

Review Article

The importance of exposure estimation in the assessment of skin sensitization risk

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The development of new ingredients and products for the consumer market requires a thorough assessment of their potential for skin sensitization and the possible clinical manifestation of allergic contact dermatitis. The process by which low molecular weight chemicals induce and elicit skin sensitization reactions is complex and dependent on many factors relevant to the ability of the chemical to penetrate the skin, react with protein, and trigger the cell-mediated immune response. These major factors include inherent potency, chemical dose, duration and frequency of exposure, vehicle or product matrix, and occlusion. The fact that a chemical is a contact allergen does not mean that it cannot be formulated into a consumer product at levels well tolerated by most individuals. Many common ingredients (e.g., fragrances, preservatives) are known skin allergens. However, all allergens show dose-response and threshold characteristics. Therefore, one should be able to incorporate these chemicals into products at levels that produce acceptably low incidences of skin sensitization under foreseeable conditions of exposure. The critical exposure determinant for evaluating skin sensitization risk is dose per unit area of skin exposed. Use of this parameter allows for comparative assessments from different types of skin sensitization tests (including cross-species comparisons), and, at least for known potent allergens, there is remarkable similarity in threshold dose/unit area determinations across species. The dose/unit area calculation enables a judgment of the sensitization risk for different product types. This is illustrated using the chemical preservative methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) as a case study.

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For new products or product ingredients that come into contact with the skin, it is necessary, prior to their introduction on to the market, to conduct a thorough skin safety testing and risk assessment program to be certain that the product will be well tolerated. One of the critical skin safety testing and risk assessment processes relates to development of allergic skin reactions, referred to as skin sensitization, the clinical manifestation of which is called allergic contact dermatitis (ACD). The skin sensitization testing and risk assessment process for new ingredients and products generally follows a step-wise approach that may involve analytical assess-

ments, preclinical skin sensitization testing, clinical testing, and benchmarking of resulting data against similar ingredients and product types. The details of these various elements and the overall process have been reviewed previously (1–5). Case studies of its application have also been described relevant to specific ingredients and product types (1, 6–8).

An essential element of the skin sensitization risk assessment process is the evaluation and understanding of the relationship between skin sensitization hazard, i.e., the inherent potential of an ingredient to cause allergic skin sensitization,

and actual skin sensitization risk. The latter relates to the potential for induction and/or elicitation of allergic contact sensitization under exposure conditions typical of all intended and foreseeable uses of the product. Allergenic chemicals demonstrate dose-response characteristics regardless of whether the sensitization process evolves in an experimental animal model system (9, 10), or in human beings (11, 12). The dose response for induction and elicitation of skin allergy can be influenced by a variety of factors including, for example, the application vehicle system (13, 14), the number (8) and duration (15) of exposures, underlying skin irritation (16, 17) and the use of occlusion (18).

While many studies have underscored the importance of the above factors in determining the extent of sensitization in experimental studies or standard safety testing protocols, it is important to realize also that they are equally critical in the development of clinically relevant ACD through product use exposures. It is well-known that sensitizing chemicals can be formulated into consumer products at levels that produce acceptably low incidences of sensitization (12, 19, 20). It is equally well known that these same ingredients are associated with a much higher incidence of ACD when formulated into products at too high a level (21). Hence, an understanding of exposure, as well as allergenic potency and dose response, is critical to the skin sensitization risk assessment process.

This paper begins with a brief overview of the biology of skin sensitization. It then reviews key factors relevant to the skin sensitization process. These include the critically important role of dose per unit area of exposure in determining the potential for allergic contact sensitization, dose per unit area exposure comparisons for different sensitization test methods, and exposure assumptions relevant to the use of different product types (e.g., leave-on versus rinse off-products). These various factors are then consolidated into the discussion of an exposure-based risk assessment process. This is highlighted by using the chemical preservative, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), as a case study.

