

Impact of glove occlusion on cumulative skin irritation with or without hand cleanser—comparison in an experimental repeated irritation model

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Summary

Background. Irritant contact dermatitis remains a substantial problem in the food processing industries. Irritants that are weak by themselves, such as glove occlusion and mild detergents, could interact to produce contact dermatitis.

Objectives. To model the irritant action of an antibacterial hand cleanser and glove occlusion, with sodium lauryl sulfate (SLS) as a positive control. The effects of a pre-exposure cream and a post-exposure cream were also investigated.

Methods. A modified repeated short-time occlusive irritation test with 20 healthy volunteers, and application of irritants over 4 days, with pre-exposure and post-exposure creams and overnight glove occlusion, was performed. The changes in transepidermal water loss (TEWL) served as a measure of the irritant damage to the epidermal barrier.

Results. The antibacterial cleanser and the glove occlusion separately induced only minor increases in TEWL. When combined, the two showed a tandem effect, as the TEWL increase was significantly higher, and was similar to that seen with the positive control, SLS. The pre-exposure and post-exposure creams alone significantly mitigated the cumulative irritation, and this effect was strongest when the two creams were combined.

Conclusions. Irritant contact dermatitis may develop through the tandem effects of long-term glove occlusion and the accumulation of barrier damage from hand washing, even when mild hand cleansers are employed.

Key words: detergents; irritant contact dermatitis; non-invasive measuring methods; occupational; skin barrier.

Irritant contact dermatitis remains a socially and economically significant public health problem, despite decades of research and the development of prevention

programmes such as the three-step skin protection programme (1–3). Workers in food processing and cooking are among the groups with a high incidence of contact dermatitis, the major proportion of which is irritant contact dermatitis (3–5). Some of the known key irritant factors in this occupation are related to wet work, namely a high frequency of hand washing, and exposure to hot water, detergents, and possibly food-derived irritants (4, 6), coupled with insufficient use of skin protection (4). As a part of its ongoing programmes to investigate and counteract the high frequency of contact dermatitis in this occupation, the Institution for Statutory Accident Insurance and Prevention in the Food Processing Industry commissioned this study with the

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Table 1. Combinations of irritant factors and topical preparations applied on the 13 test fields

	Treatment	Test fields
Negative control	No treatment	1
Positive control	SLS 0.5% for 30 min	2
Occlusion alone	18 hr of overnight occlusion alone	3
Antibacterial hand cleanser; 30 min of application	Hand cleanser for 30 min alone, without occlusion	4
	Hand cleanser for 30 min with occlusion	5
	Hand cleanser for 30 min with occlusion, plus PC	6
	Hand cleanser for 30 min with occlusion, plus Em	7
	Hand cleanser for 30 min with occlusion, plus PC and Em	8
Antibacterial hand cleanser; 10 min of application	Hand cleanser for 10 min alone, without occlusion	9
	Hand cleanser for 10 min with occlusion	10
	Hand cleanser for 10 min with occlusion, plus PC	11
	Hand cleanser for 10 min with occlusion, plus Em	12
	Hand cleanser for 10 min with occlusion, plus PC and Em	13

Em, post-exposure emollient, in our study Eucerin® hand cream; PC, protective (barrier) cream, in our study petrolatum; SLS, sodium lauryl sulfate.

primary objective of developing an *in vivo* model of the irritant factors present in a commercial kitchen. The study took as an example a particular commercial kitchen in which the relevant irritant factors were hand washing with an antibacterial hand cleanser and prolonged glove occlusion. The workers wore vinyl gloves for 6–8 hr per day, and washed their hands 10–20 times per day. Glove-wearing over such an extended period is known to be an irritant factor itself (7). The workers often had a working week of 6 days.

The workers had unlimited access to a protective ('barrier') cream and emollient, as is laid down in the German regulation and as is instructed on the basis of the so-called 'three-step skin protection concept' (2, 8, 9). Our secondary objective was to investigate the effects of these preventive measures in the irritation model.

The study used the modified repeated short-time occlusive irritation test (ROIT) (10), in which the repetitive subclinical irritant injuries are designed to model the elicitation of irritation, following Malten's hypothesis, whereby multiple repetitive subthreshold injuries build up to induce chronic cumulative irritant contact dermatitis (11). It was a practice-oriented study, but it nevertheless showed an important feature of the tandem action of occlusion and irritation caused by detergents.

