

Skin strain and its influence on systemic exposure to a glycol ether in offset printing workers

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Under workplace conditions, it is difficult to prove the influence of skin lesions on skin penetration by chemical substances. The aim of the present study was to show whether systemic exposure to glycol ether increases due to lesions of the skin in printing workers. 28 male printers, exposed to 2-(2-butoxyethoxy)ethanol (BEE), were interviewed about the workplace exposure by a standardized questionnaire. The systemic exposure in printers was determined by biological monitoring of the main metabolite of BEE butoxyethoxyacetic acid (BEAA) in urine. Furthermore, clinical examination of the skin, transepidermal water loss, capacitance and skin surface pH measurements were carried out. Erythema and scaliness were the most important factors showing an effect on dermal absorption. The mean urinary BEAA excretions for printers with skin lesions on the hands were higher (20.62 mg/l for scaliness and 14.40 mg/l for erythema) compared to that for printers without detectable skin lesions (12.08 mg/l for scaliness and 13.03 mg/l for erythema). Bioengineering measurements to predict skin strain and percutaneous absorption were only supportive. We were able to show that by using a multiple spectrum of methods an enhancement of percutaneous absorption of BEE could be demonstrated in workers with skin lesions.

Key words: 2-(2-butoxyethoxy)ethanol; bioengineering methods; butoxyethoxyacetic acid; capacitance; erythema; percutaneous absorption; printing industry; scaliness; skin surface pH; systemic exposure; transepidermal water loss. © Blackwell Munksgaard, 2003.

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The systemic exposure to chemical substances in workers arises primarily from inhalation and dermal absorption. For some chemical substances, the skin may be the most important route of intake. Hazardous substances that penetrate the skin easily lead to systemic toxicity. In animal experiments, Bronaugh et al. (1) were able to show an increased percutaneous absorption of chemicals in experimentally induced eczematous skin. Although this might allow the conclusion that in damaged skin the absorption rate of chemicals is increased, currently, only a few investigations in humans exist (2). The lack of such studies can be explained by the lack of validated methods to quantify skin damage and/or to assess the dermal absorption rate (3).

Work-related dermatoses, in particular hand dermatitis, are still among the most prevalent occupational diseases (4). It is well known that hairdressers, bakers or mechanics have an increased

risk to irritant and allergic contact dermatitis (5). The prevalence of self-reported skin complaints in printers in the printing industry in UK is 49% (6). The skin of printers is vulnerable during contact with washing and cleaning agents for printing machines, paints or other possible irritants such as alcohols or isocyanates. But mechanical factors should also not generally be underestimated in their role as irritants to the epidermal barrier (7). The most commonly involved self-reported areas were the fingers and the webs between the fingers, closely followed by the dorsum of the hand (8). Due to the 'healthy worker effect', whereby workers with more severe lesions tend to leave the job, skin damage in workers at workplaces is for a long time largely only minimal. In most cases, the strained skin shows only lesions such as circumscribed erythema or limited areas of scaliness. But just such lesions could represent an important portal and pathway for percutaneous absorption (9).

However, at present, only few investigations describe a relationship between the severity of skin strain and the amount of percutaneously absorbed chemicals at the workplace.

Glycol ethers are commonly used to replace hazardous chemical substances, and also in the printing industry as ingredients of washing and cleaning agents for printing machines, as well as in paints. In our study, printers used washing and cleaning agents with up to 15% of the glycol ether 2-(2-butoxyethoxy)ethanol (BEE). Glycol ethers have a low vapour pressure and are water soluble, their exposure time on the skin therefore possibly being relevant to significant dermal absorption.

The aim of the present study was to determine whether lesions on the skin of the hands and forearms in printing workers led to increased systemic exposure to BEE.

Materials and Methods

Subjects

The study group consisted of 28 volunteer male printers (age 23–60 years; median, 47 years) from 1 offset printing shop. This corresponded to a participation rate of 82% of all employed printers. Clinical examination of the skin and bioengineering measurements were carried out on the same day. Printers were asked about occupational conditions, domestic and occupational risk factors for contact dermatitis, skin complaints, history of skin diseases and the use of personal protective equipment by a standardized questionnaire. Table 1 summarizes the exposure conditions of printers evaluated from the questionnaire.

