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Hand dermatitis – differential diagnoses, diagnostics, and treatment options

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Summary

The pathogenesis of hand dermatitis is multifactorial, and includes factors such as genetic predisposition and exposure. A high incidence rate is associated with female gender, contact allergy, atopic dermatitis, and wet work. The most important risk factors for the persistence of hand dermatitis include its extent, contact allergic or atopic etiology, childhood dermatitis, and early onset (before the age of 20). The cost of illness of hand dermatitis corresponds to this seen in moderate to severe psoriasis. The diagnostic workup of hand dermatitis and its differential diagnoses requires a detailed assessment of occupational and recreational exposure. In case of possible work-related triggers, early notification of the accident insurer should be sought (via the dermatologist's report). Exposure to a contact allergen is a contributing factor in one-half of all cases of hand dermatitis. It is therefore imperative that all patients with hand dermatitis persisting for more than three months undergo patch testing. Successful and sustainable treatment of hand dermatitis starts with the proper identification and elimination of individual triggers, including the substitution of identified contact allergens and irritants, as well as optimizing preventive measures. Graded therapy taking the clinical severity into account is essential. Validated instruments may be used to monitor therapeutic efficacy.

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Introduction

The pathogenesis of hand dermatitis is multifactorial. Both genetic as well as environmental factors play a role in the development of hand dermatitis. Despite the small body surface area affected (maximum of 4 % according to the rule of nines [1]), hand dermatitis is marked by great economic and sociomedical significance, impacting all aspects of life [2]. Hand dermatitis represents the majority of occupational skin diseases. The present article summarizes current knowledge with respect to this pathogenetically and morphologically heterogeneous entity and its differential diagnoses, and provides practical information on diagnosis and treatment.

Epidemiology

Incidence and prevalence of hand dermatitis

Hand dermatitis is common. Based on an analysis of 36 studies (1964–2007) on the prevalence of hand dermatitis, the average point prevalence in the general

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population is 4 %, with a one-year prevalence of 10 % and a lifetime prevalence of 15 % [3].

Analysis of seven studies revealed a mean incidence of 5.5 cases/1,000 person-years (9.6 in women, 4.0 in men) [3].

The only population-based study on the prevalence of hand dermatitis conducted in Germany to date (random sample $n = 2,500$, response rate 72 %, age range 18–70 years) found a point prevalence of 3.4 % (95 % confidence interval [CI] 2.6–4.4 %) and a one-year prevalence of 6.4 % (95 % CI 5.3–7.7 %) in the Heidelberg area [4].

Risk factors

Atopic dermatitis, gender, age, contact allergy, and wet work

Numerous studies, recently summarized in a review article, have investigated the incidence and risk factors of hand dermatitis: a high incidence is associated with female gender, contact allergies, atopic dermatitis, and wet work [3]. Atopic dermatitis has been identified as the most important risk factor for hand dermatitis [3]. In the general population, hand dermatitis is associated with female gender, childhood dermatitis, and young age, whereas there is weaker evidence for wet work, occupation, contact allergy, and tobacco use [3]. For certain occupational groups, occupational exposure is a key risk factor [3].

The most important risk factors for the persistence of hand dermatitis include marked extent, allergic or atopic origin, childhood dermatitis, and disease onset before the age of 20 [3].

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Other genetic factors

Apart from atopic (skin) diathesis, other genetic risk factors for hand dermatitis have been suggested [3, 5–12]. Associated with etiologically different types of hand dermatitis, various single nucleotide polymorphisms (SNP), deletions, and loss-of-function mutations at various gene sites have been described (Table 1).

There is a particularly strong association with loss-of-function mutations in the filaggrin gene (*FLG*) [6–8]. Filaggrin plays a central role in the terminal differentiation of corneocytes, contributes to the mechanical strength of the skin barrier, and is a starting point for the production of the natural moisturizing factor (NMF). While homozygous or compound heterozygous mutations with complete loss of filaggrin have been identified as the cause of ichthyosis vulgaris, heterozygous mutation carriers already exhibit structural alterations of the skin (such as reduced stratum corneum cohesion, abnormal lamellar bilayer organization, functional changes, elevated pH in the stratum corneum, reduced hydration). Attributed to increased allergen penetration, carriers of the *FLG* mutation have an increased risk for atopic dermatitis, bronchial asthma, allergic rhinitis, and food allergies [6–8]. The increased prevalence of type IV sensitizations to nickel and early manifestations of clinically apparent nickel allergy in *FLG* mutation carriers is ascribed to a lower number of nickel chelate-forming histidine residues (principal metabolites of filaggrin), thus leading to increased nickel penetration. Mutations of the *FLG* gene are associated with an early onset and persistence of hand dermatitis, an unfavorable disease course, and a significantly more frequent need to discontinue the occupational activity [6–8].

