

Protective creams fail to prevent solvent-induced cumulative skin irritation – results of a randomized double-blind study

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Summary

Background. Occupational skin contact with lipophilic substances is a risk factor for the development of irritant hand dermatitis. Skin protection creams form part of the personal protective equipment, and some are claimed to protect against lipophilic irritants. However, their benefit against solvents is under debate.

Objectives. To evaluate the efficacy of barrier creams claimed to protect against lipophilic irritants in a newly developed repetitive irritation model.

Methods. Thirty-five healthy volunteers were enrolled in a double-blind, randomized study, and six barrier creams were evaluated against irritation induced by two occupationally relevant model solvents, n-octane and cumene. Clinical scoring and bioengineering methods (capacitance and transepidermal water loss measurements) were used to quantify the irritant reactions.

Results. None of the test products offered protection against n-octane-induced clinical irritation or stratum corneum dehydration. One test product significantly aggravated the skin irritation induced by both irritants, and a second one enhanced dehydration induced by n-octane only.

Conclusions. The lack of efficacy and the aggravation of skin irritation induced by two of six test products stress the need for standardized efficacy testing of occupational skin protection products.

Key words: barrier creams; bioengineering; efficacy; irritant contact dermatitis; repetitive irritation model; solvents.

Occupational exposure to lipophilic substances such as solvents and oils is a risk factor for the development of irritant contact dermatitis (1), and irritant hand dermatitis is the most prevalent occupational skin disease in industrial countries (2, 3). In a Danish study (4), solvents and oils ranked in third order as exogenous causes

of occupational contact dermatitis (OCD), following wet work and detergent exposure (5), and contributed to 3.6% of OCD cases. Personal protective measures, such as gloves, are used to avoid or at least to attenuate the impact of irritants at workplaces. However, even if appropriate gloves are available, skin contact with irritants may occur frequently in the daily working routine. Reasons for this include lack of applicability, owing to the working process, safety regulations in the context of rotating machines, or just the lack of understanding and acceptance of how to adequately use gloves. This is when pre-exposure skin protection products, also often referred to as barrier creams, may play a role.

A variety of skin protection creams are claimed to protect against skin damage induced by lipophilic

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chemicals, such as oils, fats, and organic solvents. It is anticipated that these cosmetics should prevent or reduce the risk of skin barrier impairment caused by exogenous irritants. However, appropriate proof of their protective effects is not available in many cases. Up to now, standardized efficacy test procedures have been lacking for products intended for use against any other types of irritants, which is in part because of the legislation in the EU, which does not demand specific claim support. The current efficacy tests performed by the manufacturers are highly heterogeneous, and mainly rely on *in vitro* or *ex vivo* methods, which are based on single exposure protocols. One example is the bovine udder model (6). Others use artificial skin models (7). The majority of the test models reflect acute toxicology rather than the effects of repeated exposures, which can be criticized as being inappropriate. Human repetitive irritation models are considered to better reflect occupational skin hazards, and are therefore recommended in interdisciplinary guidelines (8) for efficacy proofs.

The implementation of such sophisticated test methods requires the selection of suitable model irritants, which is especially challenging in the context of lipophilic chemicals. Often described as 'solvents', they represent a chemically heterogeneous group of, mainly, hydrocarbons (HCs), including aliphatic and aromatic HCs, as well as molecules that are soluble both in lipids and in water, such as acetone and glycol ethers. Because of their liposolubility, solvents easily penetrate the epidermal barrier by diffusion into the intercellular lipid lamellae (9). From a clinical perspective, their ability to dissolve and remove skin lipids of the stratum corneum results in dry and hyperkeratotic skin (10, 11). Owing to both unacceptable systemic toxicological profiles of many compounds and technical problems with experimental handling, the numbers of studies and of chemicals used are limited, as compared with water-soluble irritants such as sodium lauryl sulfate (SLS) (12, 13). Some authors have preferred toluene for repetitive *in vivo* irritation studies in the past (14–17). Other authors have used acetone, which is easily applicable in the experimental setting (18, 19), but does not represent the classical type of solvent, owing to both its hydrophilic and hydrophobic (amphiphilic) properties. Jet fuel is an example of a complex mixture of aromatic and aliphatic HCs, and has been investigated mainly in animal models (20–22). None of the substances used in the literature so far qualifies as a generally accepted lipophilic model irritant that is representative of occupational skin exposure.

