Atopic dermatitis is one of the main risk factors of occupational contact dermatitis which is one of the most frequent work-related diseases and has a great impact on health-related quality of life. The incidence of occupational skin diseases in western industrial countries is estimated at 0.5–1.9 cases/1,000 occupants/year [1, 2], but it is assumed that the prevalence of occupational contact dermatitis is underestimated by a factor of 30–50 [3]. Sick leave, lost productivity, dermatological treatment, vocational retraining and workers compensation cause high costs and have severe economic implications for companies and social security systems [4]. These factors define the high socioeconomic burden of occupational contact dermatitis.

Dependent on the causative agent, irritant-induced atopic dermatitis may become manifest at different localizations but most frequently presents as hand eczema. The high proportion of individuals with atopic skin disposition among patients with occupational contact dermatitis was shown in a previous study, where 38% of nearly 300 patients with severe occupational hand dermatitis suffered from irritant-induced atopic eczema [5]. Since atopic hand dermatitis has been shown to be associated with longstanding disease and long-lasting sick leave as compared to other forms of hand eczema [6, 7], preventive measures should specifically consider patients with skin atopy.

**Atopic Dermatitis Is a Risk Factor of Occupational Contact Dermatitis**

Employees in occupations involving a continuous exposure to irritants and wet work are at high risk of developing occupational irritant contact dermatitis. Among others, the hairdressing trade, health-care professions, cleaning occupations and the metal industry have an outstanding relevance as risk occupations.
Besides occupational exposure to irritants, several epidemiological studies have identified atopic dermatitis as a relevant risk factor for the development of occupational contact dermatitis, whereas the so called ‘minor atopic criteria’ according to the Erlangen atopy score of Diepgen et al. [8, 9] seem to be less relevant. However, due to heterogeneous methods applied in these studies, particularly the definitions of ‘morbidity (hand eczema/contact dermatitis), ‘sensitivity (atopy), ‘exposure’ and the statistical measure used to calculate the risk of developing occupational contact dermatitis (odds ratio versus relative risk versus prevalence ratio), the comparison and interpretation of the results is difficult. Moreover, some studies have a retrospective design and no physical examination was done. In most of the studies patch tests were not performed, therefore irritant contact dermatitis could not be distinguished clearly from allergic contact dermatitis.

As a part of the Swiss Prospective Metal Worker Eczema Study (PROMETES), Berndt et al. have followed more than 200 healthy male trainee metal workers from the beginning of their apprenticeship over a period of 2.5 years [10, 11]. Nearly 10% of the study population developed signs of hand dermatitis within 6–8 months after starting the training and the 2.5-year incidence was 23%. Mechanical work and an insufficient amount of skin recovery time increased the risk of hand eczema significantly. A history of flexural eczema was reported by 5% of the study population and could be identified as a relevant risk factor for the development of hand dermatitis within the 2.5-year study period (OR 4.2), whereas a pre-existing metal sensitivity increased the risk for early onset of hand dermatitis within 6 months (OR 6.96). Interestingly, the risk of developing hand dermatitis was not increased for the 4.5% of trainees who had an Erlangen atopy score indicating atopic skin diathesis (score of 10 and above) and single minor atopic features did not have a significant influence on the development of occupational contact dermatitis.

The Prospective Audi Cohort (PACO) study has investigated the incidence and risk factors of occupational hand dermatitis in more than 2,000 trainees of the German Audi AG and also white-collar workers were included [12, 13]. This study takes a variety of work-related factors into account and demonstrates clearly that irritant exposure at the workplace plays an important role in the development of occupational contact dermatitis. The 1- and 3-year incidences of hand eczema were 8.6 and 14.1%, respectively, and a particularly high rate of dermatitis occurred within the first 6 months. More than 90% of the cases were diagnosed as irritant contact dermatitis, while allergic contact dermatitis was assumed in about 6%. Within 3 years, blue-collar workers had a significant twofold elevated risk of developing occupational hand dermatitis compared to white-collar occupations. On the basis of the 1-year incidence, previous hand eczema or flexural eczema increased the risk of occupational hand eczema significantly (RR 6.0 and 4.8, respectively). Furthermore, private exposure to irritants was identified as a further risk factor. Nearly 1,500 subjects were followed up in the PACO II study (mean follow-up period 13.3 years from the beginning of the apprenticeship) [14]. Interestingly, the occurrence of hand eczema dropped after the
end of apprenticeship and the cumulative incidence of hand eczema was not significantly different between white and blue collar workers which points to the fact that the occupational environment becomes less important in the long run.