Twin studies have shown that 41 % of the risk of developing hand dermatitis can be ascribed to genetic factors (95 % CI 28–53) and 59 % to environmental factors (95 % CI 47–72) [5].

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Table 1 Besides atopic skin diathesis, other genetic risk factors for hand dermatitis have been suggested.

Gene	Genetic change	Function of the gene product	Association	References (selection)
<i>FLG</i> gene	Loss-of-function mutations R501X, R2447X, S3247X, and 2282del4	Filaggrin aggregates keratin filaments in the stratum corneum, and contributes to the mechanical strength of the skin barrier. Among other things, it is the starting point for the production of natural moisturizing factor.	Heterozygous status for <i>FLG</i> loss-of-function mutations in combination with atopy has an unfavorable effect on the disease course of hand dermatitis (significantly more frequent need to discontinue the occupational activity). Phenotype common: palmar hyperlinearity, xerosis, and hyperkeratosis of the dorsum of the hands.	[6–8]
<i>TNF-α</i> gene	Single nucleotide polymorphism (SNP); <i>TNF</i> alpha-238 (rs361525)-A allele; <i>TNF</i> α -308 (rs1800629)-A allele	As a result of irritant keratinocyte damage and IL-1 release, the proinflammatory cytokine <i>TNF</i> α is released from IL-1-stimulated keratinocytes and macrophages, and plays a key role in the development of irritant contact dermatitis.	<i>TNF</i> α -238A allele: protective effect against irritant hand dermatitis. <i>TNF</i> α -308A allele: risk factor for irritant hand dermatitis.	[9]
Late-cornified envelope gene <i>LCE3B</i> and <i>LCE3C</i>	Deletion: <i>LCE3C</i> _ <i>LCE3Bdel</i>	Cornified envelope proteins are involved in the physical epidermal barrier that protects against water loss and penetration of exogenous noxious agents.	Significant association of homozygous and heterozygous status with chronic allergic contact hand dermatitis	[10]
<i>SPINK5</i> gene	Single nucleotide polymorphism (SNP); <i>SPINK5</i> (rs6892205)-G allele	Serine protease inhibitor Kazal type 5 inhibits exogenous serine proteases, and is involved in normal keratinocyte differentiation.	Significant association with non-atopic hand dermatitis	[11]
<i>IL1A</i> gene	Single nucleotide polymorphism (SNP); <i>IL1A</i> -889 (rs1800587)-T allele	Proinflammatory cytokine. SNP is localized in the promoter region. Compared to the wild type, <i>IL1A</i> C/T genotype and T/T genotype are associated with reduced cytokine IL-1 α in the stratum corneum.	Significant protective effects with regard to irritant hand dermatitis compared to the C/C wild type	[12]

The frequency of hand dermatitis flare-ups in particular is predominantly determined by environmental factors (31 % [95 % CI 18–43] genetic factors and 69 % [95 % CI 57–82] environmental factors), emphasizing the usefulness of exposure analysis and preventive measures in the occupational and recreational realm [5].

When differentiating genetic from occupational factors in the context of an expert medical (dermatologic) assessment of hand dermatitis, one has to keep in mind that German law protects the insurant's health status present at the commencement of the harmful activity [13–15]. In Germany, according to Social Code (SGB) Volume VII, it is the responsibility of the statutory accident insurers (1.) to prevent work-related accidents and occupational diseases as well as work-related health hazards with all suitable means, and (2.), following work-related accidents or the onset of occupational diseases, to restore health and

German law protects the insurant's health status present at the commencement of the harmful activity.

productivity of insured individuals with all suitable means and to compensate them or their surviving dependents through financial benefits. By law, all employed individuals are insured.

This protection includes all genetic predispositions and constitutional impairments. Even if – apart from other essential partial causes – the occupational exposure is but *one* essential partial cause in triggering or aggravating the patient's hand dermatitis, the disease has to be recognized as occupational disease, if the other conditions according to the appendix of the Occupational Disease Regulation [BKV]) (severity and/or repeated recurrence, objective necessity to abandon the occupational activity) are met [14].

