allergenic and irritant properties, to provide a complete stimulus for sensitization, it can be argued that in circumstances where dose levels are low and/or cause little inflammation, then sensitization will be sub-optimal in the absence of a costimulus. There is some indirect experimental evidence to support this [15] and such an interpretation may serve to explain why in 1966 Kligman concluded from studies in humans that chemical or physical inflammation, if not too severe, increases the opportunity for skin sensitization [17]. This being the case it comes as no surprise that the vehicle or formulation in which a chemical allergen is encountered at the skin surface may impact on the development of sensitization [18]. Not only can the matrix in which a chemical is delivered to the skin influence percutaneous penetration, but also the degree of trauma provoked and the resultant cytokine microenvironment.

Taken together, it is apparent that the effectiveness of skin sensitization will be influenced by the inherent potency of the allergen, the amount of chemical experienced (as a function of dose per unit area) at the skin surface and the degree of trauma/inflammation induced. When all of these variables are favorable then an immunogenic stimulus will be transported by LC to skin draining lymph nodes and a T lymphocyte response provoked.

2.3. *T lymphocyte activation*

The central event in the acquisition of skin sensitization is the stimulation of a specific T lymphocyte

response. DC displaying the allergenic epitope activate responsive T lymphocytes that are induced to divide and differentiate. As a result, there is a clonal expansion of allergen-reactive T cells such that if the inducing chemical allergen is encountered again then an accelerated and more aggressive secondary immune response will be elicited. The basic immunobiological processes that result in skin sensitization are similar to those that confer cell-mediated host resistance to pathogenic microorganisms. In the case of contact allergy, however, the response is directed at an innocuous antigen that in non-sensitized individuals would be tolerated without ill effect.

There are important quantitative and qualitative aspects to allergen-induced T lymphocyte responses. Quantitatively, there exists a clear correlation between the vigor of proliferative responses induced in skin draining lymph nodes by topically applied chemicals and the extent to which sensitization will develop [19]. For this reason, as will be described later, it is possible in mice to define the relative potency of contact allergens as a function of the magnitude of induced lymph node cell (LNC) proliferative responses.

The important qualitative aspects of immune responses to skin sensitizing chemicals relate to the differential development of functional subpopulations of T lymphocytes. It is well established that in humans and rodents there exists heterogeneity among T helper (Th; CD4) cells, primarily with respect to cytokine secretion profiles [20–22]. Although there has been described a number of intermediate phenotypes, there are subsets that display the most polarized cytokine repertoires and these are designated Th1 and Th2. These cells develop from a common progenitor and diverge and differentiate as the adaptive immune response evolves with time and with repeated exposure to antigen. While some cytokines are produced by both Th1 and Th2 cells, others are associated primarily with one or the other subset. Thus, Th1 cells are characterized by the production of IL-2 and interferon γ (IFN- γ), whereas Th2 cells preferentially secrete cytokines required for the initiation and maintenance of IgE antibody responses and for the elicitation of immediate-type allergic reactions (IL-4, IL-5, IL-9, IL-10 and IL-13) [23]. The situation is complicated further by the fact that there is heterogeneity also among T cytotoxic (Tc; CD8) cells. The

major populations described (Tc1 and Tc2) have cytokine production phenotypes similar, respectively, to Th1 and Th2 cells [24,25].

It is now well established that in rodents different forms of chemical allergens (contact allergens and chemicals known to cause sensitization of the respiratory tract) provoke qualitatively distinct immune responses. Thus, topical exposure of mice to contact allergens will induce a selective type 1 response with the production by draining LNC of high levels of IFN- γ , but only comparatively low levels type 2 cytokines. In contrast, following exposure of mice to chemical respiratory allergens (by the same route and under conditions of similar overall immunogenicity), the converse is seen. In such instances, draining LNC

produce higher levels of type 2 cytokines, but only comparatively low levels of IFN- γ [3,4,26–29] (Fig. 1). Taken together, the data are supportive of the conventional view that Th1-type cells play an important role in the acquisition of sensitization and the elicitation of contact allergic reactions. However, as discussed below, although selective type 1 responses do indeed favor the generation of skin sensitization, the relevant responses at the cellular level are rather more complex. Notwithstanding this, there is no doubt that the stimulation by contact and respiratory chemical allergens of qualitatively discrete immune responses provides opportunities for distinguishing between them as a function of cytokine expression patterns. This is the basis of *cytokine fingerprinting*, a