Biology of Allergic Contact Dermatitis

Allergic contact dermatitis is a cell-mediated immune response to small molecular weight chemicals that contact and penetrate the skin. The process occurs in 2 distinct phases. In the 1st phase, called induction, the chemical penetrates into the viable epidermis and is taken up and processed by antigen-presenting cells, called Langerhans cells. The activated Langerhans cells migrate via the af-

ferent lymphatics to the draining lymph node(s) where they present the allergen to T lymphocytes. Allergen-activated T-cells then divide and differentiate into memory cells and disseminate throughout the body (including percolation through the skin) ready to act as sentinels to any subsequent encounter with the same allergen. In the 2nd phase, called elicitation, reexposure to the inducing chemical (again presented by Langerhans cells in the skin), reactivates these memory T-cells to produce a variety of proinflammatory cytokines that trigger the inflammatory response. There are a variety of characteristics that determine whether a chemical can function as a contact sensitizer (or allergen). First, it must be able to penetrate through the stratum corneum into the viable epidermis. Generally, chemicals must be relatively low in molecular weight (<1000) (22) and have appropriate physicochemical properties (e.g., lipophilicity) (23). Once in the viable epidermis, the chemical must react with protein and may be taken up and processed by Langerhans cells. The chemical (also called a hapten) may be directly protein reactive or may be converted (metabolized) from a prohaptene into a reactive form (24). The processed chemical is then expressed on the cell surface of the Langerhans cell in conjunction with major histocompatibility (MHC) antigens (25). Alternatively, it may be that a reactive hapten can directly bind to the MHC molecules on the cell surface. In addition to chemical processing, Langerhans cell activation requires the binding of cytokines produced by keratinocytes as a result of the initial chemical exposure. It is apparent that some degree of direct chemical inflammation or other concurrent trauma enhances this keratinocyte activity, produced by the allergenic chemical itself, by some other component of the chemical delivery system, or by some form of physical insult. This may account for the noted enhancing effect of primary skin irritation on the sensitization response (16, 17).

From an exposure standpoint, any process that increases the delivery of the allergenic chemical into the viable epidermis should increase the potential for induction of skin sensitization as well as the elicitation of clinically relevant dermatitis in already sensitized individuals. Obviously, one way to increase the degree of sensitization is to increase the dose of applied allergen, and, as described below, it is the dose per unit area that is the critical factor (26). Other ways to increase total exposure include increases in the duration of the exposure (15), the frequency (number) of exposures (8, 14), the use of penetration enhancing vehicles (8, 13, 14), physical trauma or chemical irritant pretreatment (27, 28) and occlusion (29).

Importance of Dose/Unit Area in the Skin Sensitization Process

Throughout the contact sensitization literature, allergen exposures are most commonly expressed in terms of percent, i.e., the weight per volume of allergen applied to the skin. The assumption from this is that, in any given test system, an equal % exposure will lead to a similar incidence and/or severity of sensitization. However, in a series of elegant human skin sensitization studies, Friedmann and his colleagues proved that it is not the % (weight/volume) of material applied that is critical, but the total dose/area of exposed skin (11, 26, 30–33). They used a potent contact allergen, dinitrochlorobenzene (DNCB), and repeatedly exposed subjects to varying doses per unit area of skin to observe the incidence of sensitization upon challenge. When they applied increasing total doses to proportionately increased skin surface areas (keeping the dose/unit area the same), the sensitization incidence was equal. When they kept the total dose constant, but varied the area of application, those subjects exposed within smaller areas of skin (and hence larger dose/unit area exposures) had the greater incidence of sensitization. The relationship, as depicted schematically in Fig. 1, broke down only at very small application areas of skin ($<0.1 \text{ cm}^2$), probably a reflection of some

Patch size (cm^2)	Total dose (μg)	Dose/unit area ($\mu\text{g}/\text{cm}^2$)	Incidence (%)
7.1	250	35.4	83
7.1	62.5	8.8	8
1.8	62.5	35.4	86
0.8	30	38	93
0.08	3	38	26

Fig. 1. Schematic representation of concept of dose per unit area in understanding of skin sensitization risk, it is the dose/area ($\mu\text{g}/\text{cm}^2$) that is proportionally related to the incidence of positive responses, not the total area of application or the total dose applied.

