

Emollients in a propanol-based hand rub can significantly decrease irritant contact dermatitis

GÜNTER KAMPF^{1,2}, WALTER WIGGER-ALBERTI³, VOLKER SCHODER³ AND KLAUS-PETER WILHELM³

¹Bode Chemie GmbH & Co., Scientific Affairs, Melanchthonstr. 27, 22525 Hamburg, ²Institut für Hygiene und Umweltmedizin, Ernst-Moritz-Arndt Universität Greifswald, Walther-Rathenau-Str. 49a, 17487 Greifswald, and

³proDERM, Industriestr. 1, 22869 Schenefeld, Germany

The objective of this study is to determine the effect of emollients in a propanol-based hand rub on skin dryness and erythema. In this prospective, randomized, controlled, double-blind trial, 35 subjects participated; of them approximately half were atopic (modified Erlanger atopy score ≥ 8). 2 propanol-based formulations were tested in a repeated open application test, 1 contained a mixture of emollients (0.81%, w/w). 2 aliquots of 0.7 ml of each formulation were applied twice per day over 2 weeks to the cubital fossa of each subject after random assignment of the preparations. Treatment areas were assessed before each application and 3 days postfinal application by visual inspection for erythema and dryness according to a standard scale. The sum score over all assessment time-points served as primary parameter. The mean sum score for erythema and dryness was significantly lower for the hand rub with emollients (0.8 ± 2.4) in comparison with that for the hand rub without emollients (1.5 ± 3.5 ; $P = 0.022$; Wilcoxon signed rank test). A comparison of the atopic and non-atopic subjects revealed no significant difference for any of the products ($P > 0.05$; Mann-Whitney *U*-test). It is concluded that the addition of emollients to a propanol-based hand rub can significantly decrease irritant contact dermatitis under frequent-use conditions.

Key words: atopics; emollients; irritant contact dermatitis; propanol-based hand rub; ROAT.
© Blackwell Munksgaard, 2005.

Accepted for publication 25 August 2005

Hand hygiene in clinical medicine is undergoing a scientific renaissance in many countries worldwide. According to the new CDC guideline on hand hygiene, hands should be washed only when they are visibly soiled (1). If hands are not visibly soiled, alcohol-based hand rubs should be used (1) because they have a broader and faster antimicrobial efficacy, a better dermal tolerance and the potential to increase compliance in hand hygiene (2). Single alcohols (3) and many alcohol-based formulations are in general well tolerated by users (4), but compliance in hand hygiene remains low (5). Improving compliance in hand hygiene by 18%, however, has been shown to significantly reduce nosocomial infections (6). Some possibilities have been identified with a potential to enhance adherence in hand hygiene, such as the dermal tolerance and the personal perception of a hand rub (7). However, the most important risk factor for occupational contact dermatitis in hospital personnel is the frequent and repeated exposure to irritants such as water, detergents and disinfectants (1, 8).

Therefore, in the US, it has been recommended that alcohol-based hand rubs should contain emollients in order to improve dermal tolerance (1). Commonly used alcohol-based hand rubs usually have evidence for a good dermal tolerance, e.g. in repetitive occlusive patch tests (9, 10). Recently, it could be demonstrated that combined exposure to detergents and alcohol-based disinfectants does not lead to enhanced skin irritation as compared to single application of these irritants (8, 11) although this was proved for another combination of irritants (12). Some studies also revealed a better dermal tolerance of alcohol-based hand rubs containing emollients compared with plain soaps or antimicrobial soaps (13–16). But the effect of emollients in a propanol-based hand rub on the skin condition has so far been addressed only in 1 study, with the user acceptability as the main outcome (17). Although there is little doubt on the potential benefits of emollients in a hand rub, its effect on the prevention of irritant contact dermatitis has to our knowledge never been shown in a controlled, randomized, double-blind trial.

Materials and Methods

Study design

A monocentric, prospective, double-blind, controlled, randomized, clinical trial was performed using a repeated open application test (ROAT). The study was conducted in accordance with the ethical principles that have their origins in the current version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Approval of the ethics committee of the medical chamber Schleswig-Holstein was granted (12 May 2004 and 3 June 2004). The study was conducted from 7 June 2004 to 21 June 2004 and sponsored by Bode Chemie GmbH & Co., Hamburg, Germany.