The German Statutory Accident Insurance (DGUV) initiated a research project aimed at developing a human repetitive irritation model for lipophilic skin irritants

to be used for efficacy testing of protection creams. In a first step, an external toxicology expert panel reviewed lipophilic chemicals that could potentially be considered as model irritants (Institute for Occupational Safety and Health of the DGUV, St Augustin, Germany, 2005, unpublished data). The substances had to be relevant in the occupational setting, and were selected according to criteria such as absence of systemic toxicity, carcinogenicity, and mutagenicity. Together with the results of subsequent pilot trials, all being approved by the local ethics committee, two substances, cumene (isopropyl benzene, CAS No. 98-82-8), belonging to the group of alkylbenzenes, and n-octane (CAS No. 111-65-9), an aliphatic HC, qualified as potential candidates at that time.

The objective of the present study was to evaluate the efficacy of different skin protection creams claimed to provide protection against lipophilic substances. The concept was a repeated irritation volunteer study with cumene and n-octane.

Materials and Methods

Study design and conditions

The study was performed as a double-blind, controlled and randomized clinical trial. All measurements were performed in a climate-controlled laboratory (temperature $21 \pm 1^\circ\text{C}$; relative humidity $45\% \pm 5\%$). Conditions were constantly monitored with a data logger (Testo 175-H2 Logger; Testo Industrial Services GmbH, Kirchzarten, Germany). The study was performed from September 2007 to February 2008.

Study population

After approval from the ethics committee of the Friedrich-Schiller-University of Jena had been obtained, 35 healthy Caucasian volunteers (23 females; 12 males) aged 19–40 years (median age 24 years), without any history of previous or ongoing skin or systemic diseases, attended the project. Female participants were approved after negative pregnancy test results. Prior to the study, all procedures and potential side-effects had been explained in detail. In accordance with the Declaration of Helsinki, written informed consent was obtained from all subjects. The volunteers refrained from using any detergents and emollients on their backs, as well as from bathing and natural or artificial UV exposure, during the study.

Irritants and test products

Neat n-octane (purity 99.2%; VwR International, Dresden, Germany) and cumene (purity 99%; Merck

Schuchardt OHG, Hohenbrunn, Germany) served as lipophilic irritants. SLS 0.5% (sodium lauryl sulfate ultra pure 99%; Carl Roth GmbH, Karlsruhe, Germany) in an aqueous solution and distilled water (aqua dest.) were used as positive and negative irritant standards, respectively. The test products consisted of six skin protection creams (A–F), which were all cosmetics according to the definition of the EU Regulation on cosmetic products, (23), and which were claimed by the manufacturers to provide skin protection against lipophilic substances and recommended to be used before and during the working process. The products had been selected according to their relevance in industrial use by an expert panel of the project (Table 1).

Treatment of test areas

Altogether, 16 test areas of 2.5×2.5 cm, arranged in four horizontal and vertical rows, were marked with a stencil on the skin of the paravertebral mid-backs of the volunteers. The pharmacy of the Friedrich-Schiller-University provided coding of the test products (H1–H6), which were supplied in 1.0-ml syringes without needles for application. According to the individual randomization scheme, a technician pretreated the skin areas with 0.05 ml of the respective test products by spreading the applied amount evenly on the skin surface with a glove-coated finger. After the skin had been left open for an interval of 5 min, 240 µl of the respective irritant, n-octane or cumene, was occlusively applied to the skin by the use of Finn Chambers® extra large with filter paper discs (both 18 mm; SmartPractice, Phoenix, AZ, USA). The test chambers were secured with adhesive tape (Fixomull® stretch; BSN Medical GmbH, Hamburg, Germany). The patches were removed after 10 min, and the skin was allowed to dry until the subjects dressed as usual. Two control areas were treated with the irritants only (areas 'H0'). In addition, two test areas were treated with SLS and aqua dest., serving as positive and negative irritant standards. We repeated the application procedure twice daily, with 3 hr (± 1) between, on 11 consecutive days, resulting in 22 subsequent treatments of each test site, provided that the break-off criteria (see below) did not necessitate premature termination. We used a mobile fume hood (Terfu-Punktabsauger; Fumex, Skelleftea, Sweden) with activated-carbon filters for organic solvent vapours (L50; Asecos GmbH, Gründau, Germany) to absorb any solvent vapours from the laboratory atmosphere during application.