Note: Areas depicted in the circles are schematic only, i.e., they are not intended to equal the cm^2 areas indicated.

Data from (33)

Table 1. Patch type and dose/unit area calculation for a 1% solution

Patch type	Patch area (cm^2)	Patch volume (μl)	Dose/unit area ($\mu\text{g}/\text{cm}^2$)
8 mm Finn Chamber	0.5	15	300
19 mm Hill Top Chamber (12 mm diameter patch)	1.13	200	1770
Professional Products Patch (1.9×1.9 cm)	3.61	200	554
Webril Patch (2×2 cm)	4	400	1000

Table 2. Contact allergen potency as determined by two different sensitization test methods

Test allergen	NOEL in HRIPT ^{a)} ($\mu\text{g}/\text{cm}^2$)	LLNA EC3 value ^{b)} ($\mu\text{g}/\text{cm}^2$)	Refs
MCI/MI	1	2.5	(12, 41, 49, 50)
p-phenylenediamine	~10	25	(49, 51)
glutaraldehyde	50	50	(49, 51)
cinnamic aldehyde	591	500	(49, 52)
hydroxycitronellal	2950	5000	(49, 53)

a) No effect level derived from human repeat insult patch studies.

b) Lowest concentration yielding a positive response (stimulation index of 3 or more) in local lymph node assay.

threshold in the total number of Langerhans cells required for sensitization (33).

Sensitization studies, whether conducted in animal models or humans, generally utilize a variety of exposure methods (e.g., open application, occluded patch, semi-occluded patch). Hence, contact allergens might be tested at identical concentrations, but at very different doses per unit area of exposed skin. To illustrate this point, Table 1 provides a comparison of different patch types commonly used in predictive or diagnostic clinical patch testing. A common test allergen concentration (1% in this case) applied in the recommended volume for each patch type, would result in up to 6-fold differences in dose/unit area. Based on the data of Friedmann and colleagues, this difference could easily lead to differences in the incidence of sensitization. This 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.

While 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. Allergic potency is still the single most important factor in evaluating sensitization hazard. What dose/unit area allows is comparison of allergic potency without the additional variability of differing doses. This relationship is depicted in

Table 2, which shows the threshold dose (per unit area – the common currency) for 5 contact allergens of very different potencies in both human and mouse test systems. Using dose/unit area, one can show very similar thresholds for these different chemicals in both species, something that would not be apparent if concentration in % were used as the exposure constant.

Other critical factors, described earlier, that have to be considered in evaluating skin sensitization hazard are such things as the vehicle system (or product matrix if the potential allergen is formulated into a finished product), concomitant irritation, and open versus occluded application. When compared to the open application of a chemical in a simple vehicle to intact skin, any factor (penetrating vehicle/matrix excipients, application over compromised skin, occlusion) that increases the bioavailability of the chemical to the immunocompetent Langerhans cell population will increase the likelihood or potency of the sensitization response. As will be discussed below, all such factors must be considered and weighed in extrapolating from ingredient sensitization hazard evaluation to the assessment of human skin sensitization risk.

Comparison of Exposures in Animal and Clinical Skin Sensitization Tests

Both animal and human skin sensitization test methods follow standard protocols in terms of the type of exposure (open or occluded patch) as well as the size of the application area and volume of test material applied. As mentioned above, it is typical in these studies to prepare and characterize dose preparations in terms of %. However, by knowing the concentration and volume of the dose and the size of the patch or area of open application, it is simple mathematics to calculate a dose/unit area. For example, the application of 0.4 ml of a 1% solution of an allergen to a 2 cm² webril patch would result in a dose/unit area of 1000 $\mu\text{g}/\text{cm}^2$ ($[10 \text{ mg/ml} \times 0.4 \text{ ml}] \div [4 \text{ cm}^2] = 1 \text{ mg}/\text{cm}^2 = 1000 \mu\text{g}/\text{cm}^2$) as noted in Table 1. These calculations are important for accurate comparisons of patch test exposures to all intended and foreseeable product use exposures in assessing sensitization risk.