Participants

A total of 40 subjects were screened. Half of the volunteers were required to have an atopic predisposition with a modified (without IgE results and Phadiatop) Erlanger atopy score of ≥ 8 (18). The Erlanger atopy score is a well-established method to diagnose atopic diathesis incorporating various anamnestic and clinical minor criteria of atopy. Although some authors criticize the individual relevance of its point values in view of a low positive predictive value in a population (19), it is very useful to classify panellists regarding their risk to be atopics.

Sample size estimation was performed prior to the study, based on the computation of one-sided 97.5% confidence intervals for ratio of means. A sample size of 30 was considered adequate to achieve a power of 80% for detecting non-inferiority of the test to the reference product, based on the following assumptions: a standard deviation of $s = 0.29$ in log scale of side differences with respect to the sum score, equality of both formulations and a non-inferiority margin of 1.2. Due to a potential dropout rate of 15%, a total of 35 subjects were included in the study.

Subjects were included if:

- (1) They were Caucasian men or women of skin type I to IV according to Fitzpatrick et al. (20).
- (2) They were between 18 and 65 years of age.
- (3) They signed written informed consent.
- (4) They had a negative urine pregnancy test (female panellists of child-bearing potential).

Subjects were excluded if:

- (1) They had active skin diseases, moles, etc. in the area tested.
- (2) They took drugs interfering with the immune system (e.g. antiphlogistics, corticosteroids, immunosuppressants or antihistamines).

- (3) They had recent intensive UV light exposure (less than 2 weeks).
- (4) They had topical therapy in the test region in the last 2 weeks.
- (5) They were insulin-dependent diabetics.
- (6) They had a known allergy to the ingredients of the test products.
- (7) They had severe illness on account.
- (8) They had psychiatric conditions that might limit the participation.
- (9) They had an infectious disease (e.g. AIDS or hepatitis).
- (10) They had a history of drug or alcohol addiction in the past 3 years.
- (11) They were pregnant or during lactation.
- (12) They were known to have poor compliance.
- (13) They had participated in a clinical trial within the last 30 days prior to the start of this study.

4 subjects did not meet all of the inclusion criteria or met 1 of the exclusion criteria and were excluded. 1 subject was regarded as a reserve resulting in a total of 35 subjects who began the study (Fig. 1).

Study preparations

2 hand rubs were used, both based on 45% propan-2-ol, 30% propan-1-ol and 0.2% mecetronium etilsulfate. 1 product contained a total of 0.81% (w/w) emollients, a mixture of myristyl alcohol, glycerol, dexpantenol, levomenol and lanolin alcohol. The other did not contain any emollients. Both hand rubs were manufactured by Bode Chemie GmbH & Co., Hamburg, Germany, and randomly assigned a letter A or B for blinding of the test formulations. Blinding codes were kept sealed until closure of final database.

Randomization

Allocation of the test products (coded as A and B) to the left and right cubital fossa was conducted according to a randomization scheme prepared at the Department of Statistics and Data Management at proDERM. Randomization was performed via randomly permuted blocks of fixed size using validated software RANCODE 3.6. Derandomization and unblinding were performed after closure of the final database.

Repeated open application test

The study was carried out as described previously (21–24). Each volunteer was treated with both formulations which were randomly assigned

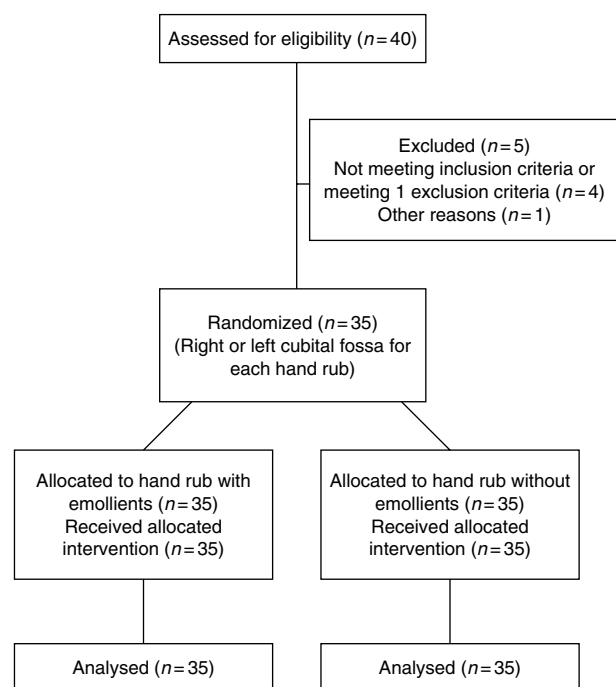


Fig. 1. Flow diagram of the repeated open application test with two propanol-based hand rubs.

before the first application to the right or left cubital fossa. Briefly, preparations were applied twice daily: in the morning at 6 ± 1 hr after the first application over a period of 14 days (with exclusion of Saturdays and Sundays). All applications were performed by a study nurse. An aliquot of 0.7 ml of the coded test material was applied and gently massaged into the skin of the cubital fossa for about 60 seconds. This procedure was repeated once per application so that a total amount of 1.4 ml was applied per product application.

