

Review Article

Prediction of irritancy in the human skin irritancy model and occupational setting

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It is of great importance to find ways to lower the incidence of chronic irritant contact dermatitis. In this process, it is crucial to have insight in the factors that can predict irritancy. This review offers a survey of recent findings in the field of skin irritancy testing, discussed in the context of renowned, older work. Extrinsic and intrinsic factors that may determine the outcome of irritancy testing in the human skin model are considered. In recent decades, there has been increasing interest in factors influencing the development of occupational dermatitis by means of prospective cohort studies. This promising new area of investigation is discussed separately.

Key words: chronic irritant contact dermatitis, extrinsic factors, intrinsic factors, irritancy testing, occupational dermatitis, prediction, prospective cohort studies. © Blackwell Munksgaard, 2003.

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Chronic irritant contact dermatitis (ICD) is the most frequently encountered skin disease in many occupations in which workers are to some extent exposed to irritants. This represents a burden of suffering from irritation or itch and may lead to absence from work. It is therefore of great importance to find ways to lower the incidence of chronic ICD. In this process, it is crucial to have insight into the factors that can predict irritancy. Whether or not chronic ICD will develop depends on the balance between the sum of all extrinsic harmful factors (irritants in the work and home environment, low humidity and high temperature, etc.) inflicted on the skin on one hand and intrinsic, constitutional factors regulating the reparative capacity of the skin on the other hand (1). Predictive irritancy testing as a method to understand and predict chronic ICD should be based on the aetiological concepts of chronic ICD. Therefore, considering predictive irritancy testing, it is helpful to make the same division into extrinsic and intrinsic factors, yielding 2 main work categories: (1) predictive irritancy testing of various substances aimed to select the least irritant substance and (2) predictive irritancy testing with one or more standard irritant(s) aimed to select a population that is at risk of developing chronic ICD. Prediction of risk of chronic ICD is performed using human skin irritancy tests in the

laboratory and in the occupational setting. Both strategies will be covered in this review.

In finding new chemicals and finished products with low irritant potential the industry making such products has increasingly to rely on human skin models, as animal models are nowadays abjured on ethical grounds, and because these methods had been proved to be poorly predictive in man (2). In order to avoid testing on humans as much as possible, *in vitro* tests have been developed (3, 4). Cytotoxicity in the *in vitro* neutral red uptake assay, using human keratinocyte cell lines, showed a good overall correlation with *in vivo* irritant potential in humans, with the exception of high molecular weight compounds (3). Upregulation of 27 kDa heat shock protein (HSP27) was observed in the epidermis upon *in vivo* and *in vitro* irritation (4). It can be expected that *in vitro* testing will be used more extensively in future for screening chemicals with low irritancy. This tendency towards *in vitro* testing will not abrogate the need for *in vivo* tests on humans, which will remain the 'gold standard' of predictive irritancy testing, at least for the near future. In this paper, several factors are described that can influence the outcome of *in vivo* irritancy testing in humans, classified as extrinsic and intrinsic factors. The subject is not treated exhaustively; for a more complete survey on factors influencing irritant

reactions, the reader is referred to the Guidelines on sodium lauryl sulfate (SLS) exposure tests, a report from the Standardization Group of the European Society of Contact Dermatitis (5).

Extrinsic Factors that Determine the Outcome of Human Skin Irritancy Models

Concentration of the compound

Increasing the concentration of a compound may elicit qualitatively different reactions; for example, SLS and croton oil in low concentrations cause erythema, whereas high concentrations induce bullae (6). Quantitative differences have been demonstrated in the form of clear dose-response relationships for SLS by means of trans-epidermal water loss (TEWL) measurements (7–9). The biological effect of a substance depends on the amount of molecules (molarity) rather than the total mass of the molecules (concentration) (10). Therefore, when the purpose of predictive testing is comparison of irritant potential between various compounds, these compounds should be tested on the basis of equal molarity, otherwise a false impression may be obtained regarding differences in irritancy. This theoretical consideration has practical limitations, when mixtures of more than one compound are to be tested, such as commercially available products.

