Non-invasive bioengineering methods in an intervention study in 1020 male metal workers: results and implications for occupational dermatology

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Background: Measurements of transepidermal water loss (TEWL) as an indicator of skin barrier function and colorimetry for quantifying erythema have been recommended for monitoring persons at risk of occupational hand dermatitis.

Objective: This study examines the practicability and usefulness of biophysical measurements at the workplace.

Patients/Material/Methods: A sample of 1020 male metal workers was enrolled; 800 participants were followed up for 1 year. TEWL results and colorimetry ($a^*$ value), respectively, were used as effectiveness outcomes, comparing the findings in the four study arms (skin care, skin protection, both combined, and control group).

Results: At 1 year follow-up, the TEWL was slightly but significantly lower in the group of participants randomized for application of barrier cream alone, indicating a protective effect. However, addressing both the individual absolute change of $a^*$ value and the differences of TEWL (delta-TEWL) of the dominant hand over the study period, no significant difference was found between the four groups.

Conclusions: Dermatological examinations at the workplace cannot be replaced by bioengineering techniques. The supplementary benefit is apparently low, possibly because of difficulties in achieving standardized measurement conditions and other technical reasons.

Key words: bioengineering; chromametry; hand eczema; occupational screening; TEWL; workplace.

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Occupational skin disease represents approximately 40% of occupational illness on an international level; differences in percentages from one country to another are associated with the extent and the type of industrialization (1). In particular, irritant hand dermatitis is a considerable problem in wet work occupations (2), including the metal industry. Funke et al. (3) reported a 1-year cumulative incidence of hand eczema of 9.2% (95% CI: 7.8–10.7%) in a sample of 1110 apprentices employed as metal workers in the automobile industry.

With the aim of yielding ‘objective’ measurements of skin irritation and epidermal barrier impairment, non-invasive bioengineering methods are widely used (4–8). Biophysical techniques are used (i) to assess treatments of dermatological disorders (9), (ii) to evaluate the clinical severity of either distinct skin diseases (10–12) or a single symptom such as dryness (13), (iii) to quantify experimentally induced irritation (7, 14, 15), and finally (iv) to assess the efficacy of skin protective means (e.g. gloves and moisturizers) (16–20). Moreover, the
measurement of transepidermal water loss (TEWL) as an indicator of skin barrier function and colorimetry for quantifying erythema has been recommended for monitoring persons at risk of irritant occupational hand dermatitis. In this context, most studies were performed in air-conditioned laboratories to avoid the interference of environmental factors (2, 8, 21, 22). However, the feasibility of these methods in ‘real life’ occupational settings – often lacking facilities for ensuring standardized climatic conditions – has not yet been evaluated in a large sample.

This study had the following objectives:

1. To examine the practicability of measurements in mostly non-standardized environments at the workplace in a sample of 1020 male white metal workers (23).
2. To analyse effectiveness in a prospective intervention study with four arms (skin care, skin protection, both combined, and control group, i.e. no particular measure) using TEWL and colorimetry, respectively, as outcomes. Post-exposure skin care with moisturizers is usually applied after work for enhancing epidermal barrier regeneration, whereas barrier creams (skin protection) are recommended for use before or (repeatedly) during work to prevent skin damage resulting from contact with irritants.
3. To compare bioengineering results with clinical findings of the hands.

**Material and Methods**

**Study population**

The metal workers were employed in 19 German factories, mainly of small or medium size. Inclusion criteria as recently described by Küttig et al. (23) comprised: (i) male sex, (ii) age ≥18 years, (iii) regular exposure to cutting fluids as indicator for wet work, (iv) a working contract for one further year at minimum, (v) fit for work at randomization, and (vi) willing to comply with the randomization result for a 12-month period. All participants provided their written informed consent to take part. Age of the participants ranged from 18 to 62 years (median: 42 years, mean: 40.6 years). The study design was approved by the local ethics committee of the University of Erlangen-Nuremberg. The study duration was 15 months, from winter 2006/2007 to spring 2008, in order to follow up each subject for 12 months.

**Bioengineering**

Bioengineering measurements were performed twice: at the beginning of the study (in winter 2006/2007) in a sample of 1020 subjects and at the second (final) follow-up 12 months later in 800 subjects then available, and on both hands. To exclude confounding by seasonal variation (e.g. tan in the summer, xerosis in winter, different climatic factors that may influence skin colour or TEWL), the bioengineering measurements were performed in the same season in the two successive years. The dominant hand was considered in all analyses, presumably being strained most. Of all, 91.8% of the subjects were right-handed, 6.5% left-handed, and the remainder ambidextrous. In this latter group, the mean value of both sides was used for analysis. The measurement of the TEWL (expressed as g/m² h) was performed on the dorsal area of both hands, whenever possible. In 986 individuals (96.6%), at least one dorsal hand was measured at baseline, and after 12 months this was possible in 90.2%, with measurements failing in the remaining subjects. In contrast, colorimetry could be performed in all subjects.