Outcomes

The treated skin was assessed visually for erythema and dryness as key symptoms of irritant contact dermatitis by a dermatologist. All evaluations were conducted blindly by the same investigator. Visual assessments were performed prior to the first application and before each application on days 2, 3, 4, 5, 8, 9, 10, 11, 12 and 15.

The following scale was used for erythema [modified from Fitzpatrick et al. (20)]: 0 = none; 0.5 = equivocal erythema; 1 = slight redness, spotty and diffuse; 2 = moderate uniform redness; 3 = intense redness; 4 = fiery red with oedema.

The following scale was used for dryness: 0 = none; 1 = slight scaling, dryness; 2 = moderate scaling, dryness; 3 = severe dryness with large flakes.

The sum score of dryness and erythema over all assessment times served as the primary outcome parameter.

Statistical methods

The primary objective of the study was the proof of non-inferiority of a hand rub with emollients to a hand rub without emollients based on an irritation sum score. For analysis, a one-sided 97.5% confidence interval based on Fieller's method was computed (25). Type 1 error was correspondingly prespecified as 0.025, and the non-inferiority margin was set to a value of 1.2, implying that a difference of 20% was regarded as clinically equivalent. In case of proven non-inferiority, switching to superiority as an additional end-point was considered as able without modifications of the type 1 error (26).

Secondary analyses included comparison of atopic and non-atopic panellists with respect to both formulations and descriptive presentation of all safety and tolerability variables.

Data are presented as mean $\pm$ standard deviation for continuous or quasicontinuous variables and as absolute and relative frequencies for categorical data.

Results are presented for the intention-to-treat (ITT) population, if not otherwise stated. Missing values in 3 participants were replaced by the method of Last Observation Carried Forward (LOCF). All statistical analyses were performed with the statistical package SPSS 12.01, including the computation of Fieller-based confidence intervals, for which a validated hand-written macro was used.

Results

40 subjects were found eligible and screened initially. 4 of them did not meet the inclusion criteria or met 1 of the exclusion criteria. 1 subject served as a reserve (Fig. 1). A total of 35 subjects commenced the study (ITT population). 26 subjects were female (74.3%), 9 were male (25.7%). The mean age was 40.1 years. Most volunteers were of skin type III (40.0%), followed by skin type II (37.1%), skin type I (14.3%) and skin type IV (8.6%). The modified Erlanger atopy score was used to categorize the volunteers into atopics (score ≥ 8 points) and non-atopics (score < 8 points). The mean atopy score among 21 atopics was 11.4 ± 2.2 (range: 8–16.5) and 2.9 ± 2.2 among 14 non-atopics (range: 0–6.5). 3 subjects were excluded during the study due to protocol violations (intake of antiphlogistics for 1 panellist and disinfection of fossa cubitalis for 2 panellists).

resulting in 32 subjects who finished the study per protocol population (PP) according to the protocol or with only minor deviations.

Score for irritant contact dermatitis

The overall mean sum score for irritant contact dermatitis among the 35 volunteers was 0.8 ± 2.4 (hand rub with emollients) and 1.5 ± 3.5 (hand rub without emollients). The difference between the 2 preparations in mean dryness scores and mean erythema scores became more obvious in the second week of application (Figs 2 and 3). Non-inferiority was examined for the preparation with emollients in comparison with the hand rub without emollients computing the upper limit of a one-sided 97.5% confidence interval for the ratio of means as 0.884. As this value falls below the prespecified non-inferiority margin of 1.2, non-inferiority can be concluded. As this value even falls below 1, it can be additionally concluded that the preparation with emollients leads to a significantly lower irritation sum score. This result is confirmed by a product comparison with the Wilcoxon signed rank test ($P = 0.022$).

No significant difference with respect to the sum score was found between the atopic and non-atopic subjects for any of the products (Table 1). 3 single scores of ≥ 2 were noticed in dryness during the study period, 2 of them with the hand rub without emollients. No single scores of ≥ 2 were noticed in erythema during the study period with any of the 2 hand rubs.