In order to compare allergenic potencies across studies, within a species or across species, it is necessary to know the precise exposure conditions in order to calculate a dose per unit area. This requires knowledge of both the area of exposure and the volume of test allergen applied. In guinea pig skin sensitization tests, only the occluded patch test of Buehler (34–36) allows for precise calculation of dose per unit area. Other methods use

either variable open application areas or intradermal injection exposures. In the mouse, there is an extensive literature on ear swelling assay methods for assessing contact sensitization; however, the induction exposures used involve various non-quantified areas of open application to the flank. The murine local lymph node assay (LLNA) also uses open application; however, standardized application to the dorsum of the ear (an area calculated to be approximately 1 cm²) (37) allows for the calculation of dose per unit area. Human patch test methods, such as the human repeat insult patch test (HRIPT) (1, 38), also use standardized patch types and volumes of application enabling the calculation of dose per unit area.

In examining dose per unit area across different types of studies, it is useful to compare data on selected chemicals that have been tested by multiple animal and human methods. A good example is DNCB, a chemical that has been extensively tested by multiple methods. Even here, the comparisons are complicated by the fact that different endpoints are being evaluated; local lymph node cell proliferation (LLNA) in the mouse (39), erythema in the guinea pig (40), and skin fold thickness changes in man (33). In spite of these differences, the comparison of the dose per unit area resulting in approximately $1/4$ to $1/2$ maximal responses for each method were remarkably similar; 25 ($\mu\text{g}/\text{cm}^2$) in the mouse (39) and guinea pig (40) and 16.4 ($\mu\text{g}/\text{cm}^2$) in man (33). For this potent lipophilic allergen, the use of occluded patch applications in the guinea pig and human tests provided little potency enhancement versus the open application of the LLNA. However, for other allergens, that might not be the case.

A 2nd case study comes from work on the preservative MCI/MI, which has also been tested in the LLNA, Buehler, and human patch tests in simple vehicles. Studies in the LLNA resulted in a threshold positive response (stimulation index of $\geq 3X$) at an applied dose of 0.01% (41) or 2.5 $\mu\text{g}/\text{cm}^2$. Buehler tests produced a threshold positive response at 0.0025% (10), which also calculates out to 2.5 $\mu\text{g}/\text{cm}^2$ under the patch test exposure conditions used in this study. The threshold for induction of sensitization in predictive testing in man was 0.002% (12). This calculates out to approximately 2 $\mu\text{g}/\text{cm}^2$ under the exposure conditions of the patch test. Hence, these studies showed threshold positive responses to MCI/MI that varied by 5-fold when the induction doses were compared as percent, but only 1.3 fold when the induction doses were expressed as dose per unit area, again showing potency threshold consistency across methods for a known potent allergen. The 2 allergens (DNCB and MCI/MI) provide for good cross spe-

Table 3. Exposure calculations for facial skin cream and shampoo

Skin cream*Assumptions (source: (44))*

- Median body surface area for female =1.69 m²
- % of total body surface area for head =7.1%
- surface area for head (i.e. 7.1/100×1.69) =0.12 m²
- surface area for half head, i.e., cream applied to facial area (0.12/2) = 600 cm²
- amount skin cream used per application day (2 applications/day) =0.8 g×2
- assume 100% retention i.e. multiply final exposure by 1 =1.6 g