The POSH project (prevention of occupational skin disease in hairdressers), a large prospective population-based study, analyzed the risk associated with constitutional and exposure-related factors of occupational hand eczema in >2,000 hairdressing apprentices [15–17]. The point prevalence of hand eczema at the end of the apprenticeship was 55%. While previous flexural or hand dermatitis was associated with an increased risk of occupational contact dermatitis in the first year of training (OR 1.7) [15], no association was found at the final follow-up examination and only the rare combination of both factors showed a tendency to being a risk factor. The attributable risk for the development of hand eczema was 4% for previous flexural eczema and 13% for previous hand eczema which means that most cases of hand eczema were not caused by atopy but by exposure to wet work and irritants. While an elevated atopy score between 7 and 9.5 points was identified as a significant risk factor, the highest score category (10 points and more) was not associated with an increased risk of developing hand dermatitis. Among the clinical signs of the atopy score, only xerosis and Herthoge sign increased morbidity. Moreover, unprotected wet work of more than 2 h duration was shown to be a major risk factor for irritant hand dermatitis while glove wearing diminished the risk. Low absolute humidity and low outside temperature were identified as significant environmental factors doubling the risk of irritant contact dermatitis.

In a recent retrospective cohort study on Swedish female hairdressers using self-administered questionnaires, the attributable fraction of hand eczema from childhood eczema was 9.6% [18]. Skin atopy and hairdressing had a synergistic effect on the development of hand dermatitis. For about half of the females with hand eczema, the onset was before the age of 20 years.

Nilsson et al. [19] studied the prevalence and risk factors of occupational hand eczema in 1,613 hospital workers and found a period prevalence of 41% over 20 months. Previous atopic dermatitis was identified as a significant risk factor (OR 3.0). Occupational and domestic wet work further increased the risk.

Few investigators have identified inhalant atopic diseases as risk factors of irritant contact dermatitis. In a prospective study on the development of occupational contact dermatitis in the car manufacturing industry, >1,500 new employees were followed during the first year of employment. Besides previous hand eczema and atopic dermatitis, wool intolerance and hay fever were significantly associated with the occurrence of hand eczema [20]. Since no adjustment for confounders was performed in this study, the data have to be interpreted cautiously. In a small retrospective cohort study which included 111 nurses, Smit et al. [21] identified respiratory atopy as a risk factor for the development of hand dermatitis in nurses. In a cross-sectional study on 1,375 geriatric nurses, a history of allergic rhinitis was associated with an increased risk of hand eczema (OR 1.5), while no association was found for childhood flexural eczema [22].
Due to the difficulties to define the term ‘atopy’ and the failure of the Erlangen atopy score to predict the development of irritant contact dermatitis, several investigators aimed to identify predictors of individual susceptibility by use of cutaneous bioengineering methods. John et al. [23] followed a cohort of hairdresser apprentices for 3 years. Neither the Erlangen atopy score nor basal bioengineering parameters such as transepidermal water loss (TEWL), microcirculation (laser Doppler flow), capacitance (relative skin moisture), pH, sebum and temperature measured under standardized circumstances previous to the beginning of the apprenticeship were indicators for the development of occupational contact dermatitis during the follow-up period. Apprentices who later developed irritant contact dermatitis showed a significantly higher increase of TEWL in repetitive measurements of exposed skin areas compared to individuals who did not develop skin lesions. Furthermore, there was no significant association between any of the bioengineering parameters and the atopy score or pre-existing atopic dermatitis (hand eczema and/or flexural eczema).

In the framework of PROMETES, different biophysical tests were performed in metalwork trainees and none of the single methods were appropriate to identify individuals at high risk of developing irritant contact dermatitis [24]. A combination of irritation tests with dimethyl sulfoxide (DMSO) and NaOH allowed to identify individuals who developed contact dermatitis during their apprenticeship with a high sensitivity of >90% but a low specificity of <25%. Therefore, the results of cutaneous bioengineering methods are not predictive for the manifestation of occupational skin diseases and do not correlate with pre-existing atopic dermatitis or the Erlangen atopy score.

