

Review Article

Augmentation of skin response by exposure to a combination of allergens and irritants – a review

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Clinical experimental studies on contact dermatitis (CD) often evaluate the effect of one allergen or one irritant at a time. In real life, the skin is often exposed to more allergens, more irritants or allergens and irritants in combination. This combined exposure may potentially influence irritant effects as well as allergenicity of the substances. Mechanisms for a changed response can be immunological effects or enhanced penetration. Knowledge about the influence on skin reaction of combined exposures may influence skin reactivity and is important for prevention of CD. For allergens, threshold values may be influenced by the presence of other allergens or irritants, and prevention of CD by regulation of threshold values may not be sufficient if this is not taken into account.

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Contact dermatitis (CD) is a common disease mainly caused by environmental factors. The risk of chronicity is high (1), which in many cases may be caused by continual exposure to irritants and relevant allergens in the environment. The damaging effect on the skin caused by irritants depends on the concentration of the irritant, as well as on exposure time. A dose–response relationship exists for allergens, and elicitation of allergic contact dermatitis (ACD) depends on the dose of the allergen. The presence of more irritants, more allergens and irritants and allergens in combination may, however, potentially influence irritant effects as well as allergenicity of the substances. Knowledge about how combined exposures may influence skin reactivity is important for the prevention of CD. For allergens, threshold values may be influenced by the presence of other allergens or irritants, and prevention of CD by regulation of threshold values may not be sufficient if this is not taken into account.

The simultaneous presence of allergens and irritants in combination has been reported to produce an altered response compared to when applied alone (2–5). Several types of interaction may exist: (i) an additive response in which the skin response is greater than that expected from addition of the responses to each of the sub-

stances applied separately; (ii) a synergistic response in which the skin response is greater than that expected from adding the separate responses; and (iii) an antagonistic response, quenching, in which the skin response is less than expected from adding the separate responses. Many other terms are used (augmentation, potentiation, enhancement, etc.), but these are not well defined (6).

The present article concentrates on possible additive and synergistic responses to combined exposures to irritants and allergens.

Combination of 2 Allergens

Danger signal

The ability of an individual to become sensitized to a specific allergen is determined by many factors, and when presented to a hapten, an inter-individual variation in sensitization capacity exists (7). It has been suggested that the ability to react to different haptens is controlled by different genes (8) and that the susceptibility to induction of allergy is specific in relation to a hapten (9). A genetic influence on sensitization capacity has, however, not been found in all studies (10, 11), and recent data also show that exposures are of major importance (12). It has been suggested that a danger signal, interpreted

as initiation of an immunological process, is of importance for sensitization and elicitation of ACD, and the concept that an irritant or an irrelevant hapten is necessary to provide this danger signal has been claimed (13, 14) (Table 1).

Many potent allergens, e.g. 2,4-dinitrochlorobenzene (DNCB), have an irritant effect additional to their sensitizing capacity, at least in high concentration. Such allergens influence the immune response in the epidermis by upregulation of tumour necrosis factor- α (TNF- α) (15–17). It is documented that TNF- α , a proinflammatory cytokine, plays a key role in ACD in both sensitization and elicitation phases as well as in irritant contact dermatitis (ICD). In other words, the danger signal in ACD is cytokine release, e.g. TNF- α from keratinocytes. Two studies on the genetic influence on the susceptibility to ACD and ICD (7, 18) proposed that a polymorphism in the gene encoding for TNF- α (TNFA-308*2) was involved in both skin irritation and sensitization, reflecting common pathogenetic pathways of these types of dermatitis. In addition, this finding may point to a genetic basis of the danger model.

Also, relatively weak allergens such as citral may become allergens of importance if the substance at the same time possesses a strong irritant potential (19).

It has been proposed by Grabbe et al. (20) that an antigen-specific cell activation as well as a non-antigen-specific proinflammatory signal is necessary to induce contact hypersensitivity (CHS) and that both actions may be provided by application of a sufficient high dose of hapten. An experiment on mice was carried out in which an insufficient dose of a relevant hapten and an unrelated, irrelevant hapten in conventional dose caused CHS, while single application of each compound did not. It was shown that a non-antigen-specific effect of an irrelevant hapten contributes to elicitation of CHS (20). A similar study in humans

would be of interest, but such a study is complicated by the fact that applications of an irrelevant allergen in a sufficiently high dose in humans introduce a high risk of the individual becoming sensitized. Application of two allergens, one relevant and one irrelevant, in low concentrations was reported not to influence the skin response, as compared with application of the relevant allergen only (3). This was also expected, because TNF- α is not upregulated by low doses of allergens and the danger signal is missing.