Adverse events

9 non-serious adverse events were observed in 7 volunteers, all were of mild severity (4 reports of headache, 3 reports of common cold, 1 report of tooth pain and 1 report of acute bronchitis). None of them were considered to be related to any of the 2 study preparations.

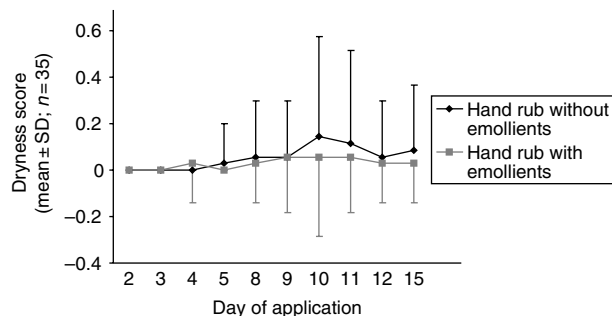


Fig. 2. Mean dryness score with SD at each assessment time-point (ITT population). ITT, intention to treat.

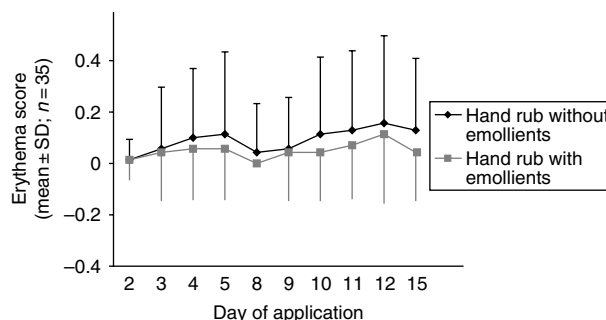


Fig. 3. Mean erythema score with SD at each assessment time-point (ITT population). ITT, intention to treat.

Discussion

To our knowledge, this is the first presentation to show that the addition of emollients to a propanol-based hand rub results in significantly less dryness and erythema after frequent and open application. This was true for both, the non-atopic and the atopic test panel. This finding is particularly important because it provides clear evidence for an existing recommendation (1). Compliance in hand hygiene is on average 50% and considered to be far too low (5). Many factors have been identified to enhance adherence in hand hygiene (27). The use of hand hygiene preparations which are well tolerated and well perceived by healthcare workers is 1 key element (1, 7). Using soap and water has been shown repetitively to irritate human skin resulting in occupational contact dermatitis (28, 29). Standard alcohols, however, are well tolerated on human skin even without the addition of emollients (3, 30, 31). Even on preirritated skin, the damage to the skin, caused by 60% n-propanol and evaluated by measurement of transepidermal water loss (TEWL) and skin surface capacitance, was very low (3). A good dermal tolerance of a hand rub was shown previously to be able to enhance compliance in hand hygiene (13, 32). A rather poor dermal tolerance of an alcohol-based hand rub, however, may not improve compliance (33). Increasing the compliance in hand hygiene can significantly reduce the incidence of nosocomial infections and is therefore a key parameter in infection control (6).

In the present study, a mixture of various emollient agents such as myristyl alcohol, glycerol, dexpanthenol, levomenol and lanolin alcohol was used. The mixture was able to significantly prevent both erythema and dryness. The effect on skin dryness may especially be explained by a promotion of water retention and by an occlusion of the stratum corneum (34). Glycerol has been shown repetitively to increase skin hydration (35, 36). Recent data suggest that glycerol is a major

Table 1. Study outcomes as mean sum scores with SD

Outcome	Intention to treat (<i>n</i> = 35)		Per protocol (<i>n</i> = 32)	
	Hand rub with emollients	Hand rub without emollients	Hand rub with emollients	Hand rub without emollients
Erythema	0.5 ± 1.27	0.9 ± 1.91	0.3 ± 0.87	0.8 ± 1.76
Atopics	0.5 ± 1.03	1.1 ± 2.12	0.5 ± 1.05	1.1 ± 2.16
Non-atopics	0.5 ± 1.60	0.7 ± 1.59	0.1 ± 0.29	0.3 ± 0.45
Dryness	0.3 ± 1.20	0.5 ± 1.77	0.1 ± 0.71	0.4 ± 1.56
Atopics	0.2 ± 0.87	0.6 ± 1.91	0.2 ± 0.89	0.7 ± 1.95
Non-atopics	0.4 ± 1.60	0.4 ± 1.60	0.0 ± 0.00	0.0 ± 0.00
Overall tolerability	0.8 ± 2.44 *	1.5 ± 3.50 *	0.5 ± 1.52 *	1.2 ± 3.11 *
Atopics	0.7 ± 1.85	1.7 ± 3.77	0.7 ± 1.89	1.8 ± 3.85
Non-atopics	0.9 ± 3.20	1.1 ± 3.16	0.1 ± 0.29	0.3 ± 0.45