In conclusion, the studies presented above demonstrate that occupational irritant contact dermatitis is a complex disease with a multifactorial pathogenesis involving several constitutional and exogenous risk factors. Wet work performed for at least 2 h daily increases the risk of developing irritant contact dermatitis by at least 2-fold. Furthermore, previous atopic dermatitis (hand dermatitis and/or flexural eczema) is an independent risk factor which adds a further minimum 2-fold risk to individuals exposed to irritants and wet work. This is a multiplicate effect, which means that the risk of hand eczema in persons with atopic dermatitis who are exposed to occupational irritants is increased at least four times. No association was found with the ‘minor atopic criteria’ or the Erlangen atopy score and only few studies identified inhalant atopy being a significant risk factor. On the other hand, private exposure to irritants and environmental factors (i.e. climate) have been found to be factors increasing the risk of occupational contact dermatitis significantly. Importantly, the impact of atopic dermatitis on the development of occupational hand eczema is dependent on the intensity of occupational exposure to irritants and wet work – in professions associated with an intensive exposure to irritants, a smaller proportion of hand eczema cases will be attributed to atopic dermatitis than in professions with a low or even no exposure to irritants. According to Rystedt et al. [25], 1 out of 4 individuals with childhood atopic dermatitis working in high risk
professions do not develop hand eczema and 2 out of 3 individuals with childhood atopic dermatitis who have no occupational exposure to irritants suffer from atopic hand dermatitis.

The data suggest that the exclusion of persons with ‘atopic skin diathesis’ or atopic dermatitis from risk occupations is not effective in terms of primary prevention and that improvement of working conditions for all employees in risk occupations, individual advice and use of skin protection measures is of fundamental importance for the prophylaxis of occupational contact dermatitis. Moreover, the relevance of periodical examinations for the prevention of occupational contact dermatitis, specifically in early phases of the apprenticeship is underlined by the study results.

Pathogenesis of Occupational Contact Dermatitis in Patients with Atopic Dermatitis

More than half of all patients with active atopic dermatitis exhibit hand involvement dependent on the age [26]. Besides inhalant allergens and food allergens, numerous non-specific trigger factors have been identified for atopic dermatitis over the last decades such as irritants, climatic factors, and colonization with microorganisms like *Staphylococcus aureus* and *Malassezia furfur* [27, 28]. With regard to atopic hand eczema, occupational exposure to irritants, specifically wet work, plays an important role in the manifestation and perpetuation of skin lesions.

According to the results of epidemiologic studies, wet work has been defined as the exposure of the skin to liquid for longer than 2 h a day. Other criteria for wet work such as the use of occlusive gloves for longer than two hours daily or frequent/ intensive hand cleaning reflect clinical experience and the results of cutaneous bioengineering investigations. Besides wet work, the exposure to detergents, solvents, cooling lubricants, and oils are common occupational skin irritants, but also environmental factors as heat, cold, low humidity, UV irradiation, and mechanical factors (e.g. friction, pressure) may irritate the skin [29]. A greater reactivity to cumulative exposure with low irritant (sodium lauryl sulfate, SLS) concentrations was found in young adults as compared with elderly individuals [30].

Patients with altered epidermal barrier function are prone to developing irritant contact dermatitis and existing dermatitis, irrespective of type, enhances reactivity to irritants in other body locations [29]. This is also the case in patients with atopic dermatitis since the constitutionally deficient epidermal barrier allows the penetration of irritants through the skin, in this way facilitating the interaction with local immune cells. In contrast, individuals with isolated mucosal atopy have a similar barrier function as normal individuals [31]. This concept is supported by a number of epidemiological studies which have been discussed above.

The permeability barrier of the skin is mainly located in the lower part of the stratum corneum and consists of corneocytes and a lipid-enriched intercellular space. It is formed during the process of epidermal differentiation when the cells of the living
parts of the epidermis in the stratum granulosum change to ‘dead’ non-nucleated cells of the stratum corneum. Intracellular lipids such as cholesterol, free fatty acids, and ceramides (sphingolipids) stored in lamellar bodies are released into the intercellular spaces and form the ‘lipid envelope’ which attaches to the ‘cornified envelope’. This layer replaces the plasma membrane and is formed by structural proteins such as loricrin, involucrin, filaggrin and small proline-rich proteins which are cross-linked by the action of transglutaminases. The protein profilaggrin is encoded by the filaggrin gene and is stored in the keratohyalin granula. During the differentiation process, it is released and split into filaggrin peptides which aggregate the keratin fibers of the cytoskeleton into bundles, thereby flattening the corneocyte. The breakdown products of filaggrin together with urea, urocanic acid and lactate form the natural moisturizing factor [32, 33].

Lesional but also nonlesional skin of patients with atopic dermatitis has a deficient permeability barrier and barrier function impairment of uninvolved skin has been related to the severity of atopic dermatitis. This is reflected by an increased TEWL, a decrease in the stratum corneum hydration and an increased permeation of irritants such as SLS or polyethylene glycol [34].