Subjects and Methods

Study design

A modification of the well-established ROIT (10, 12) was employed, as described in previous studies from our centre (6, 13). In brief, the irritant factors, that is, the antibacterial hand cleanser applied for 10 and 30 min, alone and with overnight occlusion, and sodium lauryl

sulfate (SLS) 0.5% aqua for 30 min (Table 1) were applied twice daily under 12-mm Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland, distributed by Smart Practice Germany GmbH, Barsbüttel, Germany), with an interval of 4 hr between the applications. Filter paper disks were used for the aqueous SLS solution. The test fields were rinsed with lukewarm tap water after each application of irritants. The effects of petrolatum as a model barrier cream (applied 10 min before the treatment with irritants) and of a commercial hand cream as a model post-exposure emollient (applied 10 min after the irritants) alone and in combination were also investigated, resulting in a total of 13 different test fields (Table 1). The test fields were situated on the volar sides of the forearms of the volunteers, with six fields per arm. A totally untreated control field was located on the volar side of the upper arm, and served as a quality control for the bioengineering measurements over time.

The study was single-blinded and randomized by means of a rotation scheme, which did not include the control field on the upper arm. The 12-mm test fields were marked with a permanent skin marker, with a spacing of 20 mm between the fields. The topical preparations were applied with a gloved finger on a larger area of 20 mm in diameter. The 12-mm test chambers used for the cleanser and SLS application were placed in the centre.

On some of the fields, overnight occlusion was applied after the second treatment with irritants, and was removed on the morning in the laboratory 15 min before the start of the first treatment (altogether, 18 hr).

Irritants and emollients

SLS of high purity (99%; Serva Feinbiochemie, Heidelberg, Germany) was used, dissolved at 0.5% in distilled water.

Hand cleanser. An antibacterial hand washing lotion (Ecolab® Germany GmbH, Düsseldorf, Germany) was applied undiluted at 50 µl per test field. The composition was as follows (INCI): aqua, propylene glycol, sodium cumene sulfonate, citric acid, ethanolamine, decyl glucoside, sodium laureth sulfate (also known as sodium lauryl ether sulfate), triclosan, hydroxyethylcellulose, and undecylenic acid. There were two application times for the antibacterial hand cleanser – 10 and 30 min, twice daily under patch test occlusion – in order to model two groups of workers who wash their hands, respectively, more or less frequently.

Gloves. Disposable non-powdered vinyl gloves (Vinyl 2000 PF®; Rösner-Mautby Meditrade GmbH, Kiefersfelden, Germany) were used for glove occlusion. The pieces of gloves and the Finn Chambers® were affixed to the skin with Fixomull® adhesive tape (BSN Medical GmbH, Hamburg, Germany).

Pre-exposure and post-exposure skin products. Petrolatum was used as a model of a barrier cream (14), and Eucerin® hand cream (Beiersdorf AG, Hamburg, Germany) as a model post-exposure emollient. The composition was as follows (INCI): aqua, glycerin, panthenol, hydrogenated cocoglycerides, stearyl alcohol, paraffinum liquidum, stearic acid, cetyl alcohol, aluminium starch octenylsuccinate, dimethicone, phenoxyethanol, tocopherol, PEG-100 stearate, glyceryl stearate, sorbitan stearate, methylparaben, carbomer, trisodium EDTA, sodium citrate, propylparaben, citric acid, glucosylrutin, isoquercitrin, fragrance, linalool, and butyl methoxydibenzoylmethane. The quantities of the creams were estimated according to COLIPA guidelines (15), namely 2 mg/cm², for lack of a better standard, and applied as a volume.

Volunteers

Twenty healthy volunteers (5 men and 15 women; age 19–34 years; mean ± standard deviation, 25.75 ± 4.52), skin type I–IV, were included after they had provided written informed consent. The study protocol was approved by the ethics committee of the Friedrich-Schiller University Jena. The study was conducted between the beginning of September and the end of November. Subjects agreed to keep the forearms dry for 1 day before and during the study, and to refrain from using detergents, any kind of topical cosmetics or drugs, and ultraviolet exposure.