Assessments and bioengineering measurements

Readings and bioengineering measurements were performed at the same time of day (± 1 hr) prior to the

Table 1. Constituents of the six test products according to INCI declarations

Test product	INCI
H1	Aqua, Talc, Sodium Cocoyl Isethionate, Glycerin, Silica, Glyceryl Stearate, Laureth-10, Bentonite, Xanthan Gum, Algin, Sodium Phosphate, Parfum (Fragrance), Lactic Acid, Potassium Sorbate, Dioctyl Sodium Sulfosuccinate, Silver Chloride, Propylene Glycol, Titanium Dioxide
H2	Aqua, Petrolatum, Paraffin, Talc, Cetearyl Alcohol, Paraffinum Liquidum, TEA-Stearate, Stearic Acid, Methylparaben, Propylparaben, Parfum, Alpha-Isomethyl Ionone, Citral, Citronellol, Hydroxycitronellal, Limonene, Linalool
H3	Aqua, Talc, Kaolin, Cetearyl Alcohol, Octyl Dodecanol, Petrolatum, Glycerin, Cera Alba, Algin, Sodium Lauryl Sulfate, Sodium Cetearyl Sulfate, Sodium C12–15 Pareth Sulfate, Parfum, Phenoxyethanol, Methylparaben, Ethylparaben, Propylparaben, Butylparaben
H4	Aqua, Paraffinum Liquidum, Stearic Acid, Glycerin, Cetearyl Alcohol, Octyldodecanol, Cera Alba (Beeswax), Cellulose Gum, Sodium Cetearyl Sulfate, Ascorbic Acid, Citric Acid, Sodium Hydroxide, Parfum, Methylparaben, Propylparaben, PEG-8, Tocopherol, Ascorbyl Palmitate
H5	Aqua, Cocoglycerides, Glycerin, Pentylene Glycol, Palm Glycerides, Behenyl Alcohol, Hydrogenated Lecithin, Buthyrospermum Parkii, Squalane, Palmitic Acid, Trihydroxystearin, Caprylic/Capric Triglyceride, Ceramide 3, VP/Eicosene Copolymer, Caprylyl Glycol, Xanthan Gum, Hydroxyethylcellulose, Sodium Carbomer
H6	Aqua, Glycerine, Sodium Silicate, Sodium Tallowate, Cetearith-5, Sodium Palmcernelate, Paraffin, Parfum

first treatment procedure, after the volunteers had been resting for at least 20 min in a relaxed face-down position in the air-conditioned laboratory. The cumulative irritation score, proposed by the Standardization Group of the European Society of Contact Dermatitis (24), was used for clinical assessment. Readings were performed prior to the bioengineering measurements by the same investigator, who was blinded to the application procedures and randomization throughout the whole trial. Each criterion, such as erythema, oedema, dryness, scaling, and fissuring (0/0.5/1/2/3), was rated separately, and the resulting sum score was used for final analysis. The bioengineering measurements were performed

by the same person according to pertinent guidelines (25, 26). Stratum corneum hydration measurements (MPA9/Corneometer® CM 825; Courage & Khazaka GmbH, Cologne, Germany) were performed in triplicate on each area, and the arithmetic means were used for analysis. Measurements of transepidermal water loss (TEWL) (Tewameter® MPA9/TM 300; Courage & Khazaka) were performed in duplicate on each area, and the arithmetic means were used for analysis. Visual scoring and skin hydration measurements were performed each day, from D1 to D12, and measurements of TEWL were performed on D1, D5 and D12.

Break-off criteria

In order to prevent excessive local irritation, individual test areas were not subjected to any further treatment whenever a single clinical item of the cumulative irritation score developed to a maximum score of 3 (premature termination). Final visual scoring and measurements were performed on the morning after the last treatment.