*Significant difference for primary objective between both hand rub formulations.

determinant of stratum corneum water retention (37). Myristyl alcohol at a higher concentration of 5% (w/v) was found to increase TEWL and to cause skin irritation as assessed by visual scoring (38). Dexpanthenol at a high concentration of 5% is known to have a protective effect against skin irritation (39–41); however, the concentrations of myristyl alcohol and dexpanthenol used in our emollient mixture are much lower (total of all emollients: 0.81%). If all emollient components are evaluated together, they may well explain the observed effect in the ROAT. Mixtures of emollients are variable in alcohol-based hand rubs. The best composition and concentration of emollient agents will also vary according to the type and concentration of alcohol (ethanol, 1-propanol or 2-propanol).

Alcohol-based hand rubs should contain emollients in a mixture and concentration which prevents dryness and erythema after frequent use. This can enhance compliance in hand hygiene by preventing irritant contact dermatitis.

Acknowledgement

The study was sponsored by Bode Chemie GmbH & Co., Hamburg, Germany.

References

- Boyce J M, Pittet D. Guideline for hand hygiene in health-care settings. Recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. *MMWR* 2002; 51: 1–45.
- Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. *Clin Microbiol Rev* 2004; 17: 863–893.
- Lübbe J, Ruffieux C, van Melle G, Perrenoud D. Irritancy of the skin disinfectant n-propanol. *Contact Dermatitis* 2001; 45: 226–231.
- Kramer A, Bernig T, Kampf G. Clinical double-blind trial on the dermal tolerance and user acceptability of six alcohol-based hand disinfectants for hygienic hand disinfection. *J Hosp Infect* 2002; 51: 114–120.
- Pittet D, Boyce J M. Hand hygiene and patient care: pursuing the Semmelweis legacy. *Lancet Infect Dis* 2001; 1: 9–20.
- Pittet D, Hugonnet S, Harbarth S, Monronga P, Sauvan V, Touveneau S, Perneger T V. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet* 2000; 356: 1307–1312.
- Kampf G. The six golden rules to improve compliance in hand hygiene. *J Hosp Infect* 2004; 56: S3–S5.
- Pedersen L K, Held E, Johansen J D, Agner T. Short-term effects of alcohol-based disinfectant and detergent on skin irritation. *Contact Dermatitis* 2005; 52: 82–87.
- Kampf G, Muscatiello M. Dermal tolerance of Sterillium, a propanol-based hand rub. *J Hosp Infect* 2003; 55: 295–298.
- Kampf G, Muscatiello M, Häntschel D, Rudolf M. Dermal tolerance and effect on skin hydration of a new ethanol-based hand gel. *J Hosp Infect* 2002; 52: 297–301.
- Kappes U P, Goritz N, Wigger-Alberti W, Heinemann C, Elsner P. Tandem application of sodium lauryl sulfate and n-propanol does not lead to enhancement of cumulative skin irritation. *Acta Derm Venereol* 2001; 81: 403–405.
- Wigger-Alberti W, Krebs A, Elsner P. Experimental irritant contact dermatitis due to cumulative epicutaneous exposure to sodium lauryl sulphate and toluene: single and concurrent application. *Br J Dermatol* 2000; 143: 551–556.
- Winnefeld M, Richard M A, Drancourt M, Grobb J J. Skin tolerance and effectiveness of two hand decontamination procedures in everyday hospital use. *Br J Dermatol* 2000; 143: 546–550.
- Boyce J M, Kelliher S, Vallande N. Skin irritation and dryness associated with two hand-hygiene regimens: soap-and-water hand washing versus hand antisepsis with an alcoholic hand gel. *Infect Control Hosp Epidemiol* 2000; 21: 442–448.
- Larson E L, Aiello A E, Bastyr J, Lyle C, Stahl J, Cronquist A, Lai L, Della-Latta P. Assessment of two hand hygiene regimes for intensive care unit personnel. *Crit Care Med* 2001; 29: 944–951.
- Newman J L, Seitz J C. Intermittent use of an antimicrobial hand gel for reducing soap-induced irritation of health care personnel. *Am J Infect Control* 1990; 18: 194–200.
- Rotter M L, Koller W, Neumann R. The influence of cosmetic additives on the acceptability of alcohol-based hand disinfectants. *J Hosp Infect* 1991; 18: 57–63.
- Diepgen T L, Fartasch M, Hornstein O P. Kriterien zur Beurteilung der atopischen Hautdiathese. *Dermatosen* 1991; 39: 79–83.
- Uter W, Schwanitz H J, Pfahlberg A, Gefeller O. Atopic signs and symptoms: assessing the 'atopy score' concept. *Dermatology* 2001; 202: 4–8.