Additive and synergistic effects

In a human study made by McLelland and Shuster (21), the response to 2 unrelated allergens, both of which the subjects were sensitized to, was evaluated. A total of 15 common allergens were included and tested alone and in different combinations. The mixtures were applied in sub-threshold doses of the 2 allergens, to both of which the test person was sensitized to. 7 patients were included when calculating the dose-response curve and 2–6 antigen concentrations were used. From this study, it was concluded that the threshold for a response to 1 allergen was lowered by the presence of another and, anticipating a linear dose-response curve, it was concluded that the interaction was an additive response.

Johansen et al.(3) also studied the combined effects of 2 allergens by comparing 2 groups of patients, 1 group consisting of patients with 2 allergies and a control group with only 1 allergy. Both groups were exposed to 2 allergens defined as allergen A and B (perfume ingredients) alone, and in combination, allergen A + B. In individuals sensitized to both allergens, the response was augmented by about a factor 4, as compared with the allergens tested separately. In the control subjects, no response was observed for the allergen that they were not sensitized to. It was concluded that combination of 2 allergens in individuals allergic to both substances had a

Table 1. Combination of allergens

Design	Substances	Materials and methods	Result/augmentation	References
Simultaneous exposure of 2 allergens in individuals sensitized to the allergen	Allergens mostly from the standard European series e.g. Ni combined with thiuram mix and fragrance mix combined with quinoline mix	Finn Chamber 8 mm, 48 h Vehicle: chloroform Evaluation by skin fold thickness and clinical grading	Additive effect	(21)
Simultaneous exposure of 2 allergens in individuals sensitized to the allergen. A control group sensitized to only one of the substances was tested in an identical way	Ingredients from the fragrance mix e.g. isoeugenol combined with cinnamic aldehyde	Finn Chamber 8 mm, 48 h Vehicle: ethanol Evaluation by clinical grading and laser Doppler flowmetry	Synergistic effect. No effect of combination was found in the control group	(3)

synergistic effect on the elicited response and that the dose-response curves were shifted to the left (3). It was not possible to study threshold values, as these were determined in only a few subjects. Johansen et al. (3) demonstrated a synergistic effect using a logistic dose-response model for the statistical analysis, while the effect was described as additive in the study by McLelland and Shuster (21), using statistics assuming a linear dose-response curve. The difference in statistic evaluation of data may very well explain the different conclusions in the studies as regards the size of the augmentative effect.

Repeated application of 1 allergen (Ni) has been studied by Hindsén et al. (22). This study showed an increased response to Ni in earlier Ni dermatitis test sites when retesting after 3 and 6 weeks. This was also observed after 8 months (23). Studies of sequential exposure to an allergen (Ni) and an irritant sodium lauryl sulfate (SLS) have also been made by Hindsén and Bruze (24). In this study, a decreased skin reactivity was observed 1 month after application of Ni to a previous dermatitis test site from SLS, known as the hardening effect of some irritants.

Recent studies indicate that specific immunoglobulin M antibodies are required to elicit contact sensitivity. These antibodies are specifically triggered by the antigen but may locally react with other antigens in such a way that a response is triggered by different pathways (25). This specific dual antigen initiation may, at least in theory, explain synergistic effects between synergies observed from exposure to several allergens.

Combination of 2 Irritants

ICD results from direct contact with irritant substances, and chronic ICD is due to an overbalance of irritant factors in relation to barrier function and repairing capacity of the skin (26, 27). ICD is especially common in wet-work occupations, where exposure to irritants such as detergents and also gloves may cause chronic ICD, though foods and cutting oils are also frequent causes of ICD (Table 2).

Irritants include chemical substances with varying irritant properties, and the skin response depends upon the specific irritant, reflecting the different ways in which different chemicals may penetrate and interact with components of the skin. This finding is supported by the different clinical (28) and histological (29) findings caused by different irritants, and by differences in skin surface, skin colour and barrier function after exposure to various irritants (30–32). SLS was reported to impair barrier function to a greater

extent than nonanoic acid or hydrochloric acid, although causing identical severity of inflammatory response (33), and it is generally accepted that detergents mainly affect skin barrier function, while other irritants primarily affect the inflammatory skin response. This different impact on the skin from different irritants makes the combined effect of simultaneous exposure to more than one irritant unpredictable.