Duration of exposure in the one-time occlusive patch test

For many years, closed patch testing has been the favoured test method, for both practical and traditional reasons. The 24-h patch test is used in most studies, and applied on the forearm, it may be considered as the ‘gold standard’ for one-time exposure tests (5).

Recently, SLS has been applied for 48 h on the back and forearm, in order to combine irritancy testing with routine allergic patch testing (9). Visual scores were more pronounced on the forearm than on the back, but the scores on the back and forearm showed a close correlation. Visual scores on the forearm correlated well with TEWL values on the forearm, whereas visual scores on the back and TEWL values on the forearm had a poor correlation (9). In another study by the same group, the interrelationship between the concentration of SLS and exposure time (3, 6, 12, 24 and 48 h) was determined (8). There was a clear distinction between the concentrations used only at 12, 24 and 48 h exposures (8). The factor of concentration had a greater impact on the outcome of the irritant response than the factor of exposure duration. To achieve the same irritant

response as found with a doubled SLS dose, the application time must be tripled (8). Recently, a simple 4-h patch test has been designed to examine crude differences in the effects of SLS on the skin, evaluated by a simple visual scoring system (11). When attempting to use this method to detect variation in susceptibility between summer and winter seasons, no significant differences were found, although there was a trend towards a greater susceptibility in winter (11). These differences were noted only for extremely high SLS concentrations (20 and 100%).

Other exposure methods or a search for better simulation of real-life exposure

Although the one-time 24-h occlusive patch test is a favoured test method because of its ease and rapidity to perform, the disadvantage of this technique is the fact that it mimics only an acute irritant reaction. The more common situation in real life is the development of chronic ICD resulting from multiple repeated exposures. In order to address this issue, the following test protocols have been used: repeated occlusive tests, repeated open tests and immersion tests (5).

Kligman and Wooding (12) developed a test method in which substances were repeatedly brought into contact with the skin under occlusion 24 h a day for 20 consecutive days, in order to be able to test substances with a very low irritant potential. Another way to test compounds of expected low irritancy is the chamber scarification technique in which the skin is scratched before closed patch tests are performed, repeatedly daily for 3 days (13, 14). Using this method in which the stratum corneum was bypassed, interindividual variation has still been found, demonstrating that a subject's susceptibility to irritants is also dependent on targets underneath the stratum corneum. Frosch and Kligman (15) have used an exposure model in which a substance is applied repeatedly during 5 consecutive days, the first day for 24 h and the following days for 6 h a day. To reflect better the conditions in daily practice, models have been developed in which detergents were applied in a multiple-repeated short-time occlusive way, namely 2 times daily, 45 min for 1 week (16, 17) or 3 weeks (18–20). Using this test method, it was possible to rank detergents according to their irritant potential, SLS far being the most irritant detergent (18, 20).

A further step towards a better reflection of daily life conditions may be the repeated open exposure technique. In this method, solutions are applied once daily on the forearm skin using

a glass or plastic ring, for 20 or 45 min for 1 week (21, 22) or more (20, 23). Clear differences in the irritancy of various detergents have been demonstrated by this method (20, 22). By means of a repetitive open irritation test it was possible to test the efficacy of different barrier creams (23). Using a repeated open application test of a thin film over a surface of 3 cm² on the forearms, it has been proved that a children's hand cleanser was more irritant than industrial hand cleansers (24).

Twice daily 30 min immersions of various detergents induced different degrees of erythema and scaling, and SLS was again shown to be the most irritant (25). The wash test represents another open test model, in which the act of washing is mimicked in a repetitive way (26–28). Repetitive washing with grit-containing cleansers 4 times daily for 1 week led to differences in TEWL values, skin redness and hydration (28).