Measurements and clinical scoring

Transepidermal water loss (TEWL) (quantified with an MPA9/Tewameter TM 300®; Courage & Khazaka,

Cologne, Germany) (16–18), stratum corneum hydration as determined by corneometry (measured with an MPA9/Corneometer CM 825®; Courage & Khazaka) (19), erythema as determined by skin reflectance (chromametry; Chromameter® CR 300; Konica Minolta Photo Imaging Europe, Langenhagen, Germany) (20), pH-metry (pH-meter; Courage & Khazaka) (21) and visual irritation score were measured daily. The measurements took place on the first day before the start of the study (baseline), and thereafter 4.5 hr after the removal of the overnight glove occlusion, that is, 3.5 hr after the end of the first daily application of the external preparations from D2 to D5 (end of study; there were only measurements and no irritation on D5). The measurements were conducted after 30 min of acclimatization at 21 ± 1°C and a relative humidity of 45% ± 5%, according to the above-cited international guidelines.

Visual irritation score. A modification of the Frosch score (22) was used, that is, the sum score of the elaborate European Society of Contact Dermatitis scoring system for cumulative irritation (16). If the score had exceeded 2 for any of the items, such as erythema, roughness, scaling, oedema, or fissures, the irritation of the respective test area would have been prematurely terminated, in order to prevent severe irritation (break-off criterion). No such strong reactions were observed.

Statistical analysis

SPSS™ for Windows™, version 16.0, was used for the analysis. The results are shown as medians, median differences from baseline, and conservative 95% confidence intervals, as most of the data were not normally distributed. For comparisons of the daily values and baseline, and for the difference-from-baseline values between the various fields, the paired *t*-test was used when the data were normally distributed, and the Wilcoxon signed rank test otherwise. The level for statistical significance was *p* < 0.05, with Holm–Bonferroni corrections for multiple comparisons (23).

Results

All of the tested irritants, including the antibacterial hand cleanser with both durations of application, and glove occlusion alone, induced statistically significant TEWL elevation. Of all of the parameters measured (TEWL, corneometry, erythema by skin reflectance, pH, and visual score), TEWL proved to be most reliable in showing statistically significant differences between the irritants. For example, the antibacterial cleanser alone, applied for

10 and 30 min, did not induce a statistically significant change in chromametry, most probably because the hand cleanser induced only mild irritation with minimal erythema, if any, and only occasional changes in pH were observed. Therefore, the comparisons between the irritants and the conclusions on the effects of the various treatments were based on the TEWL results.

In the corneometry measurements, the positive control and the hand cleanser applied for 10 and 30 min induced a statistically significant decrease in stratum corneum capacitance (an indirect measure of stratum corneum hydration). On the fields with additional glove occlusion, however, the occlusion completely masked the effects of the irritants in reducing stratum corneum capacitance, and a significant increase was observed instead. This effect was also evident on the fields additionally treated with topical preparations; that is, the effect of occlusion in increasing stratum corneum hydration obscured the effects not only of the irritants, but also of the creams.

TEWL comparisons (difference from baseline values)

The irritant factors were compared according to the TEWL changes from baseline, that is, the difference between the first (D1) and the last (D5) measurements (Fig. 1). The positive control, 0.5% SLS, induced the strongest increase in TEWL, which was significantly higher than that caused by the hand cleanser applied for 10 min plus occlusion, but not than that caused by the hand cleanser applied for 30 min plus occlusion. On the other hand, the effects of the antibacterial cleanser applied for 10 min plus occlusion and applied for 30 min plus occlusion did not significantly differ from each other. The increase in TEWL caused by the hand cleanser for 10 and 30 min, when applied alone, and caused by occlusion alone, was weak and significantly smaller than that caused by the irritants with occlusion and SLS. The TEWL increase did not differ significantly between these three fields.

The effects of the preventive measures, that is, the application of pre-exposure or post-exposure preparations, were best visible in the 10-min application series (Fig. 2).