Calculation for daily exposure to ingredient in facial skin cream:

$$=[\text{amount in product } (\mu\text{g/g product}) \times \text{amount product applied (g)}] / \text{surface area exposed (cm}^2\text{)]}$$

$$=\text{exposure to ingredient } (\mu\text{g/cm}^2)$$

Example: Ingredient at 500 ppm i.e. 500 $\mu\text{g/g}$ product

$$= 500 (\mu\text{g/g}) \times 1.6 (\text{g}) / 600 (\text{cm}^2)$$

$$= 1.33 \mu\text{g/cm}^2$$

Shampoo*Assumptions (source: (44))*

- Median body surface area for female =1.69 m²
- % of total body surface area for head =7.1%
- surface area for head (i.e. 7.1/100×1.69) =0.12 m²
- surface area for half head i.e. scalp (0.12/2) =600 cm²
- % of total body surface area for hands =5.1%
- surface area of the hands (i.e. 5.1/100×1.69) =860cm²
- amount shampoo used per day =12 g
- assume 1% retention on scalp, i.e., multiply final exposure by 0.01

Calculation for daily exposure to ingredient in shampoo:

$$=[\text{amount in product } (\mu\text{g/g product}) \times \text{amount product applied (g)}] / \text{surface area exposed (cm}^2\text{)}$$

$$=\text{exposure to ingredient } (\mu\text{g/cm}^2) \times 0.01$$

$$=\text{exposure to ingredient on scalp } (\mu\text{g/cm}^2)$$

Example: Ingredient at 500 ppm, i.e., 500 $\mu\text{g/g}$ product

$$= 500 (\mu\text{g/g}) \times 12 (\text{g}) / 1460 (\text{cm}^2)$$

$$= 4.1 \mu\text{g/cm}^2 \times 0.01$$

$$= 0.04 \mu\text{g/cm}^2$$

cies comparisons because they are rare examples of chemicals for which dose-response data exist in prospective human patch tests. It is not certain that the degree of potency agreement across species that has been observed for these 2 chemicals would exist for all (or even most) allergens, especially given the other variations in exposure conditions. However, these data do give some credence to the notion that, at least for strong allergens, potency evaluation under the common currency of dose per unit area provides the most appropriate method for cross-species comparisons.

Exposure Calculations (Dose/Unit Area) for Different Consumer Products

The risk assessment process requires the ability to compare the chemical exposures used in animal or human patch test procedures to relevant or exaggerated exposures from the intended and all foreseeable uses of the product. To determine the latter, one needs to know the concentration of the ingredient in the final product formulation as well as the amount of product applied and the area of application. There will also be exposure differences

based on the type of product. For example, for products that are applied to and left on the skin (leave-on products), the conservative assumption is that 100% of applied product (and all ingredients therein) is available. For products such as bath soaps or shampoos, that are applied and then rinsed off the skin (rinse-off products), there are calculations and assumptions made regarding residual product (and ingredients) remaining on the skin.

Comparative exposure estimations for a potentially sensitizing ingredient present at 0.05% (500 ppm) in a facial skin cream or shampoo are shown in Table 3. Many assumptions are used to calculate the exposures. These relate to skin surface area for the application site and other exposed skin surfaces, the number of applications per day and, for rinse-off products, the residual material left on the skin. There are government and trade association guidelines that serve as resource material for most of the assumptions used in the calculations (42–45). Based on the assumptions inherent in the calculations used, the exposure (in $\mu\text{g/cm}^2$) to the ingredient of interest for these 2 products differs by greater than 30-fold.

Table 4. Comparison of % concentration in product versus dose per unit area exposures

Product type	Concentration of active (1000 PPM or 0.1%)	Product exposure ($\mu\text{g}/\text{cm}^2$) ^{a)}
laundry detergent/hand wash	1000	0.024
shampoo	1000	0.08
body lotion	1000	0.5
facial cream	1000	2.7
stick deodorant	1000	5
parfum spray	1000	8.7

a) Product exposures determined through calculations of surface area of exposed skin, typical amounts of product applied to the exposed skin, and residual product remaining on skin (in the case of rinse-off exposures); see Table 3 for examples.