A few studies have compared the patch test with the wash test with respect to the irritancy potential ranking order of a series of detergents (25–27). In one study (26), discrepancies were found in the ranking order obtained by the 2 techniques, whereas in the other study (27), similar rankings were found. The wash test, however, appeared to have the greater power of discrimination (27). Comparing the one-time patch test with the immersion test, there was a relatively close correlation between these models, with the exception of soap, which was irritant in the patch test but not in the immersion test (25). More recently, the same finding has been observed in our study investigating 4 different detergents using one-time occlusive, repeated occlusive and repeated open tests (20). Only in the one-time occlusive test did soap induced more erythema than the other detergents, whereas in the other models SLS and sodium cocoyl isethionate had higher visual scores than soap. By means of TEWL measurement, however, the mean ranking order of the detergents was similar in all models (20). The fact that soap was the most irritant substance in the one-time patch test could be explained by the earlier observation that the pH of a soap solution decreased after prolonged contact with the skin, as is the case under 24-h occlusive conditions (29). Soap with a low pH (5.7) induced erythema and pruritus which did not occur at higher pH (9.5) (29). In another study, on the effects of occlusion, it was found that postexposure occlusion by a plastic wrap caused more severe irritation compared with unoccluded exposures to SLS (21). The degree of augmentation of the irritant response by occlusion differs between varying types of substances. The irritant effect of polar

compounds is less influenced by occlusion than that of non-polar compounds (30).

Hence, it appears that the type of exposure may influence the outcome of the ranking order in irritancy testing. The central question is: which exposure method offers the best prediction of real-life exposure? This poses another question: what are the real-life conditions encountered? In most in-use situations, the uncovered skin is exposed to irritants several times daily. In other situations, already-exposed skin is covered by 'protective' gloves or other impermeable materials. In the first situation mentioned, the repeated open test seems the best way to simulate this. In the second situation, however, the one-time or repeated occlusive test may be preferred.

Intrinsic Factors that Determine the Outcome of Human Skin Irritation Models

Human skin irritancy model

Pre-exposure barrier function. Using TEWL after 4 days of repeated exposure to SLS as a measure of susceptibility, a close correlation with pre-exposure TEWL has been found ($R=0.71$) (16). A similar correlation coefficient has been noted between TEWL values before and after a single 24-h SLS exposure (31). Subsequent studies have confirmed the close correlation between pre- and post-exposure TEWL in the one-time SLS exposure model (32, 33). In persons with a high pre-exposure TEWL, the barrier function is apparently impaired from the start. This allows the irritant to penetrate and damage the skin more easily, which renders the skin more susceptible, particularly in the initial phase of skin irritation. In other studies using one-time occlusive tests, these results could not be confirmed; no correlation (34) or poor correlation (35) between pre- and post-exposure TEWL values has been found. In long-term repeated exposure models also, lesser correlations between pre- and post-exposure TEWL have been noted ($R=0.31$) (18). After multiple repeated exposures, the skin will adapt to a certain degree (see below). Therefore, skin reactivity after multiple exposures is probably particularly determined by the ability to develop adaptation, and the influence of pre-exposure barrier function diminishes (18). It must be stressed that these reported high values have been found for SLS only. Extrapolation to other types of irritants may yield only poor correlation values, as those irritants might penetrate and attack the stratum corneum barrier in a different way (36).

Concomitant (atopic) dermatitis in another body region. It has been proven that existing dermatitis,

irrespective of which type, in another location of the body may enhance reactivity to various irritants (6). We have confirmed the validity of this phenomenon for atopic dermatitis (AD) (17). AD patients with more severe dermatitis exhibited higher levels of reactivity (17). In a study by Agner (32), only those patients with active hand eczema had an increased susceptibility to SLS on the upper arm, as opposed to chronic and healed eczema patients and normal controls. The cause of this proneness to hyperreact to chemicals in the presence of dermatitis elsewhere is not yet known. Shahidullah et al. (37) have observed barrier function impairment on the uninvolved skin sites, related to the severity of dermatitis. Furthermore, TEWL of uninvolved sites of the forearm in patients with acute ICD of the hands was higher than that in patients with healed ICD of the hands, who in turn had higher TEWL values than controls (38). TEWL values on a distant site like the thigh were similar amongst persons with acute and healed ICD on the hands but higher compared with controls (38). A correlation has been found between TEWL values measured on the forearm and on the thigh, which was speculated as a generalized barrier disturbance in ICD, although the presence of an atopic predisposition could not be ruled out (38). Because the type of dermatitis present did not appear to influence the reactivity, the enhanced susceptibility noted was regarded as secondary to dermatitis activity *per se* (39). However, van der Valk et al. (40) have found a significantly elevated TEWL before and after SLS exposure only in the subgroup of patients with a manifest AD and not in manifest ICD. In a study on patients with a history of AD and patients with a history of contact dermatitis, higher pre-exposure and post-exposure TEWL values have been noted only in patients with a history of AD (18). It was concluded that the lower pre-exposure barrier function in AD was at least in part responsible for the enhanced irritant susceptibility in AD, besides other constitutional factors such as elevated reactivity of cellular targets underneath the stratum corneum and adaptation capacity (18). In other studies, patients with active and those with inactive AD reacted more strongly to SLS as compared with nonatopic controls (17, 41).