The hand cleanser plus occlusion induced the strongest increase in TEWL, being statistically significantly higher than that with any other combination. Treating the fields with either a protective cream or a post-exposure emollient alone led to a significantly smaller increase in TEWL than that caused by the hand cleanser plus occlusion. The effects of the emollient and the protective cream were not significantly different from each other. When they were applied together, the increase in TEWL was significantly smaller than with each of them alone. There was no statistical difference between the fields

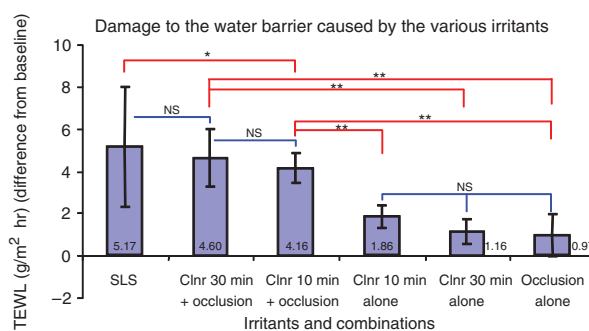


Fig. 1. Comparisons between the various irritant combinations in terms of transepidermal water loss (TEWL) differences from baseline values [D5–D1, g/cm² hr, median values (bars) with 95% conservative confidence intervals (error bars)]. The red lines denote the statistically significant differences (* $p \leq 0.01$; ** $p \leq 0.001$), and the blue lines the lack of such differences [not significant (NS)]. Clnr, hand cleanser; SLS, sodium lauryl sulfate.

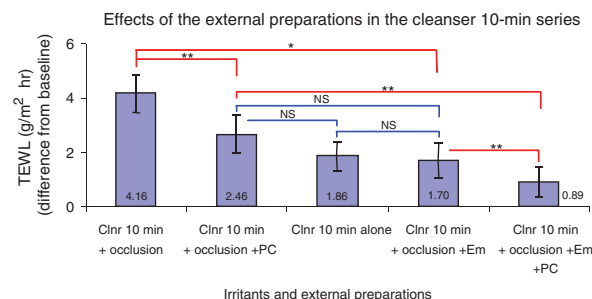


Fig. 2. Comparisons among the various combinations of irritant and protective factors within the series with 10-min application time of the antibacterial hand cleanser. The bars represent the median transepidermal water loss (TEWL) difference from baseline values (D5–D1, g/cm² hr), and the error bars represent the 95% conservative confidence intervals of the median. The red lines denote the statistically significant differences (* $p \leq 0.01$; ** $p \leq 0.001$), and the blue lines the lack of such differences [not significant (NS)]. Clnr, hand cleanser; Em, emollient; PC, protective cream.

treated with the hand cleanser alone and those treated with the combination of the hand cleanser, occlusion, and both external preparations (Fig. 2). The series with the 30-min application time for the hand cleanser were generally similar; however, fewer statistically significant differences were established.

Discussion

The central finding of our study is the tandem action of glove occlusion and the antibacterial cleanser in inducing irritant dermatitis. Occlusion alone and the mild detergent alone (with both 10-min and 30-min durations

of application) induced only a small, albeit statistically significant, TEWL increase (Fig. 1). The combined action of the mild irritant and occlusion however, was similar to that of the positive control, 0.5% SLS.

It is well established that glove occlusion potentiates the irritation caused by a strong model irritant such as SLS (24, 25). Our study shows how glove occlusion and the hand cleanser, which are both weak irritants alone, combine to give rise to cumulative irritant contact dermatitis.

The concept of the tandem effect of irritants was developed on the basis of findings that the cumulative irritation induced by two irritants applied one after the other is stronger than the irritation induced by each irritant applied repetitively alone (13, 26). The combined action of any given irritants, however, does not necessarily lead to a synergistic effect. For example, the fruit acids present in the food that soils the hands of kitchen workers have been shown not to have a synergistic effect, and even to ameliorate the irritant effect of water and detergents (6). Many irritant factors have been investigated for tandem effects (reviewed in (27)), and our study adds to these glove occlusion and mild cleansers.