Analysis and statistics

The software R for Windows™ was used for statistical analysis (Menne Biomed Consulting, Tuebingen, Germany) (27). Skin hydration and TEWL data were subjected to a mixed model analysis (28). For each test product, the slope of the target value by time was determined from the model and used as the primary efficacy variable; the interaction term of the irritant and the test product was included in the analysis to control for specific irritant-specific sensitivity. Subject and patch-within-subject were used as random variables; separate slopes were determined for each subject as required by an Akaike information criterion-based model test. To check for validity of the linear mixed model analysis, fitted values were plotted against standardized residuals, and showed no systematic deviation from randomness. Data for visual scoring (sum scores) were subjected to a generalized linear model analysis (function lmer in package lme4) (29). Scores exceeding a threshold value of 1.5 were counted as events and analysed with a binomial mixed model with a logit link. Sensitivity analysis with alternate thresholds of 1.0 and 2.0 showed that residual variance was lowest with the chosen threshold of 1.5. Subject and patch-within-subject were random variables, and a constant slope assumption was required to obtain stable results. Percentages of 'control areas H0' (skin areas treated only with irritants) attaining or exceeding the threshold were calculated from the model fit. Corresponding to the LD50 parameter used in pharmacology, the

value of 'D50' was used to compare the irritant effects obtained on the pretreated areas with those of the control fields (30). According to this definition, at 'D50' (number of treatment days), 50% of the subjects would have attained or exceeded the threshold values in the respective test areas. An efficacious test product would therefore be expected to induce a higher D50 value than that of the control area H0. Results are presented as *p*-values ($p \leq 0.05$) and 95% confidence intervals, which were adjusted for multiple tests (31). As the mixed model analysis is inherently robust against imbalances, missing data were not included in the model fitting process.

Results

Local tolerance and side-effects

Thirty volunteers (age range 19–40 years; median age 24 years) were analysed per protocol. Of a total of 5 dropouts, 3 were related to sensory irritation induced by the irritants during application, whereas 2 were not related to the study procedures. The skin reactions observed were confined to self-limited local irritant reactions, such as mild to moderate erythema, oedema, scaling, and subsequent mild hyperkeratosis. Follow-up visits showed that no treatment was necessary in any case. Mild post-inflammatory hyperpigmentation occurred in single areas both after *n*-octane treatment and after SLS treatment. In 57 (10.2%) fields, the treatments were prematurely discontinued because of the above-mentioned break-off criteria. *n*-Octane induced more intense irritant reactions than cumene, which correlated with a higher number of premature field terminations in the *n*-octane-treated areas than in the cumene-treated areas. Two test products, H2 and H5, aggravated the degree of *n*-octane-induced irritation, thus causing a noticeably higher number of premature terminations than the control area H0, which had been irritated but not pretreated (nine and 14 premature terminated fields, respectively, as compared with five areas for H0).

Subjective sensory irritation, such as stinging, burning, and itching, was reported frequently during the application of both lipophilic irritants, with cumene inducing more sensory irritation than *n*-octane. Characteristically, the subjects reported complete cessation of symptoms within minutes after removal of the patches, and the overall intensity tended to diminish in the course of the study, in particular following the second day; this has meanwhile been confirmed in other trials performed by our group (32).

Fig. 1. Course of the stratum corneum capacitance (corneometry, arbitrary units) as mean values over time in all test areas that were not pretreated with skin protection products ($n = 30$) [negative standard, aqua dest.; positive standard, sodium lauryl sulfate (SLS) 0.5% aqua; and H0 control areas treated only with the irritants n-octane and cumene].

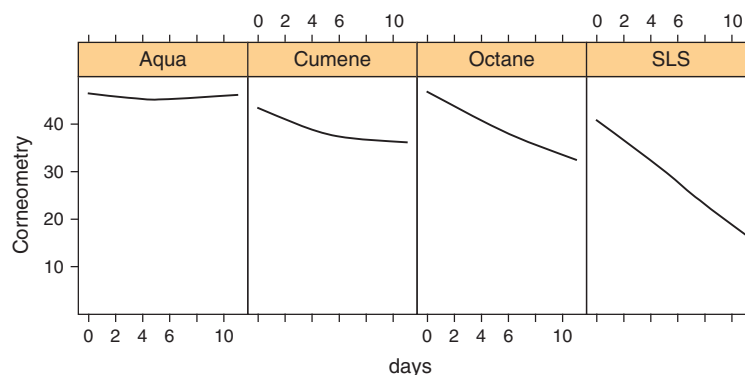


Table 2. Capacitance values in arbitrary units (AU) of the solvent-treated areas: mean total differences from baseline and 95% confidence intervals (CI) at D12