Nickel

REACH (Annex XVII) defines threshold values for nickel release from jewelry and other products marked by direct and prolonged skin contact.

Although nickel allergy has been described as a risk factor for hand dermatitis, the association between nickel allergy and hand dermatitis appears to have diminished in recent years. This may likely be attributed to European legislation, especially the European regulation for the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH [Annex XVII]: www.reach-compliance.eu/english/REACH-ME/engine/sources/reach-annexes/launch-annex17.html), resulting in decreased nickel exposure [3]. REACH (Annex XVII) defines threshold values for nickel release from jewelry and other products marked by direct and prolonged skin contact. Articles exceeding these threshold values must not be sold in Germany.

Tobacco use

Hand dermatitis may be associated with tobacco smoking, however, current data is not unequivocal. In a population-based study of a sample of 7,931 adults aged between 18 and 69 years (response rate: 44 %) in Copenhagen, Denmark, the prevalence of hand dermatitis was higher in former smokers (odds ratio [OR]: 1.13; 95 % CI: 0.90–1.40) as well as in light smokers (< 15 g tobacco/day) (OR: 1.51; 95 % CI: 1.14–2.02) and heavy smokers (> 15 g tobacco/day) (OR: 1.38; 95 % CI: 0.99–1.92) than in never-smokers [16].

In a systematic review of publications from 1980–2013 with a meta-analysis of tobacco smoking as risk factor for hand dermatitis, three out of 43 studies met the inclusion criteria previously defined, including one cohort study and two cross-sectional studies. In contrast to the results of one of these studies, analysis of pooled data failed to show a significant association between smoking and hand dermatitis. Given the heterogeneity of these three studies, the authors conclude that an effect of tobacco smoking on the disease course of hand dermatitis cannot be excluded based on available data [17].

An attempt at smoking cessation with clinical follow-up of hand dermatitis may be useful.

In another recent review of 20 published articles on the correlation between tobacco smoking and hand dermatitis, three of seven articles with an occupational background and four of eight population-based studies revealed a significantly positive association between tobacco smoking and the prevalence of hand dermatitis. Two of five studies on disease severity showed a positive association between smoking and the severity of hand dermatitis [18], while none of the studies demonstrated a protective effect of smoking [18]. Based on current data, the influence of tobacco use on the development and maintenance of hand dermatitis cannot be conclusively assessed at present. Considering all factors that may contribute to maintaining hand dermatitis on a case-by-case basis, an attempt at smoking cessation with clinical follow-up of hand dermatitis may be useful. An association with alcohol consumption has not been observed [3, 16].

Table 2 R and S statements (risk and safety statements) characterize specific hazards of hazardous chemicals and compounds. R statements indicating skin-damaging effects are listed.

R statements	Meaning
R 34	Causes chemical burns
R 35	Causes severe chemical burns
R 38	Irritates the skin
R 43	Sensitization possible due to skin contact
R 66	Repeated contact may cause dry or cracked skin

Risk-associated occupations and occupational substances harmful to the skin

Risk-associated occupations

In a study of consecutive hand dermatitis patients in ten European health centers, more than one-half of patients revealed an occupational causation (52 %) [19]. Occupations associated with the highest risk (≥ 7 new disease cases per 10,000 workers and year) for acquiring an occupational dermatosis (presenting as hand dermatitis in over 90 % of cases) included hairdressers, bakers, florists, pastry chefs, tilers, welders, solderers, dental technicians, mechanical engineers, metal surface workers, and healthcare employees [20].

High-risk occupations for the development of hand dermatitis (3–7 new disease cases per 10,000 workers and year) include: cooks, painters, and varnishers, metal workers, mechanics, assembly workers, construction and cement workers, individuals involved in leather and fur processing, housekeepers, food service staff, and cleaning staff [20].

Substances harmful to the skin

Substances and compounds (mixtures of substances) that may have harmful effects on the skin following contact (for example, due to a corrosive, irritant and/or sensitizing effects) are considered hazardous to the skin [21]. Risk (R) statements on the safety data sheets indicate corresponding characteristics (Table 2). Substances or compounds that do not meet the criteria for R statements, but that may still damage the skin due to prolonged or repeated exposure, are also considered hazardous to the skin (for example, water when working in a wet environment) [21]. According to the technical rules for hazardous substances (TRGS 401), working conditions that lead to skin hazard or increase the effect of substances include [21]:

- ▶ Heavy contamination or mechanical stress (microlesions due to sharp-edged particles) that may pre-damage the skin,
- ▶ Exposure to other substances that have a harmful effect on the skin but are not classified as such according to criteria of the Hazardous Substances Ordinance (GefStoffV; www.gesetze-im-internet.de/gefstoffv_2010/) (such as detergent solutions, disinfectants, cooling lubricants, and some degreasing solvents), and
- ▶ Acid or alkaline environment that does not result in a classification but can lead to irritant skin changes after prolonged contact.