Hence, AD may be regarded as unique in its high skin reactivity.

Adaptation or inflammation? The traditional statement on the pathogenesis of chronic ICD, namely, that its development depends on the balance between the sum of all extrinsic influences on one hand and intrinsic constitutional factors regulating the reparative capacity of the skin on

the other hand, has been elaborated into a broader hypothetical view (42). In this scenario, the epidermis is nowadays considered as a highly active site of lipid synthesis that is under direct control of alterations in barrier status (42, 43). Barrier injury, regardless of what type (detergents, solvents and tape stripping), evokes a recovery or adaptive response that leads to normalization of barrier function within hours to days. Perturbation of the ionic gradient in the epidermis and various cytokines [such as interleukin-1 (IL-1) and tumour necrosis factor (TNF)- α] and growth factors are involved in this process (42). This barrier-initiated cascade of cytokines is seen as a normal response, always accompanying the repair process after barrier disruption. In normal skin, chronic exposure of the epidermis to damaging insults will result in a compensatory hyperplastic state of the epidermis, also called adaptation or 'hardening'. However, in AD skin, the impaired barrier function is considered to be of essential importance in its pathophysiology, in that it sustains the disease process. In AD, exposure to these damaging insults induces recruitment and stimulation of inflammatory cell types in the epidermis, so that previously uninvolved skin sites turn into involved sites.

In healthy persons without a history of skin disease, it has been demonstrated that there are interindividual variations in TEWL time course after a one-time patch test, which was inversely correlated with the responses after repeated occlusive exposures ($R = -0.61$) (44). TEWL increases observed in the days after patch removal was associated with higher TEWL values in the repeated test model, indicating the importance of adaptation in a functional way (44).

Thus, when the question is adapt or not adapt, AD patients can be grouped in the latter category, as is the case for some other subgroups of persons with a susceptible skin.

The influence of mucosal atopy on skin susceptibility. The impact of mucosal atopy investigated in the experimental skin irritancy model is not as clear-cut as the impact of its dermal counterpart, AD. Greater responses to graded SLS solutions were observed in AD patients and in patients with mucosal atopy without a history of AD, compared with nonatopic controls (41). In each atopic group, the effective SLS concentration causing irritation in 50% or more of the subjects (ED_{50}) was significantly lower compared with the controls. The ED_{50} values of active AD, inactive AD, mucosal atopy and controls were 0.0625, 0.31, 0.19 and 0.6%, respectively (41). In a small study on a use test with a dishwashing liquid, persons with a

history of mucosal atopy were not amongst the hyperreactors (45). In a more recent study, AD patients had an impaired barrier function compared with mucosal atopy and control subjects, with the latter groups having a similar barrier function (46). However, as has been stated before in this review, an individual's susceptibility is dependent not only on their barrier function but also on other factors such as reactivity of cellular targets beneath the stratum corneum and reparative capacity.

Genetic factors. Recently, the influence of a genetic marker on irritant susceptibility was investigated (47). Visual irritant thresholds were determined using graded concentrations of SLS and benzalkonium chloride in a large group of nonatopics. Transition polymorphism has been identified in the TNF- α gene. Individuals carrying a haplotype that includes the A-allele are high secretors of TNF- α , which is a key mediator in the pathogenesis of ICD (47). In the low irritant threshold groups of both SLS and benzalkonium chloride, a significantly increased number of persons having the A-allele has been found (47). This study offers the first description of a non-barrier-related marker of susceptibility in nonatopics. Keratinocytes of AD patients exhibited higher levels of TNF- α and IL-1 after non-specific stimulation than keratinocytes of nonatopics (48). The strength of response to irritants is not only influenced by the levels of TNF- α and IL-1 but also by the individual's ability to quench free radicals, levels of antioxidant enzymes and the ability to form protective heat shock proteins. It has been hypothesized that the above-mentioned mechanisms may all be under genetic control, which thus determine the variability in responsiveness to irritants (43).