	Corneometry (AU)	Lower CI	Upper CI	<i>p</i> -value
O H0	−15.1	−20.3	−9.9	<0.0001
O H1	−16.9	−22.1	−11.6	<0.0001
O H2	−22.4	−27.7	−17.0	<0.0001
O H3	−14.7	−19.9	−9.6	<0.0001
O H4	−18.6	−23.9	−13.4	<0.0001
O H5	−21.5	−27.3	15.6	<0.0001
O H6	−15.4	−20.4	−10.5	<0.0001
C H0	−6.9	−11.8	−2.1	0.001
C H1	−9.0	−13.8	−4.2	<0.0001
C H2	−13.4	−18.3	−8.4	<0.0001
C H3	−4.0	−8.9	0.9	0.184
C H4	−3.7	−8.6	1.2	0.293
C H5	−4.8	−9.6	0.1	0.055
C H6	−10.0	−14.8	−5.1	<0.0001

O, octane; C, cumene; H0, area without pretreatment; H1–H6, areas pretreated with skin protection products.

Stratum corneum hydration

Both SLS and both irritants alone (H0) gradually decreased stratum corneum hydration over time, with the steepest slope being induced by SLS, followed by n-octane and cumene (Fig. 1). No significant change in the capacitance values occurred in the negative standard. In all fields, the decline induced by n-octane was significant over time (as compared with baseline), irrespective of considering areas that had been treated exclusively with the irritant H0 or had been pretreated with the test products H1–H6 (Table 2). Regarding the differences between the test products and H0 (Fig. 2), H2 and H5 significantly enhanced skin dehydration. No significant differences were noticed for H1, H3, H4 and H6 as compared with H0. Thus, none of the test products offered significant protection against stratum corneum dehydration caused by n-octane.

Cumene, in contrast, induced a significant decrease over time only in H0 and in the test areas pretreated with H1, H2, and H6. H3, H4, and H5 also induced a decrease over time; however, this was not significantly different from baseline (Table 2). H2 significantly aggravated the degree of cumene-induced dehydration, in accordance with the findings for n-octane. Altogether, H3, H4 and H5 showed a tendency to protect against cumene-induced dehydration, but without statistical significance (Fig. 2).

Transepidermal water loss

Despite occlusive exposure to the lipophilic irritants, neither n-octane nor cumene caused any significant changes in TEWL over time, either in the control areas (H0) or in the pretreated fields (not shown). In contrast, SLS caused a significant increase in TEWL in the course of the study. The negative standard (aqua) did not cause any significant rise in TEWL over time (data not shown).

Visual scoring

The sum scores attained were generally higher in the areas treated with n-octane than in the areas treated with cumene. Owing to adherence to the clinical break-off criteria, the maximum sum scores observed did not exceed 8. The percentage of control areas (H0) reaching the threshold sum score of 1.5 in the course of the experiment remained below 50% at D12. Therefore, D50 values were calculated by extrapolation, which resulted in D50 values of 26.5 for cumene H0 and of 13.2 for n-octane H0. As already mentioned, an efficacious test product would be expected to show an even higher D50 value, as it should be able to attenuate the irritation and thereby delay attainment of the irritation threshold. However, all test products failed to offer protection against cumene-induced clinical irritation, as indicated by lower rather than higher D50 values. With respect to n-octane, all products except for H3 showed significantly