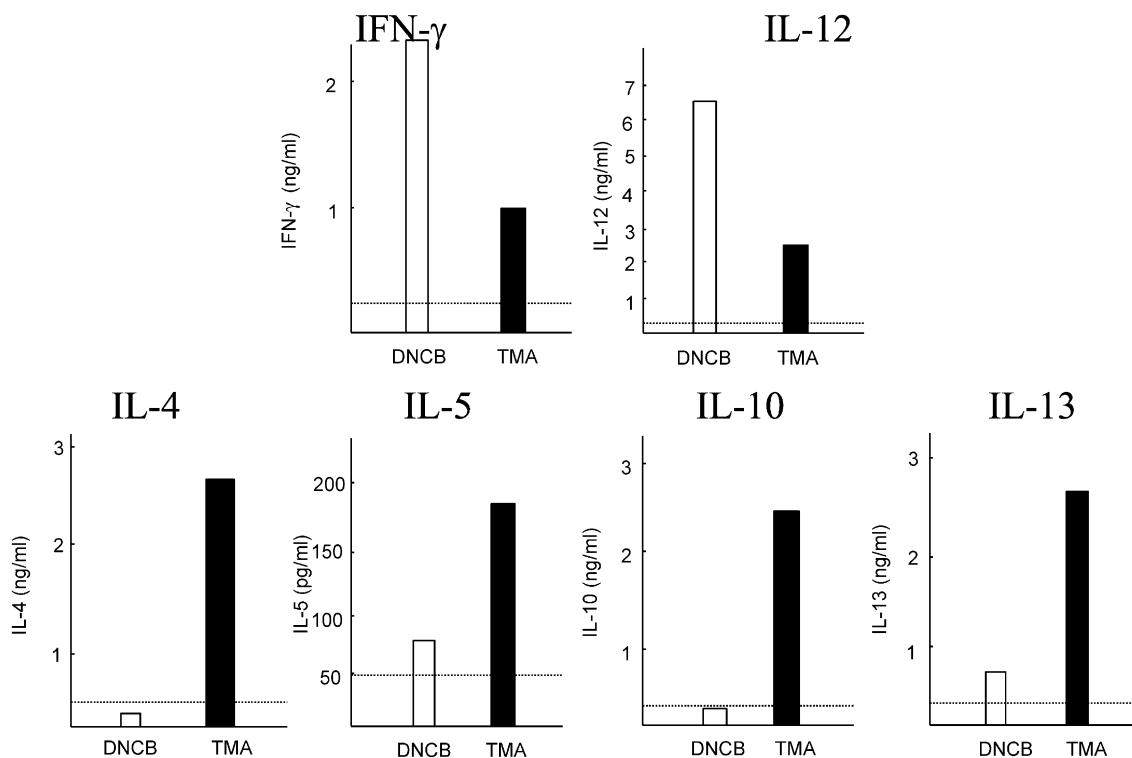


Fig. 1. Cytokine secretion profiles of allergen-activated lymph node cells (LNC). BALB/c strain mice ($n = 5$) were exposed topically to 1% 2,4-dinitrochlorobenzene (DNCB) in acetone:olive oil (AOO; 4:1) or to 10% trimellitic anhydride (TMA) in AOO. Thirteen days after the initiation of exposure, draining auricular lymph nodes were excised, pooled on an experimental group basis and a single cell suspension of LNC prepared. Supernatants were prepared after culture of LNC at 10^7 cells/ml for 24 hr in the presence of 2 μ g/ml of concanavalin A (interleukin 4; IL-4). Additional supernatants were prepared after culture of LNC at 10^7 cells/ml in the absence of concanavalin A for 120 h (interferon γ , IFN- γ ; interleukin 5, IL-5; interleukin 10, IL-10; interleukin 12, IL-12 and interleukin 13, IL-13). Cytokine concentrations were determined using cytokine-specific enzyme-linked immunosorbant assays (ELISAs). The limit of detection for each ELISA is indicated by the broken horizontal line. Results of a single representative experiment are shown.

novel method for the characterization and classification of chemical allergens [30].