Urine samples were collected at the end of exposure after an exposure period of 1–5 days. The samples were stored deep frozen (–20°C) before analysis.

Clinical examination of skin

The skin of each printer was screened for lesions by a dermatologically trained physician. Exposed skin areas of the hands and forearms were examined for erythema, scaliness and other pathological

findings. The classification of erythema and skin scaliness was performed immediately after clinical examination in accordance with recently published studies (10, 11) with reference to the OECD guideline (12): grade 0, no pathological skin findings; grade 1, very slight erythema or discrete scaliness; grade 2, well-defined erythema or fine lamellar scaliness; grade 3, moderate erythema or rough lamellar scaliness; and grade 4, severe erythema or extensive scaliness.

Bioengineering measurements

The bioengineering measurements were carried out at a room temperatures of 23.4–24.5°C (median, 23.8°C) and at a relative humidity of 60%. The skin surface temperature was measured using a digital precision thermometer GTH 1160 (Greisinger Electronic, Regenstauf, Germany) on the volar forearm and ranged from 30.2–33.1°C (median, 31.3°C).

Transepidermal water loss and capacitance

To objectify the skin barrier status in printers, measurements of transepidermal water loss (TEWL) were performed. Furthermore, the hydration of stratum corneum was assessed by the measurement of capacitance. The TEWL and capacitance were calculated automatically by the Skin Monitoring Centre TC350 (Courage + Khazaka Electronic, Cologne, Germany). The measuring heads were always placed in the middle of the dorsum of the left hand and of the left volar forearm.

Skin surface pH

Skin surface pH was determined with the pH meter MP 220 using the InLab 426 pH electrode (Mettler Toledo, Giessen, Germany) on the same areas of the left hand and of the left volar forearm. To avoid an influence on the TEWL and capacitance values of the moist pH electrode, the pH measurements were conducted at the end of the measurement sequence. According to manufacturer's information, the accuracy of the pH

Table 1. Exposure conditions

Exposure variables	Range (median; mean)
Duration of occupation as a printer (years)	1.5–38 (1.5, 14.7)
Concentration of 2-(2-butoxyethoxy)ethanol in cleaning agents (%)	10–15
Daily exposure time to cleaning agents (min)	10–480 (90; 119)
Daily wearing time of gloves (min)	5–300 (120; 120)
Hand washing frequency (times per day)	3–20 (6; 8)

meter used is ± 0.01 pH units. The calibration was performed at 30°C that is within the range of the skin surface temperature.

Biological monitoring

The systemic exposure to BEE in printers was determined by analysis of the main metabolite butoxyethoxyacetic acid (BEAA) in postshift urine by gas chromatography-mass spectrometry. The analyses of BEAA were performed with a validated analytical method. The detection limit of urinary BEAA was 0.5 mg/l (13, 14).

Statistics

For the statistical analysis, SPSS 11.0 computer software (SPSS Inc., Chicago, IL, USA) was used. The correlation analyses were calculated with the Pearson's correlation coefficient. As level of significance, $P \leq 0.05$ was chosen. Results with $P \leq 0.1$ were considered as a statistical trend.

Results

Exposure conditions

The workplace exposure conditions (Table 1) can have an impact on the skin status of the printers. With an average duration of occupation of 14 years as a printer, it seems clear that printers have a long occupational history of skin strain. A significant correlation between the duration of occupation as a printer and skin strain could be found only for the variable 'skin scaliness on the forearm' ($P = 0.011$). However, the total number of printers with skin scaliness on the forearm was

small ($n = 5$). None of the printers wore respirator masks against pulmonary intake of BEE and none of them applied skin protection or skin care creams. All printers had used nitrile rubber gloves when working with cleaning agents. The protective gloves were on average replaced after a period of 4 weeks. The median daily exposure time to BEE during the use of cleaning agents was 90 min according to the questionnaires. The workplace-related exposure to BEE was similar for all printers. A positive correlation between the exposure duration to BEE and the concentration of BEAA in urine could not be found. Other variables presented in Table 1 did not influence the systemic exposure to BEE. Figure 1 shows the effect of daily wearing time of gloves on systemic exposure, expressed as BEAA concentrations in urine. Up to a wearing time of gloves of 90 min, a tendency to a reduced systemic exposure was observed ($P = 0.057$). In printers with an increased systemic exposure using gloves not longer than the median exposure time, only a small protective effect could be demonstrated. In contrast, a prolonged daily wearing time of gloves increased the systemic exposure (Fig. 1).