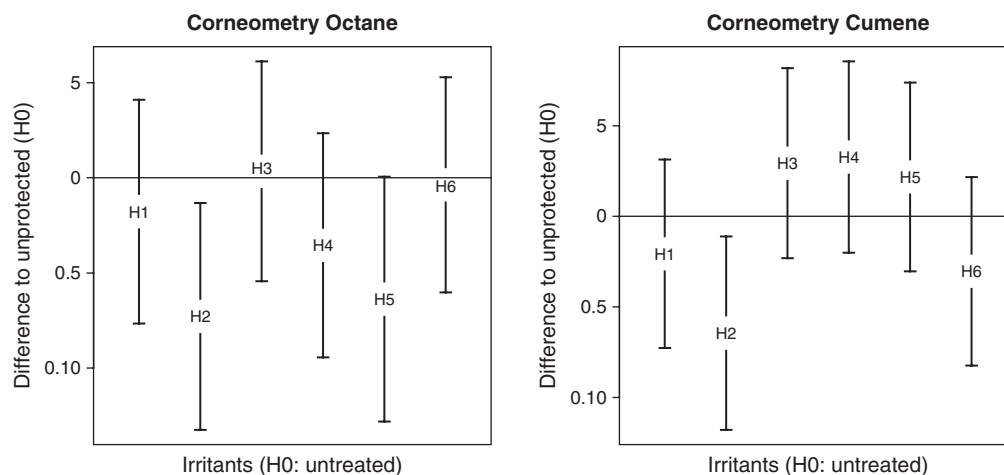


Fig. 2. Mean stratum corneum hydration values (arbitrary units) and 95% confidence intervals of the test areas pretreated with the protective creams H1–H6 on D12 in relation to the values obtained in the control areas (H0) that were treated only with the irritants n-octane (a) and cumene (b) ($n = 30$). Protective creams H2 and H5 significantly aggravated the octane-related dehydration as compared with H0, whereas the remaining creams showed no significant difference. H2 also significantly aggravated the dehydration caused by cumene.

Table 3. D50 values of the visual sum scores of the solvent-treated areas

	Del D50	Lower CI	Upper CI	<i>p</i> -value
O H1	−3.7	−5.6	−1.7	<0.0001
O H2	−7.5	−9.5	−5.6	<0.0001
O H3	−1.8	−3.7	0.2	0.108
O H4	−5.0	−6.9	−3.0	<0.0001
O H5	−8.2	−10.2	−6.3	<0.0001
O H6	−2.0	−3.9	0.0	0.044
C H1	−5.2	−7.2	−3.3	<0.0001
C H2	−13.8	−15.8	−11.9	<0.0001
C H3	−3.5	−5.5	−1.6	<0.0001
C H4	−7.4	−9.3	−5.4	<0.0001
C H5	−8.0	−9.9	−6.0	<0.0001
C H6	−7.9	−9.9	−6.0	<0.0001

Relative changes as compared with H0 in the course of 12 days. Del D50 delay of D50 as compared with H0. CI, confidence interval; O, octane; C, cumene; H1–H6, areas pretreated with skin protection products.

lower D50 values than H0 (Table 3). The results were similar when another threshold of 1.0 was chosen for the calculation of D50 values (data not shown).

Discussion

In our study, we aimed at developing suitable parameters to evaluate the efficacy of skin protection products against two lipophilic model irritants. In contrast to water-soluble irritants, solvents do not primarily affect epidermal barrier function, which makes the otherwise well-established

and very sensitive measurement of TEWL unfeasible. We therefore focused on measurement of the stratum corneum capacitance with Corneometer[®], and compared the results obtained with the clinical scoring by using a new method of threshold calculation (D50). Both methods showed the same ranking of the irritant potential of the solvents, which was far more distinct for n-octane than for cumene, as published previously (33). We observed a lack of efficacy of all protective products selected from the market. With respect to n-octane, all test products failed to offer protection against dehydration of the stratum corneum. In fact, two products significantly enhanced octane-induced dehydration, and one of the latter also aggravated cumene-induced dehydration. Three products (H3, H4, and H5) offered, at best, some protection against the cumene-induced decrease in the capacitance, although this was not a significant finding. Regarding the results of the clinical assessments, none of the test products provided any protective efficacy, as indicated by the D50 values, which were lower rather than higher for all test products as compared with both cumene and n-octane alone (H0). With respect to the visual scoring, the results obtained here were influenced by the threshold that was chosen for determination of D50. However, we observed the same results for two different thresholds, 1.5 and 1.0, and, in principle, the same lack of efficacy was observed against both solvents.