20. Fitzpatrick T B, Pathak M, Parrish J A. Protection of human skin against the effects of the sunburn ultraviolet (290–320 nm). In: *Sunlight and Man, Normal and Abnormal Photobiological Responses*. Fitzpatrick T B, Pathak M A, Harber L C, Seiji M, Kukita A (eds): Tokyo: University of Tokyo Press, 1974: S751–755.
21. Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986; 14: 221–227.
22. Hannuksela A, Hannuksela M. Irritant effects of a detergent in wash, chamber and repeated open application tests. *Contact Dermatitis* 1996; 34: 134–137.
23. Tupker R A, Schuur J, Coenraads P J. Irritancy of anti-septics tested by repeated open exposure on the human skin, evaluated by non-invasive methods. *Contact Dermatitis* 1997; 37: 213–217.
24. English J S, Ratcliffe J, Williams H C. Irritancy of industrial hand cleansers tested by repeated open application on human skin. *Contact Dermatitis* 1999; 40: 84–88.
25. Locke C S. An exact confidence interval from untransformed data for the ratio of two formulation means. *J Pharmacokinet Biopharm* 1984; 12: 649–655.
26. Committee for proprietary medicinal products (CPMP). The European Agency for the Evaluation of Medicinal Products (EMA). Points to consider on switching between superiority and non-inferiority 2000; CPMP/EWP/482/99.
27. Pittet D. Improving adherence to hand hygiene practice: a multidisciplinary approach. *Emerg Infect Dis* 2001; 7: 234–240.
28. Malten K E. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; 7: 238–247.
29. Tsai T F, Maibach H I. How irritant is water? An overview. *Contact Dermatitis* 1999; 41: 311–314.
30. Widmer A F. Replace hand washing with use of a waterless alcohol hand rub? *Clin Infect Dis* 2000; 31: 136–143.
31. Kampf G, Löffler H. Dermatological aspects of a successful introduction and continuation of alcohol-based hand rubs for hygienic hand disinfection. *J Hosp Infect* 2003; 55: 1–7.
32. Girard R, Amazion K, Fabry J. Better compliance and better tolerance in relation to a well-conducted introduction to rub-in hand disinfection. *J Hosp Infect* 2001; 47: 131–137.
33. Harbarth S, Pittet D, Grady L, Zawacki A, Potter-Bynoe G, Samore M H, Goldmann D A. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002; 21: 489–495.
34. Rawlings A V, Canestrari D A, Dobkowski B. Moisturizer technology versus clinical performance. *Dermatol Ther* 2004; 17: 49–56.
35. Li F, Conroy E, Visscher M, Wickett R R. The ability of electrical measurements to predict skin moisturization. I. Effects of NaCl and glycerin on short-term measurements. *J Cosmet Sci* 2001; 52: 13–22.
36. Pedersen L K, Jemec G B E. Plasticising effect of water and glycerin on human skin in vivo. *J Dermatol Sci* 1999; 19: 48–52.
37. Hara M, Verkman A S. Glycerol replacement corrects defective skin hydration, elasticity, and barrier function in aquaporin-3-deficient mice. *Proc Natl Acad Sci USA* 2003; 100: 7360–7365.
38. Kanikkannan N, Singh M. Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. *Int J Pharm* 2002; 248: 219–228.
39. Biro K, Thaci D, Ochsendorf F R, Kaufmann R, Boehncke W H. Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. *Contact Dermatitis* 2003; 49: 80–84.
40. Ebner F, Heller A, Rippke F, Tausch I. Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol* 2002; 3: 427–433.
41. Gehring W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration. Results of a human in vivo study. *Arzneimittelforschung* 2000; 50: 659–663.

Address:
PD Dr Günter Kampf
Bode Chemie GmbH & Co.
Scientific Affairs
Melanchthonstr. 27
22525 Hamburg
Germany
Tel.: +49 40 54006-0
Fax: +49 40 54006-128
e-mail: guenter.kampf@bode-chemie.de