The Tewamer and Corneometer TC 350 (Courage & Khazaka electronic, Cologne, Germany) was used only for TEWL measurement. Skin surface temperature, following the guidelines by Pinnagoda et al. (24), was measured using IR No Touch Technique (IR-350, VOLTCRAFT®, Germany) (25), particularly because ambient air room temperature often deviated from the standard range (20–22°C). Measurements of erythema were performed using a portable tristimulus Chromameter CR 400 (Konica-Minolta®, Europe GMBH, Langenhagen, Germany) with a flexible hand-held probe. The measured area is 8 mm in diameter; however, the design of the probe requires a flat and even contact area of 40-mm diameter. Three consecutive readings were taken at the same site and the mean value calculated and recorded. The instrument was calibrated with a calibration plate before each measurement. The colour coordinates are expressed in the L*a*b* three-dimensional colorimetric system as recommended by the Commission Internationale de l’Eclairage (CIE). The L* value (luminance) gives the relative lightness, ranging from total black (L* = 0) to total white (L* = 100), and is likely to be influenced by both pigmentation and erythema. The b* value, representing the balance between yellow (positive value) and blue (negative value), is a good indicator of the tanning level. The a* value represents the balance between red (positive value) and green (negative value), and shows a significant linear correlation with the dermatologist’s perception of erythema. For this reason, we restricted our analysis on the a* values, again using the dominant hand for analysis.
Clinical examination
We used a scoring system for the clinical examination of initial hand eczema of both hands (23). In brief, the scoring system comprised all morphological criteria and physiological abnormalities (e.g. dryness) characteristic of hand eczema. As one part of this scoring system, erythema intensity was separately measured. To arrive at an operational definition of occupational hand eczema, for evaluation of the predictive value of bioengineering measurements at baseline, the skin score at final follow-up was categorized into ‘none/subclinical’ (score lower than the first quartile of skin score), ‘slight’ (score between the first and the third quartiles), and ‘moderate/severe’ (score above the third quartile).

Results
Environmental conditions
Room temperature at baseline examination ranged from 17°C to 27.7°C (median: 22.6°C; mean: 22.5°C). The mean skin surface temperature at the back of the right hand was on average 0.68°C higher than that of the left hand (P < 0.0001, Wilcoxon signed rank test). On the dominant hand, the mean skin surface temperature was 33.8°C (median: 34.0°C; range: 21–39°C). Similarly, relative humidity in the air of the measuring chamber was higher when measuring the right hand (by 1.5% on average, P < 0.0001, Wilcoxon signed rank test). The value of relative humidity of the dominant hand was 64.9% (range: 28.6–88.4%, median: 64.5%). At the visit after 12 months (winter 2007/2008), room temperature ranged from 14.4°C to 27.6°C (median: 22.4°C; mean: 22.4°C). The mean skin surface temperature at the back of the dominant hand was 34.6°C (median: 35.0°C; range: 24–39°C). Relative humidity was 61.2% on average (range: 27.8–85.3%, median: 60.6%). Considering these factors, environmental conditions at baseline and after 12 months were similar.

Transepidermal Water Loss
Only a minor proportion of the participants (23.5% at baseline and 12.4% at the second examination 12 months later) had skin surface temperatures within the range considered compatible with standardization requirements, i.e. between 28°C and 32°C. Table 1 gives an overview of TEWL measurements [mean, median, minimum, maximum, and interquartile ranges (IQR)] according to the corresponding skin surface temperatures (given in three categories: below the optimum, at optimum, and higher than the optimum range) and the corresponding skin score values. The distribution of these three categories

<table>
<thead>
<tr>
<th>Table 1. Measurements of TEWL (g/m² h) in three strata of skin surface temperature at baseline (visit 0) and after 12 months (visit 12), given for the dominant hand</th>
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</thead>
<tbody>
<tr>
<td>Skin surface temperature at the optimum (≥28°C) and ≤32°C according to guidelines</td>
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<tr>
<td>Visit 0</td>
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<tr>
<td>TEWL number of subjects</td>
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<tr>
<td>Mean</td>
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<td>Range</td>
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<td>IQR 1–3</td>
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<td>Skin score</td>
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IQR: Interquartile range. *IQR 1–3 means the range between the first and the third quartiles.