Prior exposure to irritants. In guinea pig skin, 8 applications of detergents induced an increasing irritation (49). After 30 applications, however, there was a complete accommodation (49). The same phenomenon has been identified by our group, in multiple repeated exposures on humans (18). Clinical changes were accompanied by a downgrade curve in the TEWL time course, after an initial TEWL increase. A similar TEWL time course was observed on skin sites showing no or only mild clinical signs (18). TEWL decrease after initial increase was also noted in a 21-day repeated use test (45). In another study, it has been shown that there was hyporeactivity towards a challenge with a one-time SLS patch at sites already repeatedly exposed to SLS, after 6 and 9 weeks but not after 3 weeks (50). The

hyporeactivity found in these studies signifies a functional adaptation, or hardening, of the skin. Hardening of the skin may be an important factor in predictive testing on subjects with a different occupational background. For this reason, the skin of a cleaner may be less susceptible than that of an office worker. The specificity of hardening is not yet exactly known. If the specificity of hardening is high, one must be cautious of this phenomenon in predictive irritancy tests comparing different chemicals.

Predictive testing in the occupational setting

In the past decade, several field studies have been conducted in which the incidence or prevalence of hand dermatitis has been investigated in a cohort of trainees in high-risk occupations. In these prospective studies, the aim was to examine the impact of one or more potential risk factors on the incidence of hand dermatitis. Table 1 shows the key features of these investigations. Important risk factors were history of AD (51–53), history of hand dermatitis (51), history of metal dermatitis (51), degree of chemical and mechanical exposure (52, 54) and insufficient recovery time during the work (52). In some studies, the factor of history of AD has not been identified as a risk factor, probably because of selection bias (54–57). Apparently, only those persons having no history of dermatitis had chosen these high-risk occupations or remained in these occupations ('healthy worker effect'). Dry skin and mucosal atopy were risk factors in a study on hairdressers and nurses (54). Possibly these high-risk persons belong to the group which may be regarded as having an 'atopic skin diathesis', a term coined by Lammintausta et al. (58). Atopic skin diathesis was denoted as the presence of dry skin and low itch threshold for 2 of 3 irritants (sweat, dust and rough materials), in combination with white dermographism and facial pallor/infra-orbital darkening. In their cross-sectional study on 'wet' hospital work, they found a strong influence of a history of AD but a very weak influence of mucosal atopy (58). However, past or present mucosal atopy in combination with atopic skin diathesis was proven to increase the risk of hand dermatitis (58). Diepgen (59) has constructed an 'atopy score', based on the criteria for AD by Hanifin and Rajka (60), to better assess the likelihood of developing dermatitis in high-risk environments. In some field studies, however, the value of this atopy score, was less contributive than a history of AD (53, 61). In a large-scale investigation on car industry workers, the following independent factors could predict the

occurrence of hand dermatitis to a large extent: history of AD, history of hand dermatitis, wet work more than 3 h per day and dyshidrosis (62). For hairdressers, predictive factors were atopic skin diathesis, wet work more than 4 h per day and exposure to permanent wave liquids (62).

In contrast to the findings in experimental skin irritancy studies, prospective field studies could not demonstrate the importance of pre-exposure barrier function as a risk factor for hand dermatitis (53, 54, 56, 63), with the exception of a study by Coenraads and Pinnagoda (55). In this relatively small study, the incidence of hand dermatitis was much lower than in the field studies conducted afterwards. A possible reason for the elevated pre-exposure TEWL in the persons who turned out to be cases later on is the fact that these persons might already have been exposed during previous occupations. In other studies, increased TEWL values were observed preceding the occurrence of hand dermatitis (53, 56).