Skin strain and results of bioengineering measurements

Based on the questionnaire data, one printer was identified with atopic skin diathesis. At the time of the examination, he did not show any signs of skin strain. Erythema or scaliness could be detected only on the dorsum of hands and on the forearms. Severe skin lesions such as rhagades

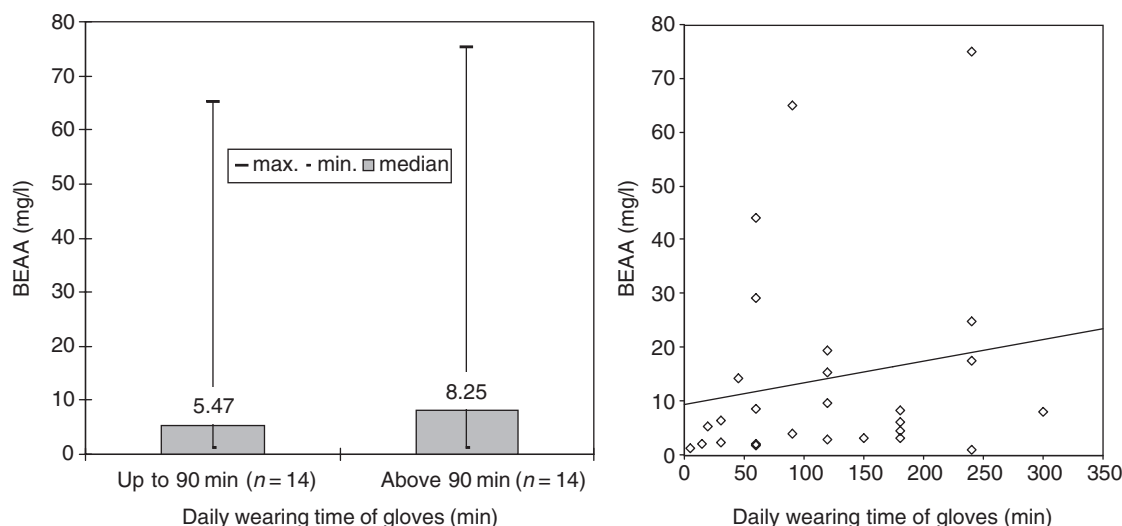


Fig. 1. Effectiveness of glove use v systemic exposure expressed as urinary butoxyethoxyacetic acid (BEAA) concentrations.

or callosities were not found. Table 2 summarizes the results of the clinical examination of the skin. 21 printers (75%) showed slight (grade 1) signs of skin strain. More defined erythema (grade 2) were found in 3 printers on the dorsum of the hands and in 2 printers on their forearms. For further calculations, the printers with higher graded skin alterations were subdivided into 2 groups: one group with erythema and scaliness on the hands or forearms and the other without signs of skin strain.

The results of bioengineering measurements did not indicate a strong and uniform relationship with skin lesions (Table 3).

The room temperature of 23.4–24.5°C was relatively high. There was no statistically significant relationship between room temperature and temperature of skin surface. A significant influence of room temperature and humidity as well as skin surface temperature on the bioengineering results could not be detected. A higher skin surface temperature was not correlated with an elevated urinary BEAA excretion. Even though capacitance was able to indicate skin scaliness (mean capacitance values on hands and forearms were higher in persons with such scaliness), the results of TEWL were not uniform. However, there were higher TEWL and capacitance values ($P=0.155$ and $P=0.048$ respectively) in printers with erythema on the forearms than that in those without such erythema. Also a trend towards higher systemic exposure to BEE was shown by increased TEWL on the forearms ($P=0.058$). These relationships indicate that the forearms represent a more sensitive site for examination of skin lesions by bioengineering techniques. A possible reason could be that the TEWL of the forearms is less influenced by occupational and non-occupational factors than that of the hands. No correlation was found in our study between erythema or scaliness and skin surface pH.