It has become clear that these differential cytokine profiles are not necessarily a reflection solely of polarized Th cell populations. The relative contribution of CD4 and CD8 T lymphocyte subsets to preferential cytokine production patterns was investigated in mice comparing responses to DNCB with those stimulated by a known chemical respiratory allergen, trimellitic anhydride (TMA). The high levels of IL-4 and IL-10 production by LNC following chronic exposure to TMA were shown to be attributable exclusively to CD4 cells. However, the very low levels of IFN- γ secreted by LNC following treatment with TMA were found to derive largely or wholly from CD8 cells. In the case of DNCB, the relatively high levels of IFN- γ were derived from both CD4 and CD8 cells, and the much lower levels of type 2 cytokines were produced only by CD4 cells. Collectively, these observations reveal that both CD4 and CD8 T lymphocytes contribute to immune responses and the patterns of cytokine secretion stimulated by exposure to chemical allergens. With respect to DNCB, the data indicate that both Th1- and Tc1-type cells are induced, with a much less substantial contribution by Th2-type cells. Conversely, in the case of TMA, there was no evidence for any induction of cytokine secreting Th1-type cells; the little IFN- γ produced was found to be secreted by LNC derived exclusively from CD8 (Tc1-type) cells [31]. The intriguing question is to what extent do these cell types contribute to the elicitation of contact allergic reactions.

2.4. Effector T lymphocytes and the elicitation of contact hypersensitivity

The pathogenesis of allergic contact reactions requires that effector T lymphocytes are recruited into the sites of dermal exposure and this involves complex cell–matrix interactions regulated by adhesion molecule and integrin–receptor interactions with directional guidance supplied by relevant cytokines and chemokines [1,2]. The focus here, however, is consideration of which T cell phenotypes effect the reaction. The accepted view was that allergen-specific Th1 cells play the predominant role. However, other cell types may be of equal or greater importance [32].

During the last 10 years, evidence has accumulated to suggest that in mice, CD8 T lymphocytes are the major or sole effector cells in allergic contact reactions and that CD4 cells may instead have counter-regulatory activity [33–38]. In humans also there are indications that CD8 T lymphocytes may represent the critical subpopulation. Cavani et al. [39] examined nickel-specific T cell responses in nickel allergic and nickel non-allergic subjects. Although both groups possessed memory CD4 T lymphocytes that were able to respond to nickel *in vitro*, only in those with nickel allergy were there discernible CD8 nickel-specific T lymphocyte responses. In parallel with a growing recognition of the important role played by Tc cells in contact hypersensitivity, evidence is emerging that cytotoxicity for skin cells mediated by allergen-specific CD8 (and CD4) T lymphocytes is a key pathogenetic feature of cutaneous allergic reactions [40–42]. On the basis of these observations, a case can be made for CD8 Tc1-type cells being major mediators of allergic skin reactions, although for full development of contact hypersensitivity there may be a requirement for CD8 and CD4 type 1 effector cells to act in concert [43]. However, it must be emphasized that in some circumstances, and with some chemical allergens, other cells (type 2 cells) may be important. A case in point is provided by the results of investigations conducted recently with fluorescein isothiocyanate (FITC) [44]. This chemical allergen induces in mice a selective type 2 cytokine profile, and on this basis would be predicted to have the potential to cause allergic sensitization of the respiratory tract. In common with other chemical respiratory allergens, FITC is able to provoke a biphasic dermal hypersensitivity reaction in sensitized mice. The immediate (within 1 h of challenge) reaction is mediated by IgE antibody, whereas the more delayed response (24 to 48 h after challenge) is cell-mediated. Using selective depletion and adoptive transfer techniques, it was found that the conventional (delayed) contact hypersensitivity reaction elicited in FITC sensitized mice was mediated only by Th2-type CD4 T lymphocytes [44].

The conclusion drawn is that a variety of cells may contribute to the elicitation and regulation of contact allergic reactions, with the nature of the inducing chemical allergen possibly influencing the relative importance of discrete functional subsets.

3. Hazard identification and characterization

Historically, guinea pigs were the species of choice for the assessment of ACD, the approach being to examine the ability of test chemicals to elicit challenge-induced cutaneous reactions in previously exposed animals [45]. More recently, however, attention has focused on the mouse, in which species much of the detailed information on relevant immunobiological mechanisms has become available. The mouse ear swelling test (MEST), first described in a systematic way by Gad et al. [46], also seeks to identify potential contact allergens on the basis of challenge-induced increases in ear thickness in sensitized animals. An altogether different strategy is used in the local lymph node assay (LLNA). In this method, the skin sensitizing potential of chemicals is measured by their ability to stimulate proliferative responses in lymph nodes draining the site of topical exposure [47–50]. In practice, those chemicals which, at one or more application doses, are able to provoke a 3-fold or greater increase in draining LNC proliferative activity compared with concurrent vehicle controls

