SHORT TERM EXPOSURE TO VOLATILE ORGANIC COMPOUNDS (VOCS) CAUSES IMPAIRMENT OF SKIN BARRIER FUNCTION IN MAN

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ABSTRACT
Exposure to indoor concentrations of formaldehyde was reported to cause disturbance of the epidermal barrier function in healthy volunteers and patients with atopic eczema (AE). No such data are available on VOCS which are widely occurring indoor air contaminants. In a double-blind crossover study we exposed 12 adults with AE and 12 matched controls to a mixture of 22 VOCS in an exposure chamber for 4h (TVOC: 5mg/m³). The transepidermal water loss (TEWL) was measured in all subjects before, during and after exposure. Pronounced changes in TEWL were observed 48h after the VOCS exposure as compared to the exposure with cleaned air alone (mean change: +34.1%; 95% confidence interval: 6.6 – 68.6%). Significant differences between the patients and controls could not be detected. The results indicate an impairment of the epidermal barrier function in patients with AE and in healthy controls induced by VOCS exposure in concentrations encountered in indoor environments.

INDEX TERMS
VOCS, TEWL, Skin Barrier Function, Atopic Eczema, Human Exposure Chamber

INTRODUCTION
It is generally accepted that the prevalence of atopic diseases (allergic rhinoconjunctivitis, bronchial asthma, atopic eczema) has increased over the last decades (Burney et al., 1994; Burr, 1993; ISAAC Steering Committee, 1998; Wüthrich, 1989). The reason for this worldwide development is not known. Among many theories, the idea of environmental pollutants playing an important role in this process has attracted the attention of an extended scientific and public audience (Behrendt et al., 1992; Behrendt et al., 1995; Miyamoto and Takafuji, 1991; Rusnak, 1994). As the majority of people in industrialized countries spend around 90 % of their time indoors pollutants which are found predominantly in indoor environments have been investigated concerning their impact on human health (Otto et al., 1992; Hudnell et al., 1992). In this context a previous study on the effect of formaldehyde and NO₂ at domestic concentrations on human skin showed an increase in transepidermal water loss following 4 h exposure to these substances (Eberlein-König et al., 1998). A Danish study revealed that VOCS lead to an impairment of the lung function in asthmatics when exposed continuously over 4 h at a concentration of 25 mg/m³ (Harving et al., 1991). For this investigation the patients where exposed to a mixture of 22 VOCS, called M 22, which were shown to be found regularly in the indoor air.

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To our knowledge no study has focused so far on the effect of VOCs at domestic concentrations on human skin. We therefore investigated the effects of VOCs on physiological parameters of the skin of patients with atopic dermatitis. A double-blind crossover study was carried out in an interdisciplinary approach by the Fraunhofer Institute of Building Physics, Holzkirchen, and the Division of Environmental Dermatology and Allergology, GSF/ Technical University Munich.

**METHODS**

**Study subjects**

12 adults with AE (6 male, 6 female; age 35.6±11.1 years) recruited from patients attending the Department of Dermatology and Allergy Biederstein of the Technical University Munich and 12 matched healthy volunteers as controls (6 male, 6 female, age 35.5±10.7 years) were included in the study. All individuals were examined thoroughly prior to inclusion. Informed consent was obtained from each subject before the study, which was approved by the local ethics committee. Inclusion criteria for patients were a doctor-diagnosed atopic eczema according to the definition of Hanifin and Rajka (Hanifin and Rajka, 1980), demonstration of specific IgE antibodies, positive prick test results and a positive atopy patch test (Ring, 2001) as well as the lack of a specific therapy with internal or external steroids or antihistamines 3 weeks before and during the exposure experiments.

Volunteers were characterized as healthy controls if they did not show any signs of skin disorders in the dermatological examination as well as no indications for an atopic disease with clinical relevance.

**Exposure experiments**

48 exposure experiments were performed in the Fraunhofer Institute for building physics during February to May 2001. Each person participating in the study was exposed twice with bare forearms in a 40 m³ exposure chamber (steel/glass frame construction) for 4 h: once with VOCs and another time with cleaned air alone as control. The VOC mixture was composed of 22 compounds (the “Mølhave mixture”: m/p-xylene and n-butylacetate, each 1.613 mg/m³; n-hexane, n-nonane, n-decane, 1-decene, ethylbenzene, α-pinene, n-hexanal, n-butanol, ethoxyethylacetate, 1,2-dichlorehane, each 0.161 mg/m³; n-undecane, 1-octene, cyclohexane, 1,3,5-trimethylbenzene, n-propylbenzene, n-pentanal, isopropanol, 2-butanone, 3-methyl-2-butanone, 4-methyl-2-pentanone, each 0.016 mg/m³) (Hudnell et al., 1992). VOCs were added to the chamber air via air supply (3 air changes per h) by a specially adapted micro-dosing system MD-K-30/MD-E-201 (Microdrop, Nordersted, Germany) to generate the final TVOC-concentration of 5 mg/m³ in the chamber air. Samples from the chamber air were taken every 30 min and analysed subsequently with gas chromatography-mass spectroscopy for the single components of the VOC mixture. Air temperature and relative humidity (rh) were adjusted to 23±1 °C and 50±5 % rh respectively and registered continuously throughout the experiment.