Skin strain and systemic exposure

In all printers, the systemic exposure to BEE expressed as urinary BEAA concentration was

found to be above the detection limit for urinary BEAA of 0.5 mg/l. The biological monitoring results of BEAA in relation to the clinical status of the skin are presented in Table 3. It was found that an enhancement of percutaneous absorption of BEE was already detected for slightly strained skin. The mean concentration of BEAA in urine was distinctly higher in workers with scaliness on the hands than that in workers without such scaliness (20.62 versus 12.08 mg/l), in workers with erythema on the forearms than that in workers without such erythema (18.66 versus 10.83 mg/l) and in workers with scaliness on the forearms than that in workers without forearm scaliness (19.97 versus 12.59 mg/l). However, these differences were statistically not significant, probably due to the small size of the study group. Figures 2 and 3 present the relationship between skin strain and systemic exposure in term of boxplots. A consistent relation is ascertainable towards higher values of BEAA in the urine of printers with strained skin.

Discussion

BEE is a solvent with a low vapour pressure and commonly used in industry. *In vitro* studies indicate that BEE penetrates through the stratum corneum and is dermally absorbed in significant amounts (15). Solvents with high volatility evaporate rapidly from the skin of exposed workers, and solvents with low volatility lead to prolonged skin contact. This can be the most prominent factor for percutaneous absorption (16). Due to the low vapour pressure for BEE of 0.027 mbar at 20°C, the systemic exposure of printers at the workplace results predominantly from dermal absorption. It is generally assumed that the prolonged wearing of gloves can be an independent risk factor for skin damage followed by an increased uptake of chemicals (17–19). Comparing daily exposure time to cleaning agents and the wearing time of gloves, it can be concluded that printers in our study used the gloves long enough to provide effective protection. This assumption is supported in our study by the consistent trends

Table 2. Results of the clinical examination of the skin

Strain grade	n (%)					
	Erythema			Skin scaliness		
	Hands	Interdigital	Forearms	Hands	Interdigital	Forearms
0 (healthy skin)	10 (35.7)	26 (92.9)	17 (60.7)	24 (85.7)	25 (89.3)	23 (82.1)
1	15 (53.6)	2 (7.1)	9 (32.1)	4 (14.3)	3 (10.7)	5 (17.9)
2	3 (10.7)	—	2 (7.1)	—	—	—
Total (strained skin)	18 (64.3)	2 (7.1)	11 (39.3)	4 (14.3)	3 (10.7)	5 (17.9)

Table 3. Results for skin parameters and urinary butoxyethoxyacetic acid (BEAA) in relation to skin strain

Skin status	<i>n</i> (%)	Mean $\pm$ SD			
	Printers	BEAA in urine (mg/l)	Transepidermal water loss (g/m ² h)	Capacitance (Corneometer units)	Skin surface pH (pH units)
Hands					
Without erythema	10 (36)	13.03 $\pm$ 19.72	35.2 $\pm$ 17.4	48.6 $\pm$ 11.8	4.89 $\pm$ 0.36
With erythema	18 (64)	14.40 $\pm$ 18.80	31.2 $\pm$ 15.0	49.3 $\pm$ 14.4	4.95 $\pm$ 0.33
Without scaliness	22 (79)	12.08 $\pm$ 15.58	30.7 $\pm$ 14.7	48.3 $\pm$ 10.9	5.00 $\pm$ 0.33
With scaliness	6 (21)	20.62 $\pm$ 28.57	39.2 $\pm$ 14.6	51.8 $\pm$ 21.2	4.68 $\pm$ 0.27
Forearms					
Without erythema	17 (61)	10.83 $\pm$ 15.71	15.7 $\pm$ 9.5	44.9 $\pm$ 6.0	4.81 $\pm$ 0.44
With erythema	11 (39)	18.66 $\pm$ 22.73	21.7 $\pm$ 11.9	51.5 $\pm$ 10.6	4.75 $\pm$ 0.35
Without scaliness	23 (82)	12.59 $\pm$ 17.45	18.2 $\pm$ 11.4	47.2 $\pm$ 9.4	4.73 $\pm$ 0.42
With scaliness	5 (18)	19.97 $\pm$ 25.51	17.3 $\pm$ 8.1	49.0 $\pm$ 3.5	4.99 $\pm$ 0.24

to higher values of BEAA in printers with skin lesions compared to healthy skin and the reduction of systemic exposure through appropriate use of gloves (Fig. 1).