are classified as skin sensitizers. Following rigorous inter-laboratory comparisons and exhaustive comparisons with guinea pig test data and clinical experience, this method was endorsed widely as an acceptable full alternative to the standard guinea pig tests. Detailed reviews of the LLNA, the approaches used for evaluation and validation and the use of this method for hazard identification are available elsewhere [47–50]. While accurate hazard identification is the foundation for any toxicological evaluation, an additional requirement for risk assessment is an understanding of relative potency. During recent years, we have been interested in the possibility that, in addition to providing a sensitive and selective approach to the identification of contact allergens, the LLNA might also provide a means of characterizing relative skin sensitizing potency. Enthusiasm for this approach was based on the demonstration (described above) that there exists a close correlation between the vigor of proliferative responses induced in draining lymph nodes and the extent to which skin sensitization will be acquired [19]. For this purpose, a slightly modified form of the standard LLNA is used to determine the

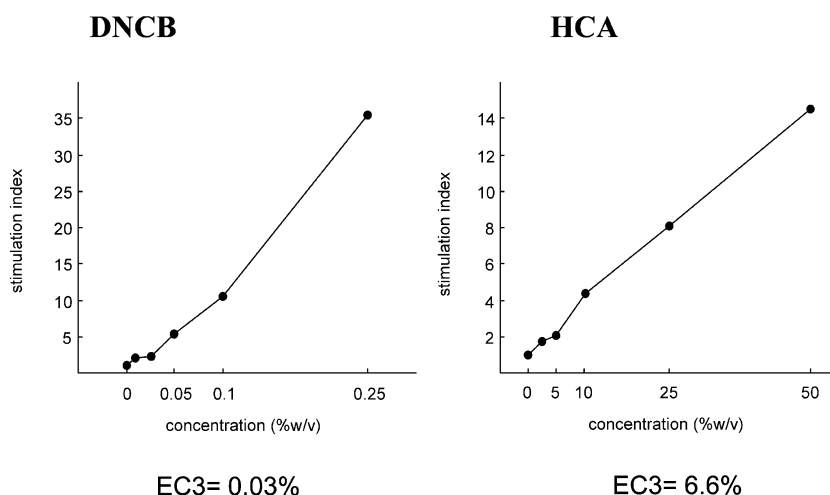


Fig. 2. Local lymph node assay dose response analyses: comparison of 2,4-dinitrochlorobenzene (DNCB) with hexyl cinnamic aldehyde (HCA). Groups of CBA/Ca strain mice ($n = 4$) received 25 μ l of various concentrations of 2,4-dinitrochlorobenzene (DNCB) or hexyl cinnamic aldehyde (HCA) in acetone:olive oil (AOO; 4:1) vehicle, or an equal volume of vehicle alone, one the dorsum of both ears daily for 3 consecutive days. Five days after the initiation of exposure, all mice were injected intravenously with phosphate-buffered saline containing 3 H-thymidine. Draining lymph nodes were excised 5 h later and pooled on an experimental group basis, a single cell suspension prepared and 3 H-thymidine incorporation was measured by β -scintillation counting. Results are displayed as stimulation indices for each experimental group; determined as the increase in 3 H-thymidine incorporation relative to the concurrent vehicle-treated control. The estimated concentration of material required to induce a stimulation index of 3 (EC3 value) has been calculated for both chemicals by linear interpolation of the dose response data.

concentration of chemical required to cause a 3-fold increase in LNC proliferation compared with concurrent vehicle control values. This is known as the Effective Concentration 3 (EC3) value and is derived from LLNA dose responses using linear interpolation [51,52]. In recent analyses, it has been demonstrated that EC3 values calculated from LLNA studies correlate very closely with what is known of the relative sensitizing potency of chemicals among human populations [53,54].

An example of how, in practice, EC3 values are used is provided by the data illustrated in Fig. 2, where studies performed with DNCB and hexyl cinnamic aldehyde (HCA) are summarized. In these particular experiments, DNCB was found to have an EC3 value of 0.03%, whereas the EC3 value for HCA was 6.6%. On this basis, and under the conditions of the exposure where a mixture of acetone and olive oil was used as the vehicle matrix, DNCB was judged to be approximately 200 times more potent than HCA (data that are consistent with what is known of the relative potency of these chemicals in humans). Of course, it is possible to measure relative potency in terms of molar concentrations or amount of chemical per unit area of skin instead of percentage application concentration. In practice, however, this makes little difference to the overall assessment of relative potency. The important point is that using this approach, a clear estimate of relative skin sensitizing potency can be determined with which to aid the risk assessment process and derivation of safe exposure levels.