A number of different exposure estimations have been made for different types of consumer products. It is instructive to compare calculated exposures (in $\mu\text{g}/\text{cm}^2$) for a common ingredient across different product types. This is shown (Table 4) for products ranging from laundry detergents to fine fragrance products. This type of exposure variation is factored into any risk assessment for marketing of different types of products containing a given ingredient, as will be discussed below.

Exposure-Based Risk Assessment

Before a product is introduced onto the market, all of the sensitization test results and exposure calculations are compiled and evaluated to determine a maximum allowable exposure limit for an ingredient in the intended product (5). As part of this process, a variety of factors are considered and used to determine an appropriate "safety" or "uncertainty" factor. This factor simply represents the exposure "gap" between the highest (or at least a known) no-effect concentration (in $\mu\text{g}/\text{cm}^2$) of an ingredient in the human repeat insult patch test divided by the maximum allowable human exposure. Various considerations go into determining what is an appropriate safety factor for an ingredient and each consideration incorporates its own level of uncertainty. 3 important categories of these variations include inter-individual response variability, matrix differences between what was tested in the patch test versus the product formulation to which the consumer will be exposed, and variations in product usage patterns (e.g., leave-on, rinse-off, occluded or non-occluded, frequency of application, etc.). Using weighting factors of 1–10 for each of the 3 categories and multiplying the factors together provides an overall safety/uncertainty factor that can range from 1 to 1000. In

practice, the factors will differ greatly among different product types, particularly when comparing rinse-off and leave-on products and products used intermittently rather than daily.

Once an ingredient safety factor for a given product is defined (and these are commonly defined on the basis of product category), it is used with the known no-effect dose of ingredient from human patch testing to determine the maximum human exposure limit for the ingredient in the product of interest. Simply stated, the maximum exposure limit for an ingredient in the product is equal to the no-effect level divided by the safety factor. So, for example, if the no-effect level for an ingredient is $5 \mu\text{g}/\text{cm}^2$ and the defined safety factor is 100, the maximum product-use exposure limit would be $0.05 \mu\text{g}/\text{cm}^2$. Theoretically, the marketing of a product for which the product-use exposure is greater than the calculated maximum exposure limit might be expected to lead to sensitization in consumers using the product. Again, we can consider MCI/MI as an excellent case study.

Based on human patch test data (in water), the threshold for skin sensitization by MCI/MI is approximately $2 \mu\text{g}/\text{cm}^2$, with approximately $1 \mu\text{g}/\text{cm}^2$ defined as a no-effect level (12). The weighting factors used to determine a safety factor for MCI/MI in a shampoo are shown in Table 5. In this instance, weighting factors of 10, 5, and 2 were derived for inter-individual variability, matrix effects, and use patterns, respectively. The value of 10 for inter-individual variability is a default value that assumes that volunteer subjects for HRIPT studies are generally less responsive than the general popu-

Table 5. Retrospective assessment of MCI/MI acceptable exposure estimates for shampoo and facial skin cream formulations

<i>Shampoo Assessment</i>
HRIPT no-effect level: $1.0 \mu\text{g}/\text{cm}^2$
<i>Safety factor assumptions</i>
10× for inter-individual variability
5× for product matrix (surfactant matrix)
2× for use patterns (long time use; product misuse)
100× safety factor
Theoretical acceptable level for shampoo products: $1.0/100=0.01 \mu\text{g}/\text{cm}^2$
<i>Facial skin cream</i>
HRIPT no-effect level: $1.0 \mu\text{g}/\text{cm}^2$
<i>Safety factor assumptions</i>
10× for inter-individual variability
5× for product matrix (penetration enhancers)
5× for use patterns (long time use; skin condition)
250× safety factor
Theoretical acceptable level for facial cream: $1.0/250=0.004 \mu\text{g}/\text{cm}^2$