Measurements of TEWL will increasingly be used as a sensitive method for early detection of minimal skin strain (10, 11), even though a clear increase of TEWL in experimentally induced skin irritation could not be shown in all studies (20, 21). The application of skin barrier creams may influence TEWL values (22) or may reduce skin irritation (23). Because the printers in our study did not apply skin barrier creams or skin care creams, such an influence could be excluded.

In general, the conventional bioengineering techniques do not reliably distinguish between old and young skin in most anatomic regions. Only for TEWL were significantly lower values

in older persons found (24). Some studies showed different reactions to irritation in younger and older skin (25, 26). The skin of older people seems to react in a delayed fashion and less intensively when exposed to irritant substances like sodium lauryl sulfate (26). However, the experimental results partially correlated with epidemiological data (27). In support of the above thesis, we could show in our study a significant positive correlation between skin lesions in terms of scaliness on forearms and the age of printers ($P = 0.004$). The general validity of these findings needs to be verified with a larger number of exposed persons.

The results of bioengineering measurements in our study did not show a strong and uniform relationship with skin lesions. A significant positive correlation between erythema in printers and

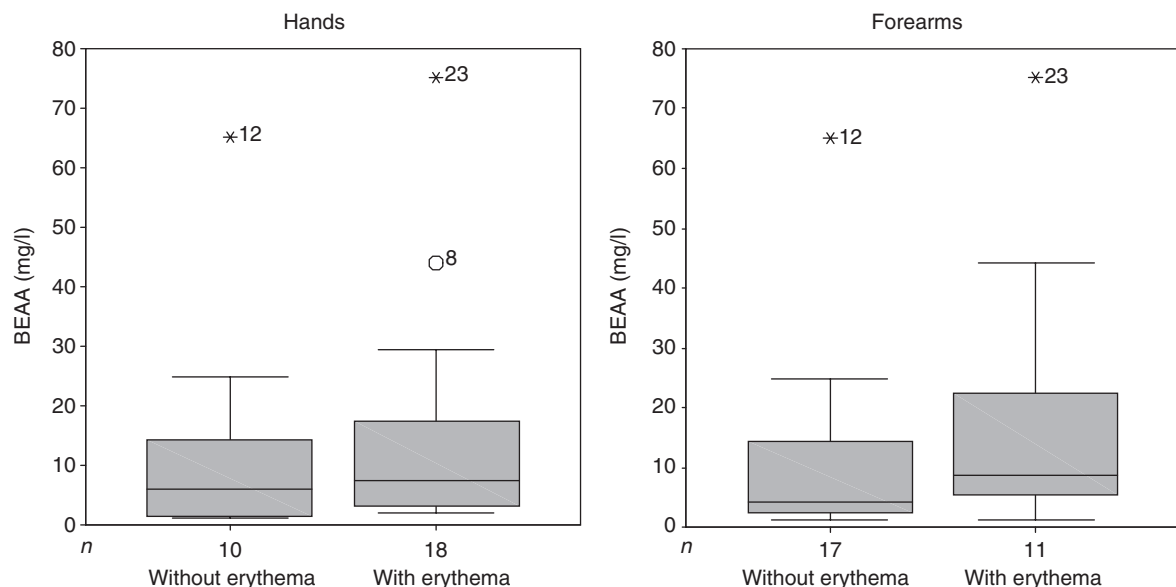


Fig. 2. Relationship between erythema and systemic exposure expressed as urinary butoxyethoxyacetic acid (BEAA) concentrations.