In a study including 20 volunteers, Wigger-Alberti et al. (5) studied the skin response to SLS and toluene (an organic solvent) in a repeated irritation model. The irritant was applied under occlusion for 30 min $\times$ 2 daily for 4 days, using SLS/SLS, toluene/toluene or SLS/toluene for 2 daily applications. An increased skin response to combined exposure of SLS/toluene was found as compared with each irritant on its own, when evaluated by visual score, transepidermal water loss (TEWL), chromametry and skin capacitance (5).

The same authors also investigated the combined effect of SLS and *n*-propanol (34) using the same repeated irritation model. 20 volunteers were exposed to SLS/SLS, *n*-propanol/*n*-propanol and SLS/*n*-propanol, and in this study application of SLS and *n*-propanol did lead to augmentation of cumulative skin irritation, as compared with quantitatively identical application of the same irritant only. The mechanism of skin impairment depends on the type of irritant (35–37), and these findings confirm the difficulty in predicting the interactive effect of even well-known single irritants, and show that the effects of interaction between different irritants are quite complex. This is supported by the study of Effendy et al. (38), in which biological responses to 2 irritants suggest a different mode of action of retinoic acid (RA) and SLS. The SLS + RA combination caused significantly higher responses when evaluated with TEWL, visual scoring (such as scaling) and laser Doppler flowmetry, compared to the combination RA + SLS. For capacitance measurements, decreased responses occurred when the skin was pretreated with SLS before RA exposure, compared to pretreatment of the skin with RA before SLS. One interesting finding was that pretreatment with RA appeared to reduce irritant responses to SLS, and perhaps RA may obstruct the percutaneous permeation of SLS (38, 39). Pharmacological antagonism or synergism between the irritants may also play a role in the different mode of action. However, this seems not to be the case when combining SLS and toluene and SLS and *n*-propanol (5, 34). Investigation of the combination of the 2 irritants SLS + RA by Ale et al. (39) showed a synergistic effect, except by measurement of electrical capacitance.

Table 2. Combination of irritants

Design	Substances	Materials and methods	Results	References
Sequential exposure of 2 irritants in healthy volunteers	Combination of SLS/toluene (undiluted) Vehicle: water	Finn Chamber, 12 mm, 30 min repeated $\times 2$ daily for 4 days Evaluation by clinical scoring, TEWL and colourimetry	Additive effect	(5)
Sequential exposure of 2 irritants in healthy volunteers	Combination of SLS/ <i>n</i> -propanol Vehicle: water	Finn Chamber, 12 mm 30 min repeated $\times 2$ daily for 4 days Evaluation by visual scoring, TEWL and colourimetry	Additive effect	(34)
Sequential exposure of 2 irritants in healthy volunteers	Combination of retinoic acid + SLS Vehicle: ethanol and water, respectively, and SLS/retinoic acid	Polypropylene chamber (1.8 cm, Hilltop Laboratory), 24 h repeated for 18 days. Evaluation by clinical scoring, TEWL and cutaneous blood flow	Combination of SLS/retinoic acid: synergistic effect	(38)
Sequential exposure of 2 irritants in healthy volunteers	Combination of SLS + retinoic acid Vehicle: ethanol	12 mm Finn Chamber, 24 h, after varying time intervals ranging from 1 h to 2 weeks reexposure to retinoic acid. Evaluation by clinical scoring, TEWL and colourimetry	Synergistic effect	(39)

SLS = sodium lauryl sulfate; TEWL = transepidermal water loss.

Combination of an Allergen and an Irritant

In real-life situations, combined exposure to irritants and allergens is very common, and the understanding of possible mechanisms of interaction is therefore important.

Combined exposures might have an effect on the immunological response. The danger signal theory, assuming that an upregulation of TNF- α caused by an irritant or by irritant effects of an allergen is important for initiation of CHS, has already been discussed. Another possible way of interaction may be that the irritant may facilitate the penetration of the allergen, and in this way increase the skin response and lower the threshold value for the allergen. Detergents especially harm the barrier (40, 41) (Tables 3 and 4).