Over the last decades, lipid abnormalities and an abnormal differentiation process of keratinocytes have been identified as causes of epidermal barrier defects in atopic dermatitis [32, 33]: Atopic dermatitis has been shown to be associated with a decreased level of ceramides and a reduced sphingomyelinase activity, an impaired metabolism of omega-6 unsaturated fatty acids and an elevated cholesterol and phospholipid content of the epidermis. In patients with atopic dermatitis, the skin pH of lesional and nonlesional skin is higher than in normal controls which may inhibit barrier recovery and facilitate barrier breakdown. In addition, an increased epidermal proliferation was observed which is associated with a reduced expression of the differentiation keratins K1 and K10, whereas the expression of the basal keratins 5 and 14 and the proliferation-associated keratins 6 and 16 as well as the inflammation-associated keratin 17 is increased. The expression of the cornified envelope proteins involucrin and loricrin and of filaggrin is altered. Recently, it became evident that changes in at least three groups of genes encoding structural proteins, epidermal proteases, and protease inhibitors predispose to a deficient skin barrier and increase the risk of developing atopic dermatitis, mutations of the filaggrin gene being the most relevant. Filaggrin ‘loss of function’ mutations (FLG mutations) were detected in about 20% of patients with atopic dermatitis in European countries and the risk of developing atopic dermatitis is significantly increased for carriers of these mutations – in a recent meta-analysis the odds ratio was calculated with 4.1 in case control studies and 2.1 in family studies [32, 33, see also chapter by Weidinger and Kabesch, this vol.]. Due to FLG mutations, several barrier functions are impaired, such as the formation of the cornified envelope, modelling of the corneocyte shape, moisturization through natural moisturizing factor, and lipid lamellae synthesis as well as the desquamation process (consequences of the increased pH). The described defects are
thought to be causal for the dysfunctional epidermal barrier and the susceptibility to irritant contact dermatitis in patients with atopic dermatitis.

Cutaneous contact with irritants causes a nonspecific reaction of the skin [29]: Irritants such as detergents may emulsify the skin surface lipids which are then washed off. Even more important is the increase of the skin pH, leading to an inhibition of enzymes which exhibit a low acid pH optimum and are critical for the synthesis of epidermal lipids such as β-glucocerebrosidase whereas enzymes with a neutral pH optimum such as the serine proteases KLK5 and KLK7 are activated which play a role in desquamation [32]. Besides skin barrier dysfunction, direct cellular damage and induction of pro-inflammatory mediators are mechanism which lead to the clinical signs of irritant contact dermatitis such as red, dry, scaly and fissured skin. Keratinocytes play a significant role in the elicitation and perpetuation of irritant contact dermatitis. Skin barrier damage is followed by an upregulation of major histocompatibility complex II antigens and cell adhesion molecules on keratinocytes. Furthermore, pro-inflammatory cytokines such as TNF-α, IL-1α and IL-1β are released. The chemokine CCL21 is also upregulated and attracts T lymphocytes expressing the CLA antigen to the skin. As shown by Proksch et al. [35], barrier disruption is also followed by an increase of epidermal Langerhans cell density. On the basis of these findings, it was postulated that skin barrier disruption alone leads to cytokine production and inflammation.

These processes will likely be facilitated if the skin barrier is constitutionally deficient and inflammatory cells are already increased in the skin as is the case in atopic dermatitis. Indeed, after irritation with SLS, the TEWL was significantly increased in patients with atopic dermatitis as compared to normal controls [36].

As FLG polymorphisms affect the skin barrier, they may also lead to an increase in the susceptibility to irritants and allergens and to the development of irritant contact and allergic contact dermatitis.

Recently, loss of function mutations in the filaggrin gene have been found to be associated with an increased susceptibility to chronic irritant contact dermatitis [37]. In a recent study, an association between FLG mutations and combined irritant and allergic contact dermatitis was detected [38]; however, the methodology used is disputable.

**Role of Allergic Contact Dermatitis in Atopic Dermatitis**

Irritant allergic contact dermatitis is a risk factor for the development of allergic contact sensitization and the impaired barrier function in lesional skin as well as the cutaneous inflammatory milieu has been shown to favor the penetration of contact allergens and alleviate type IV sensitization [39].

The role of atopic dermatitis as a risk factor for the occurrence of type IV sensitization and contact allergy is still a matter of debate and it has been speculated that the