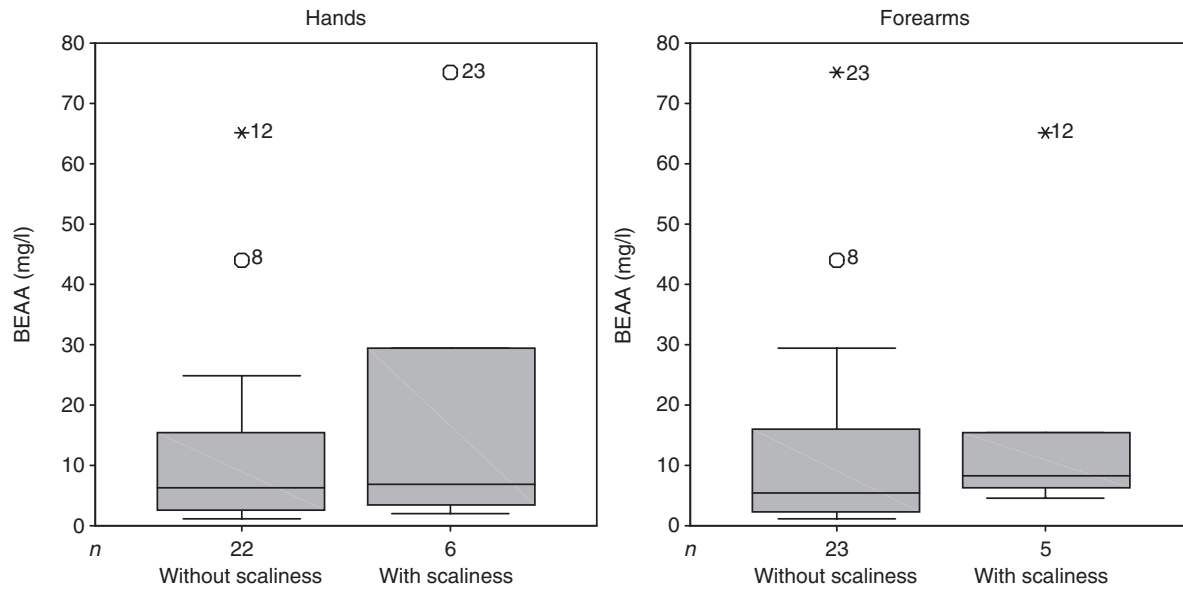


Fig. 3. Relationship between scaliness and systemic exposure expressed as urinary butoxyethoxyacetic acid (BEAA) concentrations.

the results of bioengineering measurements could not be detected, although a positive trend between erythema on the forearms and TEWL ($P=0.077$) as well as capacitance ($P=0.056$) was found. Capacitance could sensitively predict skin scaliness. The mean values for capacitance in scaly skin on the hands and forearms were higher than that in skin without scaliness. In contrast, the results of TEWL can be interpreted as showing that TEWL is less useful to indicate skin scaliness. Rippke et al. (28) considered an acidic pH to be required for the formation of lamellar structures in mixtures of horny layer lipids, as well as being important for skin barrier function. As summarized in Table 3, skin surface pH values were in the acidic range on the hands and forearms of all printers in our study group. A linear relationship between skin surface pH and the results for systemic exposure could not be detected.

In our study, we found consistently higher BEAA concentrations in the urine of printers with strained skin in comparison with that of printers without erythema or scaliness. The differences in systemic exposure were not significant for either group, probably due to the small size of the study group. It is likely that a trend to higher BEAA excretion values in persons with skin lesions resulted solely from higher percutaneous absorption. A possible explanation for the small difference in systemic exposure to BEAA for erythema between the hands and forearms may be the more difficult recognition of erythema on the hands. This could lead to an underestimation compared to the findings on the forearms,

whereas the larger exposure area of the forearms should not be a relevant factor, because detection of scaliness on hands and forearms showed no difference. In general, the systemic exposure can be influenced by several other factors (29).

The causes for the observed skin strain in our study group cannot precisely be assessed. In 2 case reports, a possible allergic reaction after contact with BEE is proposed (30, 31). On the other hand, toxicological data do not indicate BEE to be a causative agent of skin irritation. Zhai and Maibach (18) state that skin occlusion, e.g. the use of gloves, among other things may damage the skin barrier, and this results in an increased risk for irritant contact dermatitis. Therefore, increased percutaneous absorption of applied chemicals could often be demonstrated (19). The findings of our study did not allow the conclusions of Zhai and Maibach to be convincingly supported. The positive correlation between systemic exposure and the duration of glove wearing time shown in Fig. 1 is in agreement with the conclusions of Zhai and Maibach (19). However, the number of workers with intensive use of gloves is very small.

The risk of dermal absorption of chemicals at the workplace is often underestimated. Based on the findings of clinical examinations in our study, a relationship between visible skin lesions and the systemic exposure to BEAA was established. The use of bioengineering methods in occupational field studies may give additional information about the influence of skin lesions and percutaneous absorption. The most important draw-back

to the use of bioengineering techniques for workplace conditions is their low specificity in objectifying signs of skin strain. The results of clinical examination of the skin are more reliable. Thus, clinical examination should be preferred for the determination of the skin status.

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