A lowered threshold value for irritants influencing the elicitation response to ACD has been discussed (42). In a previous study comparing the skin response to SLS in normal subjects and patients with colophonium allergy, it was reported that subjects with a positive colophonium patch test have a lower irritant threshold, and thus a greater susceptibility to skin irritation, than normal subjects (43). In consequence of the danger signal theory, the increased degree of skin irritation in susceptible individuals promotes the induction of sensitization. The observation that individuals with enhanced susceptibility to skin irritation are more liable to develop allergic skin reactivity, however, needs to be confirmed. In another study, skin reactivity to irritants in relation to sensitization and/or elicitation to DNCB allergy was investigated (44). In this study, no association between elicitation reaction to DNCB and irritant threshold (reaction to SLS)

was found when evaluated by visual scoring, indicating that variation in allergic skin reactivity may be determined by several specific factors in the individual. However, when evaluated by echographic measurements, the enhanced allergic reactivity of individuals with a lower irritant threshold was apparent, though only with low concentrations of DNCB. This is consistent with the hypothesis that individuals with a low irritant threshold is also more liable to develop allergic skin reactions.

Simultaneous application of irritants and allergens has been evaluated in a number of studies. An early study of combination of allergens and irritants was carried out by Kvorning and Svendsen (45), who found that addition of a detergent solution to patch test nickel chloride and potassium dichromate in patients allergic to these substances would elicit allergic reactions that would otherwise remain latent. Kligman et al. (46) performed a study in which they found that pretreatment of the skin with 10% SLS 1 h before application of Ni magnified the response, compared to single application of the allergen. In a study on the concentration threshold values for nickel in nickel-sensitive individuals, open application of SLS did not influence threshold values for the allergen, but this result may be due to the combination of open application and use of quite low concentrations of both the allergen and the irritant (47).

These studies overall confirm the hypothesis that concurrent application of allergens and irritants and pretreatment with an irritant before application of an allergen promote a stronger response than when applied separately, either

Table 3. Combination of allergens and irritants

Design	Substances	Materials and methods	Result/augmentation	References
Simultaneous exposure of allergen and irritant in individuals allergic to Ni and Cr	Ni + detergent or Cr + detergent Vehicle: ethanol and water, respectively, Ni + SLS	Linen patches 1 × 1 cm, 24 h Evaluation by clinical grading	Addition of irritant elicited allergic reactions, which would otherwise remain latent	(45)
Simultaneous exposure of allergen and irritant in Ni-sensitized individuals		Hand immersion model: repeated immersion twice daily for 23 days with SLS and addition of Ni	Repeated open treatment on surfactant-damaged skin with up to 1 p.p.m. Ni does not elicit an allergic reaction	(48)
Simultaneous exposure of allergen and irritant in Ni-sensitized individuals	SLS + Ni Vehicle: water	12 mm Finn Chamber, 24 h Evaluation by clinical scoring, TEWL and colourimetry	Clinical scoring and colourimetry: synergistic effect TEWL: additive effect	(2)
Simultaneous exposure of allergen and irritant in individuals allergic to the allergen	Hydroxycitronellal + SLS Vehicle: ethanol	8 mm Finn Chamber, 48 h Evaluation by clinical scoring and laser Doppler flowmetry	75% had a stronger patch test elicitation reaction when patch tested to hydroxycitronellal + SLS, compared to hydroxycitronellal alone	(54)
Simultaneous exposure of allergen and irritant in MDBGN-sensitized individuals	Combination of SLS + MDBGN Vehicle: water	8 mm Finn Chamber, 48 h Evaluation by clinical scoring, TEWL and colourimetry	Additive effect	(49)
Sequential exposure of allergen and irritant in individuals allergic to the allergen	7 different allergens: Ni, chromate, fragrance, thiurams, lanolin, benzothiazyls or colophonium Vehicle: chloroform Irritant: SLS or anthralin	8 mm Finn Chamber, 48 h with the allergen and immediate afterwards application of the irritant for further 24 h Evaluation by clinical scoring and skin fold thickness	Doses of allergen applied alone did not produce a response (produced a response by addition of an irritant)	(4)

MDBGN = methyldibromo glutaronitrile; SLS = sodium lauryl sulfate.