TR did not differ significantly between the four intervention groups. There was a (very) weak but significant correlation between skin surface temperature and TEWL both at baseline (r = 0.24, 95% CI: 0.18–0.30) and at follow-up (r = 0.16, 95% CI: 0.09–0.23). Figure 1 illustrates this weak correlation in a scatter plot diagram, the black vertical lines mark all TEWL values obtained under optimal skin surface temperatures (28–32°C). Taking into account only the TEWL values obtained under optimal conditions, no significant correlation could be detected between measurement of TEWL and skin score value of the corresponding hands both at baseline and after 12 months.

Between the four groups, i.e. barrier cream alone (I), moisturizer alone (II), both combined (III), and none (IV), no significant difference between TEWL measurements could be detected both at baseline and at the follow-up visit after 12 months in a per protocol (PP) analysis (defined by actually performed skin protection measure). In contrast, using
the intention-to-treat (ITT) analysis (defined by randomized measure), the TEWL on the dominant hand was significantly lower in the group of participants randomized for application of barrier cream alone after 12 months, compared with that in all other groups \( (P < 0.02\), non-parametric closing test procedure), indicating a protective effect of barrier creams in this analysis (only). However, addressing the development of TEWL (delta-TEWL) between baseline and 1-year follow-up, differences between the groups were non-significant both in the ITT and in the PP analyses.

Moreover, the TEWL at baseline did not differ significantly between the three subgroups of eczema classification after 1 year.

Taking into account only the TEWL values obtained under optimal skin temperature conditions, no significant correlation could be detected between TEWL and global skin score values of the corresponding hands both at baseline and after 12 months.

**Chromametry**

Measurements of \( a^* \) values were obtained from all subjects at baseline \( (n = 1020) \) and after 1 year \( (n = 800) \). Table 2 gives an overview of mean, median, and range for \( a^* \) value and for the score values for erythema, as one component yielded from the clinical examination aggregated to the ‘skin score’. As the \( a^* \) value is supposed to indicate redness and should therefore correspond to the clinical perception of erythema (albeit regarding the entire hand), correlation (Spearman Rho) between these two values was analysed. The correlation at baseline was 0.08 (95% CI: 0.02–0.14) and at follow-up was 0.13 (95% CI: 0.06–0.20), i.e. significant but (extremely) weak.
As erythema is one of the most frequent morphological changes in acute hand eczema, $a^*$ values were evaluated as a possible indicator of effectiveness in skin protection. However, analysing our data we did not detect a significant difference in the $a^*$ values of the dominant hand between the four study arms in a PP analysis, both at baseline and at follow-up. Conversely, in the ITT analysis, higher $a^*$ values were observed in subjects following the skin protection regimen correctly (skin care + skin protection) than in all the other groups ($P<0.045$, non-parametric closing test procedure) on follow-up. Finally, addressing the individual change in non-parametric closing test procedure on follow-protection) than in all the other groups ($P<0.045$).

In our sample including many cases with slight irritation or mild hand eczema, at most, chromametry results showed only a very weak correlation with clinically diagnosed erythema. However, the weakness of the correlation is quite easily explained by the fact that all measurements (chromametry and tewametry) were taken in a pre-defined identical manner in the workplace, instead of correcting measurements by mathematical modelling.

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Earlier studies had proposed different formulas to convert TEWL at any given temperature to a standard reference temperature of 30°C (34, 35); however, a generally accepted conversion formula does not exist until now. Therefore, more recent publications (2, 21, 22) emphasize on standardization of surrounding factors (28), instead of correcting measurements by mathematical modelling.

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Assessing the effectiveness of intervention using the bioengineering outcomes, and also clinical outcomes (23), for that matter, the individual change (delta) over the observation period of 1 year is most appropriate, as the skin condition at baseline is taken into due consideration. Disappointingly, both delta-TEWL and delta-$a^*$ failed to discriminate any intervention effect, in contrast to our results based on the clinical signs (23), which identified the combined application of barrier cream and moisturizer as the best regimen, followed by skin protection alone. Biophysical techniques may fail to detect this clinical difference for the technical reasons mentioned above. Moreover, the bioengineering results obtained at baseline were not predictive...
regarding prevalent skin changes at final follow-up, which is in accordance with other studies employing such point measurements without irritant provocation testing (25).

Conclusions

(1) Dermatological examinations at the workplace cannot be replaced by bioengineering techniques.

(2) The supplementary benefit of both bioengineering methods is low and can probably not be increased much by establishing standardized conditions for measurement.

(3) Based on our results, bioengineering as part of occupational screenings cannot be regarded as effective.

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