4. Skin sensitization and risk assessment

It is critical to ensure that products and their ingredients do not cause ACD in the worker or consumer. Risk assessment is of fundamental importance—skin sensitization tests in general evaluate only hazards, and to some extent potency. The risk assessment process enables these abstract hazards to be placed into a practical context (relative to likely exposure) and, where appropriate, permit risk management/risk reduction measures to be defined.

To evaluate the contact sensitization potential of a new ingredient before exposure of employees or consumers, various testing strategies have been proposed

[55,56]. These use a multistep risk assessment approach. It is critical to understand that in spite of the decision-tree approach often used to illustrate the testing and risk assessment process, the process itself is neither static nor overly prescriptive. Each step in the approach includes an element of “assess risk” that requires the toxicologist to evaluate carefully available data on the chemical. The tools used to conduct a risk assessment include (quantitative) structure activity relationship (Q)SAR analysis, exposure assessment, pre-clinical testing (e.g., LLNA) and clinical testing (e.g., Human Repeat Insult Patch Testing). Thus, the risk assessment process involves evaluating both the inherent toxicity of and exposure to the chemical.

4.1. Exposure-based risk assessment

While exposure for other endpoints is often expressed in units of mg/kg body weight, the relevant dose metric for skin sensitization potential is the amount of chemical allergen per unit area on the skin [57]. In a series of elegant human skin sensitization studies, Friedmann et al. [14,58–60] demonstrated that it is not the percent (weight/volume) of material applied that is critical, but the total dose/area of exposed skin. The potent contact allergen DNCB was utilized and subjects were exposed to varying doses per unit area of skin to observe the incidence of sensitization upon challenge. When increasing total doses were applied to proportionately increased skin surface areas (keeping the dose/unit area the same), the incidence of sensitization was equal. When the total dose remained constant, but the area of application was varied, those subjects exposed within smaller areas of skin and hence larger dose/unit area exposures had the greater incidence of sensitization. Thus, it is critical to express the sensitization dose as a dose per unit area measurement (e.g., $\mu\text{g}/\text{cm}^2$) when conducting a quantitative skin sensitization risk assessment.

The concept of dose per unit area provides a “common currency” enabling comparison of sensitization incidences across studies and facilitating comparison of the potencies of different chemicals. For example, if one compared exposure to an ingredient at 0.1% in both a laundry product versus a facial skin cream, there would be a greater than 100-fold difference in exposure when compared on a dose per unit basis [57]. It is also necessary to consider dose per unit area

when reviewing or conducting patch testing since different patch types come in different sizes and require different volumes to load the patches [57].

Although dose per unit area is an important parameter to use in comparative skin sensitization assessment, it is by no means the only factor to consider. Allergenic potency is another essential factor for consideration when conducting skin sensitization risk assessments. Sensitizing potency in this context is best described as a function of the amount of chemical that is required to induce contact sensitization in a previously naïve subject or animal, and on this basis it has been estimated that chemicals vary significantly in terms of their intrinsic allergenic activity [61–63].

Despite the importance of potency estimation in the development of accurate risk assessments, there has been relatively modest progress in the definition of appropriate experimental models. As discussed above, the LLNA provides new opportunities for the objective and quantitative estimation of skin sensitization potency [49,51]. Experience to date with this approach has been encouraging; clear differences between skin sensitizing chemicals can be discerned and such differences appear to correlate closely with the ability of the materials to induce contact allergy in experimental models and with what is known of their sensitizing activity in humans [53,54,62,63].

For ethical reasons, there are no well defined or widely applied methods for the determination of relative skin sensitization potency in humans. However, review of the published literature for reports of dose response induction studies in humans yields valuable information on the sensitizing potency of a variety of chemicals. Using available human repeat patch test data, together with expert judgement, over 25 compounds were classified as strong, moderate, weak, extremely weak or non-sensitizers [53,54]. Additionally, it has been shown that LLNA EC3 values for the same chemicals are very comparable with the clinical no observed effect levels (NOELs) calculated from the literature [54]. These investigations demonstrate that the LLNA can be used to provide quantitative estimates of relative skin sensitizing potency (EC3 values) that correlate closely with NOELs established from human repeat patch testing and from clinical experience.