Our results contribute to the critical debate as to whether pre-exposure skin barrier creams are beneficial against lipophilic irritants (34, 35). Significant efficacy of a particular protective cream was previously shown for

combined exposure to SLS and toluene, with the tandem repeated irritation test (36), thus generally confirming the applicability of a study protocol that is closely related to ours. Overall, the results from controlled clinical *in vivo* studies with protective creams are diverse, and can hardly be compared with each other. Depending on the design and irritants applied, the literature available provides conflicting results regarding the benefit of the respective products (37). Claims made for the test products investigated here typically included 'protection against oils, fats, lacquers', protection 'against lipophilic' or 'water-insoluble' working materials, and 'protection against organic solvents'. The results obtained with our model suggest that protective creams might not be useful against organic solvents, although it should be noted that only a random selection of products was considered. As a consequence, claims of efficacy of skin protection creams against lipophilic irritants should be taken with caution as long as sustainable efficacy proofs are lacking, and manufacturers should specify in a more precise way the methods used and the working materials and substances against which their products have been investigated. It appears to be necessary to include repeated exposure models, which are able to mimic occupational exposure patterns and the development of cumulative irritant contact dermatitis in a better way. Skin protection creams may indeed facilitate the removal of adhesive dirt from the skin surface. This is a benefit, as aggressive cleansing procedures may contribute to the overall occupational irritant skin burden (38). However, this feature was not investigated in our trial. We also did not address the question of barrier creams potentially enhancing the skin absorption of solvents (39). This finding is of concern regarding systemic toxicity induced by skin contact at workplaces. We cannot provide information on this question, as we focused only on cumulative skin irritancy.

Some might raise the critical question of whether the lack of efficacy shown was attributable to the model itself, especially to chosen mode and time of application of the irritants and the selected target parameters. From the experimental perspective, occluded exposure to the solvents is necessary in order to ensure standardized application and dose–response relationships. Open exposure results in rapid evaporation from the skin surface that is influenced by various factors, such as skin and room temperature, and type of solvent, and is therefore unfeasible in an experimental setting. Although open exposure reflects the typical way in which occupational exposure to solvents occurs, semi-occluded and even occluded exposures at workplaces cannot be ruled out, being caused, for example, by soaked gloves,

soaked bracelets, or handling of contaminated objects. The use of a short-time repeated occlusive irritation test for lipophilic solvents is therefore justified, as with water-soluble irritants in experimental models (40).

Skin capacitance appeared to be the most promising target parameter in our model. Dehydration of the stratum corneum correlates well with the clinical characteristics of occupational solvent exposure (11, 41). Capacitance measurements have been well-established and validated (42), can be easily performed, and showed a continuing decrease in the capacitance values over time in the control areas. It is necessary to include irritant standards such as SLS in order to rule out seasonal effects and ensure the quality of the measurements over time. In contrast, TEWL, which represents a very sensitive parameter of skin barrier integrity for monitoring irritation induced by hydrophilic irritants (24, 40), cannot be recommended for aliphatic and aromatic HCs. Unlike exposure to SLS, exposure to the solvents does not impair the water barrier function of the stratum corneum, in accordance with previous findings (16, 33), although there are exceptions to this rule, especially with regard to some amphiphilic irritants, such as acetone (19). Despite the general understanding of the variable routes of penetration into the barrier and different epidermal alterations, more detailed insights into the complex interactions caused by different types of chemical will be needed (43, 44).

The lipophilic model irritants that were chosen in this study, according to previous toxicological expert opinions, showed satisfactory applicability, in terms of both volunteer tolerance and induction of an intended degree of skin irritation (32, 33). However, new data on cumene safety have shown evidence of potential toxicity with respect to high inhalation doses in rodents (45). Although inhalation of vapours was prevented in our experimental setting, these data imply that cumene can no longer be recommended without restriction as a human model skin irritant.

In summary, the present study confirms the principle of *in vivo* efficacy testing for cumulative irritation induced by lipophilic model irritants, and stresses the need for standardized efficacy proofs of occupational skin protection products. All investigated skin protection products from the market failed to offer sufficient protection against the model solvents chosen. As long as substantial efficacy proofs are lacking for such products, appropriate gloves should be preferred as personal protective measures against solvent irritants. Our preliminary results should not be generalized to all products or to other fields of occupational exposure, such as detergents in wet work professions, where their benefit has been proven under various circumstances (46–48).

Further investigation of the relevance of our method, including correlation of open and occluded exposure data, is needed.

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