**Clinical investigation and TEWL measurement of the skin**

Besides a dermatological investigation of the exposed skin the TEWL as parameter of the integrity of the epidermal barrier was measured by a Tewameter (TM 210, Courage & Khazaka, Colone/Germany). A rise of the TEWL is a reliable sign for an impairment of the skin barrier function in vivo (Gfesser et al., 1996). The measurement was carried out at the volar forearms at the following time points: Immediately before (t0), after 2 h (t1) as well as 4 h (t2) during exposure and 24 h (t3), 48 h (t4) and 72 h (t5) after exposure. A draught screen was used to allow stable measurement of the TEWL according to the guidelines of the
Standardization Group of the European Society of Contact Dermatitis (Pinnagoda et al., 1990).

**Statistical analysis**
Since the TEWL values showed a log normal distribution we did all tests after logarithmic transformation and determined the quotient between the measurements after exposure with VOCs and the control experiments with cleaned air alone for all time points (t0 – t5). Results were considered as significant if p was < 0.05 (t-test for paired comparisons). First we investigated if at any time point the quotients differed between patients with AE and healthy volunteers. Since there were no significant differences found between the two investigated groups we took all subjects together for data analysis.

**RESULTS**
The lowest TEWL values were measured in healthy volunteers exposed to cleaned air (mean TEWL from all subjects at the time points t1 – t5: 5.5 g m$^{-2}$ h$^{-1}$; range: 4.6 – 6.6 g m$^{-2}$ h$^{-1}$), followed by healthy volunteers exposed to VOCs (mean TEWL: 7.6 g m$^{-2}$ h$^{-1}$; range: 5.3 – 12.3 g m$^{-2}$ h$^{-1}$). Higher TEWL measurements were obtained from patients with AE exposed to cleaned air (mean TEWL: 12.5 g m$^{-2}$ h$^{-1}$; range: 11.1 – 14.1 g m$^{-2}$ h$^{-1}$) exceeded by the values after VOC exposure (mean TEWL: 14.2 g m$^{-2}$ h$^{-1}$; range: 12.8 – 16.1 g m$^{-2}$ h$^{-1}$).

Concerning the difference between the two exposure procedures a significant rise of the TEWL could be detected 48 h after exposure with VOCs in patients with AE and in healthy volunteers (mean change: +34.1 %; 95 % confidence interval: 6.6 – 68.6 %). The measurement at all other time points showed stable values indicating no significant differences between VOCs versus clean air exposure experiments. Concerning the comparison between patients with AE and control subjects the mean change in TEWL 48 h after exposure was very similar with +31.3 % (confidence interval: -10.4 – 92.5 %) in patients with AE and +37.2 % (confidence interval: -1.4 – 90.9 %) in healthy volunteers.

![Figure 1](image.png)

**Figure 1.** Mean TEWL changes in all study subjects (healthy volunteers (n=12) and patients with AE (n=12) taken together) at different time points: immediately before (t0), after 2 h (t1) and 4 h (t2) during VOC exposure and 24 h (t3), 48 h (t4) and 72 h (t5) after the exposure as compared to the exposure with cleaned air alone. Error bars show the 95 % confidence interval. * indicates a significant rise under VOC exposure compared to cleaned air.
DISCUSSION
This study showed for the first time an adverse effect of VOCs in indoor air concentrations on the epidermal barrier function in patients with atopic eczema and healthy volunteers.

Previous human exposure studies showed that formaldehyde and NO\textsubscript{2} at domestic concentrations caused an impairment of the skin barrier function in patients with atopic eczema. In healthy volunteers only NO\textsubscript{2} but not formaldehyde led to an increase of TEWL (Eberlein-König \textit{et al.}, 1998). The present results indicate that 4 h of exposure with VOCs at a total concentration of 5 mg/m\textsuperscript{3} leads to a significant rise of TEWL after 48 h, but not with cleaned air, in patients with atopic eczema as well as in control subjects. The VOC concentration used in our study was slightly higher than the maximal concentration found in German households (3.3 mg/m\textsuperscript{3}) (Krause \textit{et al.}, 1987). Main sources for VOCs are wall paints which can cause concentrations of up to 3 mg/m\textsuperscript{3} in the indoor air after 2 month in newly built or renovated rooms. These concentrations were reported to decrease to 0.9 - 1.3 mg/m\textsuperscript{3} within the first 10 month. Subjects living in such rooms complained significant more frequent about soreness of the throat, irritations of mucous membranes, headache and increased weariness (Pitten \textit{et al.}, 2000). Interestingly significant changes in TEWL developed with a delay of 48 h after 4 h of exposure. This could be due to the time being necessary for VOCs to exert their adverse effect on the epidermal barrier. Another important finding was that skin of patients with AE as well as healthy volunteers was effected in the same way by VOC exposure. This result suggests that VOCs influence the skin independent of its pathology.

Turning back to the increase in prevalence of atopic diseases it can be speculated that long-term exposure of VOCs at domestic concentrations leads to an impairment of the skin barrier in all subjects but only becomes clinical relevant in patients with atopic eczema, which already possess a disturbed epidermal barrier function. The impaired skin barrier in patients with AE could then facilitate further skin damage through indoor allergens which play an important role in the pathogenesis of this disease.

CONCLUSION AND IMPLICATIONS
It could be shown that VOCs at domestic concentrations cause an impairment of the skin barrier in humans. For patients with AE this effect might add to the constitutionally disturbed epidermal barrier and lead to the clinical manifestation of the skin disease. Since other substances found in the indoor air e.g. house dust mite allergens can elicit eczematous skin reactions as well (Ring \textit{et al.}, 2001) the role of interaction between different indoor air contaminants influencing the epidermal barrier in healthy and diseased skin should be further investigated.

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