Thus, for the conduct of a sound skin sensitization risk assessment, a thorough understanding of chem-

ical exposure is required, as well as allergenic potency and dose response. The importance of exposure and potency estimation in assessment of skin sensitization risk has recently been reviewed, including examination of an exposure-based risk assessment process using methylchloroisoithiazolinone/methylisothiazolinone (MCI/MI) and cinnamic aldehyde as case studies [56,64]. These studies show how one can judge the sensitization risk for different exposure conditions using an exposure-based risk assessment approach.

5. Clinical considerations

In this final section, a brief overview is given of the main clinical aspects of ACD. For detailed information on the topic, the reader is referred to recent comprehensive texts [65,66]. In the context of the flow of logic of this paper, then the occurrence of ACD, the clinical expression of skin sensitization, can be regarded as the point where risk assessment and management have failed. However, that is an overly simplistic view. ACD depends not only on exposure to, and the potency of, an allergen, but also on the susceptibility of the exposed individual. Thus, although skin sensitization to nickel is very common (approximately 10% of females in Western Europe are allergic to nickel), many more are equally exposed, but do not develop sensitization to this haptenic metal. The most sensitizing exposures to nickel arise via body piercing, but not all those with such adornments develop ACD or skin sensitization. Furthermore, once an individual is sensitized to nickel, not all exposure to this metal results in ACD. A proportion of individuals who are clearly positive to nickel at diagnostic patch testing do not display clinical symptoms that can be related to nickel exposure; for those that do have an obvious nickel ACD, not all nickel exposure results in dermatitis. For example, the great majority of nickel allergic individuals can tolerate everyday exposure to nickel-containing objects such as coins, kitchen utensils, etc.

Nickel is not the only metal which can cause skin sensitization; chromium salts are clinically important allergens, particularly in the construction industry. Low levels of chromium salts in cement are responsible for a considerable degree of morbidity and provide a good example of both success and failure of risk management. In countries where ferrous sulphate

is added to cement sharply lowering the solubility of chromium via reduction to its trivalent form, the incidence of chromium allergy in construction workers has fallen sharply. Where this has not been done, the incidence remains high. This is unfortunate, as chromium dermatitis is well recognized as one of most refractory expressions of ACD. Other metals which cause ACD include mercury, cobalt and gold.

Considering organic chemicals, the most common allergens are often found in plants. Pentadecylcatechol is the highly potent allergen found in poison ivy in North America and is responsible for sensitizing approximately 50% of the US population. Oakmoss, a natural material extracted from a lichen and used in perfumes, is regarded generally as the most common fragrance sensitizer. Other chemicals used in fragrances are relatively potent and common allergens; one example is isoeugenol where the increasing understanding of its potency and evidence of ACD has led to a renewed vigor in its risk management [67]. Preservative materials such as formaldehyde and certain isothiazolinones also have been relatively common causes of ACD. For these the balance between obtaining adequate preservation activity and sensitization is often very subtle. As such, they frequently show a pattern of increasing ACD over time as they become more generally used, followed by a steady decline in the incidence of ACD as the fine degree of understanding needed to accurately manage the risk is developed [68].

Many other chemicals can cause ACD, including epoxy resin chemicals, acrylates, rubber chemicals, certain emulsifiers and dyes. Of these, much of the ACD which occurs results from occupational exposure. However, non-occupational exposure, for instance to allergens in cosmetics, in clothing and footwear, in medicaments and in plants, represent important causes of ACD.

As mentioned above, major determinants of both the induction and the elicitation of ACD are the nature, extent and duration of skin exposure to the allergen and the potency of the allergen. Another aspect is the susceptibility of the exposed individual, a factor that is only partially understood. So for example, the impact of concomitant irritation on elicitation thresholds for ACD has been studied [69], but except for general acknowledgement that irritation increases the likelihood that sensitization will be induced, little knowledge exists in this latter area.

Furthermore, primary determinants of individual susceptibility are not well understood and thus it is very difficult to predict which individuals are most likely to become sensitized. Those who have skin which is more easily irritated may be a little more susceptible [70], but those with atopic dermatitis clearly are not [71]. So far, study of identical twins has demonstrated that genetic factors seem much less important than exposure.

The brief summary provided above serves to illustrate that limitation of the clinical expression of skin sensitization, ACD, is best achieved at present by ensuring proper understanding of hazards, particularly allergen potency, and by subsequent risk assessment and implementation of appropriate risk management.

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