Occlusion refers to covering the skin with impermeable or semipermeable materials, which prevent normal evaporation from the skin surface. Its irritant effects are considered to arise from the accumulation of moisture. Additional effects on the skin are considered to arise from increased temperature, sweating, and increased pH (28). The duration of occlusion is decisive for the irritant effects to occur, probably because time is needed for the moisture to build up. Subclinical hyperhydration of the stratum corneum, which is detectable by bioengineering methods, occurs after only 20 min of glove occlusion (29). The effects of such short episodes of occlusion are also short-lived. It takes 3 hr for the bioengineering parameters to return to normal after a single 4-hr glove occlusion (30). No significant TEWL increase was shown after 4 hr of glove occlusion daily for 7 days in the same study (measured on the eighth day). Wearing a water-impermeable glove for 6 hr per day for 3 days does not negatively affect water barrier function, although it enhances the irritant properties of SLS (24). However, 6 hr per day for 14 days did lead to increased TEWL (7). As the 6-hr occlusion for 14 days is similar to the occlusion times of the workers in the wholesale kitchen that we wanted to model (6–8 hr daily), and as it is a proven irritant, we used even longer times in order to be able to reproduce an irritant response within a ROIT protocol of just 4 days.

The cited studies also show that, whereas normal skin is relatively resistant to the mildly damaging effects

of the occlusion, an increase in irritation caused by additional irritant factors may be brought about even by a short occlusion time (24, 25, 28). It has been shown by means of ^{14}C -labelled detergents and autoradiography of rat skin that, after washing and rinsing, a certain amount of the detergent remains in the skin, mainly in the stratum corneum and the hair follicles (31). A more recent study examined the penetration of SLS on human skin, and showed, by means of tape-stripping, that, after SLS application under a patch test, some of the SLS remains in the stratum corneum (32). Occlusion after even a short duration of contact with detergent increases the penetration of the remaining detergent or releases some of the deposited detergent from the stratum corneum, as shown through the biological effects of the detergents in increasing TEWL. In an *in vivo* study with volunteers, mild detergents were applied on the skin for only 5 seconds and then rinsed off (33). After drying, the areas were covered with aluminium chambers for 24 hr. There was a significantly higher increase in TEWL than in the control areas (treated only with water) for the test areas where one of the mild cleansers was applied (33). This methodology, that is, eliciting a biological response by means of occlusion, was developed in the 1960s to show the formation of a reservoir in the stratum corneum after application of topical corticosteroids (33). This and other studies (25) show the ability of occlusion to release substances deposited in the stratum corneum, in our case detergents.

The effects of the protective cream and the post-exposure emollient were also investigated in our study. Our results confirm earlier findings that the best protection is conferred by the combination of the two (8). When used alone, the two were approximately equally effective in our study, whereas in earlier studies the protective (barrier) cream seemed to be more effective (8). Such differences probably arise from the specific choice of products and their constituents. Another possible explanation is that we used a smaller quantity of the creams, that is, 2 mg/cm^2 , than earlier studies, which used much higher quantities, that is, 16 mg/cm^2 ($50\text{ }\mu\text{l}$ per test field of diameter 20 mm) (12, 34). A recent and not yet published investigation by our group showed that the quantity of a protective cream applied on the hands is below 2 mg/cm^2 . A possible limitation of our study is that we used a rather sophisticated post-exposure emollient as compared with the most simple possible barrier cream, which could explain why we could not replicate the superior efficacy of the protective creams in earlier studies. However, there are published examples supporting the choice of petrolatum (14), and there are

still examples of it being used as a protective cream in practice (Antonov, unpublished observation 2011). The randomized controlled studies comparing the protective creams with the post-exposure emollients agree on the conclusion that these two are most effective when combined (35, 36).

An important choice in the methods of this study was the time point when TEWL was measured. A value should be obtained that reflects the barrier function, and not the residual water on the skin surface or the excess water in the swollen stratum corneum, which together are generally referred to as skin surface water loss. It is recommended that TEWL be measured at a minimum of 3 hr and preferably 24 hr after removal of SLS test chambers (37). In our study, the last measurements were performed ~22.5 hr after the end of the patch tests with irritants on the previous day. The period of 4.5 hr after the removal of the overnight glove occlusion in our study is also in line with the recommendations of

earlier studies on the time course of occlusive effects (30, 37, 38).

In conclusion, the practice guidelines recommend that the cleanser used in the occupational setting should be as mild as possible, yet capable of removing the dirt. Our study shows that, even though such cleansers are used, irritant contact dermatitis can develop through the tandem effects of glove occlusion and the accumulation of injury to the skin barrier caused by the mild cleansers. Mere occlusion is much less harmful to the skin barrier than the combination of a mild cleanser, as used in this study, and glove occlusion.

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