The use of provocation tests as a tool for the prediction of risk for hand dermatitis has recently been investigated, as pre-exposure barrier function had been proven to be of no value for this purpose (57, 61). Tests with SLS or dimethyl sulfoxide (DMSO) were not able to predict hand dermatitis, in contrast to those with NaOH (61). The combination of the provocation values of DMSO and NaOH and skin moisture had a high sensitivity (94%) but a low specificity (24%) (61). In a small study by Smith et al. (57), 9 out of 24 apprentice hairdressers developed hand dermatitis. In these cases, the pre-exposure irritation threshold tended to be lower than in non-cases. Unfortunately, a 4-h one-time SLS test was performed, which was assessed visually, in this investigation in which 16 out of the initial group of 42 persons were lost to follow-up for 'administrative reasons' (57).

The point prevalence of ICD was higher during the first observation period (52, 56, 64). This is probably due to the phenomenon of hardening which has developed during the later periods. Another possibility is a more intense exposure to irritants in trainees during their first work period.

Comments

What do we learn from the literature on prediction of irritancy? When the programme is to use predictive irritancy testing of various substances in order to select the least irritant compound, substantial progress has been made in recent decades. *In vitro* testing has replaced animal tests as a screening method, which enables us to make a rough division into safe/not safe. The most reli-

able test methods are still the human models in which compounds are brought into contact with the skin in an occlusive (one-time 24-h or repeated) or open (repeated) way. The model of choice (occlusive versus open) depends on the presumed circumstances under which these compounds are met with in daily life. Recently, a modification of the one-time 24-h patch test has been introduced by Basketter's group (11), with the intention of examining crude responses. Indeed, this modification may be used as an intermediate method between prescreening *in vitro* models on one hand and more delicate human test models on the other hand. These latter models should be considered to be more reliable until properly conducted comparative testing with the 4-h modified test has demonstrated equal predictivity.

One way to refine the human test methods is to assess the test responses by means of TEWL measurements. In this case, guidelines on this matter should be adhered to in order to achieve trustworthy results (5). It has been stated in the literature on several occasions that these guidelines have been followed, although, in fact, authors made deviations in important aspects such as performing measurements only 30 min after patch removal. This will result in false outcomes, as the measured value is 'contaminated' by post-occlusive hydration. Therefore, when authors decide not to follow a particular aspect of the guidelines, they should make this absolutely clear by stating that they have not adhered to the guidelines in this respect and also give the reason for this.

TEWL measurement should never be a goal *per se* and always be accompanied by a reliable visual scoring system (5). On the other hand, visual scoring has its limitations such as in dark-skinned persons, in whom detection of erythema is more difficult.

Field studies on workers in high-risk occupations have shown that pre-work barrier function is not a valid predictor of the risk of hand dermatitis, in contrast to pre-exposure barrier function in experimental irritancy models. In these laboratory models, irritants are exposed for a relatively short time period on the skin. In daily practice, however, the result of repeated exposures to damaging influences of various kinds is a complex interrelationship of different (partly unknown) factors, such as severity of chemical and mechanical insults, recovery time between exposures, seasonal influences, barrier function, history of AD, ability to develop adaptation and other factors that are probably under genetic control. Determining who is at risk probably demands a

combination of anamnestic data, well performed irritancy tests and genetic tests (in the future). Predictive irritancy testing by means of one or more standard irritant(s) may be useful in the occupational setting. This probably requires that several irritants be tested, as, in reality, there is exposure to different kinds of irritating factors (63). It is a challenge to find out which testing method is most appropriate for a particular occupation. Once it is decided which method is most appropriate, officially agreed guidelines for that method should be developed.

In view of the complex interrelationship of the above-mentioned factors in daily practice, multiple repeated exposure models should be used as a tool to identify persons at risk for hand dermatitis in field studies, because only in this way essential factors, such as the ability to develop adaptation, can be tested. The disadvantage of such a repeated model, however, is its lower practicability in the field. A solution for this problem might be to perform TEWL measurements before and after some weeks of relevant exposure to the types of irritants involved in the occupation concerned, as field studies have demonstrated TEWL increases in workers who later turned out to be cases of hand dermatitis (53, 56).

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