lation and that hyper-reactive subjects also may exist in the general population. The value of 5 was assigned to matrix effects. This number was derived from the fact that the HRIPT conducted on MCI/MI was done in water as the vehicle (12), whereas the shampoo formulation contains surfactant ingredients. This 5X assumption may be appropriate given the known ability of surfactants to increase the skin penetration of chemicals (28, 46). However, a more accurate weighting factor might be obtained by analyzing skin penetration of MCI/MI in water versus the actual product matrix. Finally, the value of 2 is assigned to use pattern. Although a shampoo is a rinse-off product, the product is used daily over long periods of time and there is a potential for product misuse. Multiplying the weighting factors results in a safety factor of 100. As Table 5 indicates, dividing the HRIPT no-effect level of $1.0 \mu\text{g}/\text{cm}^2$ by the safety factor gives a maximum product exposure limit of $0.01 \mu\text{g}/\text{cm}^2$. The typical formulation of MCI/MI into shampoo products at 5 ppm produces in-use exposure levels well below that limit. The fact that most sensitized individuals can safely use rinse-off products containing those levels of MCI/MI (12, 47) indicates that this combination of in-product concentration and in-use exposure represents an acceptable formulation of this known contact allergen.

The safety factor and exposure limit determinations for MCI/MI in a leave-on facial skin cream application are also summarized in Table 5. In this situation the weighting factors are slightly different. While inter-individual variability and matrix considerations are the same as they were for the shampoo product, the usage pattern should receive a greater weighting factor (for example, 5 versus 2) because of the leave-on product use and potential for chronic exposure to compromised areas of skin. Factor multiplication in this instance gives a safety factor of 250, and dividing this value into the HRIPT no-effect level of $1.0 \mu\text{g}/\text{cm}^2$ gives a maximum exposure limit for the ingredient of $0.004 \mu\text{g}/\text{cm}^2$. Some reported use levels of MCI/MI in facial creams and other leave-on products previously marketed in Europe have exceeded this exposure level by as much as 20 fold and have clearly been implicated in the development of clinically relevant allergic contact dermatitis to MCI/MI associated with the use of those products (48). A thorough review of the MCI/MI skin sensitization potential and manifestations of clinical dermatitis under different occupational and consumer product exposure conditions has recently been published (20).

It must be emphasized that there are many assumptions inherent in developing appropriate safety/uncertainty factors and resulting maximum

exposure limits for ingredients. One generally defines conservative safety factors so as to approach zero risk of sensitization in the market. MCI/MI provides an illustrative retrospective example. While the problem of sensitization to MCI/MI has not been eliminated, the incidence has clearly been reduced to acceptable levels by careful formulation into appropriate product categories (20). The safety/uncertainty factors derived for this very potent skin allergen might not be appropriate for much weaker sensitizers. Hence, allergenic potency is another key factor in defining safe ingredient exposure limits. Also, each product exposure scenario is unique. Therefore, one needs to exercise caution in developing generic safety/uncertainty factors for different product types.

Conclusions

The development of skin sensitization and its clinical manifestation, allergic contact dermatitis, is a complex process influenced by a variety of factors related to chemical exposure. In producing and marketing consumer products, it is critical to understand the exposure characteristics for different product types and the ingredients contained therein, especially if any of those ingredients have the potential to be contact allergens. It is well understood that contact allergens, like all immunogens, show threshold and dose-response characteristics, and that individuals can be exposed to allergens at levels below which the induction of skin sensitization and/or the elicitation of ACD is unlikely to occur. For skin sensitization risk assessment, it is important to understand the threshold or no-effect levels of potentially sensitizing ingredients, in man, in the common currency of dose per unit area. It is also critical to be able to estimate the extent of exposure to the chemical when formulated into different product types. Then, through the application of general (though commonly product-type-specific) safety factors, a conservative determination of maximum product exposure limits can be determined. This approach, exemplified by the case of MCI/MI, can provide for the appropriate formulation of effective, though potentially sensitizing chemicals, into consumer products at acceptable levels, and allow for the determination of those formulation levels and/or product types that pose an unacceptable sensitization risk.

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