Table 4. Combination of allergens and irritants

Design	Substances	Materials and methods	Result/augmentation	References
Sequential exposure of allergen and irritant in individuals allergic to the allergen	Sub-irritation concentrations of SLS, DMSO or phenol before allergen challenge with 16 different allergens	Provocative patch test: Pretreatment with, e.g. 10% SLS 1 h before allergen challenge. Patch: 1 inch square of a non-woven cloth (Webril Curity), 48 h	Augmentation of response compared to allergen challenge alone	(46)
Sequential exposure of allergen and irritant in Ni-sensitized individuals. A control group was included and tested in an identical way	Ni + SLS Vehicle: water	Open application of 15 μ l Ni on 1 cm ² of the forearm combined with SLS. Evaluation by clinical scoring	No allergic reaction was seen at 100 p.p.m. Ni either with or without SLS. At 1000 p.p.m. and 4000 p.p.m. Ni with SLS 22 allergic reactions were seen	(47)
Sequential exposure of allergen and irritant in Ni-sensitized individuals. 2 control groups were included. One exposing the SLS-treated area to Ni, the other arm serving as control. One exposing the forearm skin to Ni or vehicle	Ni + SLS Vehicle: ethanol and water	Hand immersion with Ni of ulnar finger and open exposure to 2 drops of Ni on the forearm and one patch with SLS, 8 mm Finn Chamber, 24 h. Evaluation by visual scoring and laser Doppler flowmetry	A concentration of 10 p.p.m. and 100 p.p.m Ni provoked significant inflammatory skin changes on SLS-treated skin in Ni-sensitized individuals. In controls, no effect of combination was seen	(50)

DMSO = dimethylsulfoxide; SLS = sodium lauryl sulfate.

due to an immunological effect or due to an increased penetration of the allergen. Because detergents were the types of irritants used in all these studies, an increased penetration is likely to be at least part of the explanation. Allenby and Basketter (48) reported that immersing an arm in the anionic surfactant SLS greatly enhanced patch test reactivity to nickel on the dorsal forearm, when compared with normal skin on the contralateral non-immersed forearm.

In a study by McLelland et al. (4), patch tests with different standard allergens for 24 h followed by 24 h irritant patch testing (SLS or anthralin) were performed, and an increased (additive) skin response was found, as compared with application of the allergen alone. The authors argue that due to the use of low irritant concentration, and to the fact that the allergen was applied 24 h before the irritant, it was less likely that the enhanced response was due to increased penetration, and more likely to be an immunological effect of combined exposure to irritant and allergen.

Agner et al. (2) studied 2 groups of patients with nickel allergy. 1 group was exposed to a dilution series of SLS and a constant concentration of nickel, and another group was exposed to a dilution series of nickel and a constant concentration of SLS. Data were analysed using a logistic dose-response model, and it was estimated that the skin response was augmented by a factor of 4, as compared with each of the substances applied separately. When evaluated by clinical scoring and colourimetry, the response was found to be synergistic. This difference from the findings of McLelland et al. (4) is probably due to the use of more advanced statistical analysis.

A recent study (49) showed that the patch test response to methylidibromo glutaronitrile (MDBGN) is significantly influenced by the presence of SLS. The penetration profile of an allergen may differ according to the chemical properties of the allergen. MDBGN is an organic compound, and the route of penetration may be different from that for Ni and thus affected in a different way by SLS. The increased skin response following SLS application reported for both allergens is therefore of interest. Nielsen et al. (50) studied the effects of exposure to Ni in concentrations of 10 p.p.m. and 100 p.p.m. on the hands and forearms of patients with hand eczema and Ni allergy, including test sites treated with SLS. 10 p.p.m. and 100 p.p.m. of Ni provoked inflammatory skin changes on SLS-treated skin in patients allergic to Ni.

Data on the relationship between hand eczema and perfume allergy has recently been published

(51). The hands are often in contact with household products containing both detergents and perfume allergens. An experimental model for hand exposure to allergens and irritants was established using the forearm. It was shown that a stronger response was elicited to the perfume allergen hydroxycitronellal, when applied together with SLS than if applied alone (52). However, if the hands were exposed to only the perfume allergens in sensitized subjects, no difference was found in comparison to the vehicle control, supporting the multifactorial nature of hand eczema and the role of combined exposures in producing clinical symptoms (53).

In conclusion, several studies confirm that an interactive effect is present when combining allergens and irritants. In most of these studies, detergents have been used as model irritants. Additional knowledge about the combined effect of allergens and irritants, including information about the effect of a non-barrier injuring detergent, would be interesting.

Conclusion and Perspective

Combined effects of more allergens, more irritants or allergens and irritants together are reported to produce an altered response compared to when applied separately. The mechanism for this may be an immunological effect or a change in skin penetration. Threshold values for allergens (and irritants) may be changed. Due to the complex exposure situation in real life, with multiple contact allergens and irritants, other types of studies need to be performed. More knowledge about combination effects may be an important aspect in future prevention of CD.

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