Wet work

Workplaces requiring wet work are associated with an increased risk for hand dermatitis.

Workplaces requiring wet work are associated with an increased risk for hand dermatitis. Criteria for wet work [21] are met when workers engage in activities that include

- ▶ Regularly working with their hands in a wet environment for more than two hours per day or
- ▶ Having to clean their hands often or especially thoroughly or
- ▶ Wearing protective gloves with an occlusive effect (heat and moisture buildup) for a corresponding period.

The liquid-proof effect of protective gloves prevents the evaporation of sweat, hence resulting in skin maceration with continued glove use and diminished barrier function. Pre-damaging the skin in this manner facilitates the penetration of irritants, potentially allergenic (sensitizing) substances, or infectious agents.

Hand dermatitis as occupational disease

If preventive measures fail altogether, occupationally induced or aggravated hand dermatitis may lead to an occupational disease (BK no. 5101).

If preventive measures fail altogether, occupationally induced or aggravated hand dermatitis may lead to an occupational disease (BK 5101), accounting for the vast majority of BK 5101 cases. Occupational dermatoses (according to BK 5101 of the Occupational Disease Regulation [BKV]) are the most frequent reason for occupational disease notification (about one-third of all cases), and constitute more than half of all cases with confirmed occupational causation [22]. In 2013, out of a total of 71,579 occupational disease notifications, 24,033 were suspected BK 5101 cases. Occupational causation was confirmed in 36,202 of all suspected BK cases, 20,643 of which were skin diseases [22].

This large number illustrates why there is a precursor procedure – known as the “dermatologist’s procedure” – prior to occupational disease notification, which is aimed at preventing the development of an occupational disease and exclusively applies to BK 5101. It is initiated by filing a dermatologist’s report [23].

Monetary and non-monetary effects of hand dermatitis

According to a 2010 publication, 70 % of patients with hand dermatitis seek medical attention; > 20 % experience inability to work for more than 7 days; and 10 % end up having to change their place of work [3]. In a recently published cost-of-illness study, annual costs for chronic occupational hand dermatitis were estimated at about EUR 9,000, 30 % of which were caused by medical care (direct costs) and 70 % by indirect costs (loss of productivity). The overall costs are therefore at the same level as those of moderate to severe psoriasis [24].

Another study found that average annual treatment costs for statutory health insurance patients with hand dermatitis that interfered with their work were EUR 3,164. They amounted to EUR 3,309 for individuals with occupational hand dermatitis insured by occupational insurance associations. Both were thus more than twice as high as treatment costs for non-working statutory health insurance patients (EUR 1,271) or working statutory health insurance patients without chronic hand dermatitis (EUR 1,442) [25]. The authors concluded that particularly high costs arise when the patient’s ability to work is impaired by chronic hand dermatitis, which is why preventive measures are necessary.

Most individuals affected by hand dermatitis experience negative psychosocial effects (e.g., sleep disturbances, mood swings, interference with everyday activities and hobbies) and impairment of quality of life [2, 3, 24, 26].

Individuals affected by hand dermatitis experience negative psychosocial effects and impairment of quality of life.

Etiology

The majority of hand dermatitis cases is multifactorial. It is necessary to identify and eliminate all causative factors in order to achieve sustained improvement and resolution.

Only rarely triggered by a single cause, the majority of hand dermatitis cases is multifactorial [27–29] (Table 3). It is therefore necessary to identify *all* causative factors, and establish corresponding avoidance measures in order to achieve sustained improvement and resolution.

A recently published study conducted at a specialized occupational dermatology clinic revealed various etiological factors responsible for triggering and maintaining hand dermatitis: in 82 % of patients, a cumulative irritant (subtoxic) partial cause was found; in 49 %, a clinically relevant contact allergy (triggered by haptens); in 45 %, an atopic component; and in 13 %, protein contact dermatitis (PCD) [27]. While 66 % of patients had multiple causative factors (partial causes), 33 % only had a single etiological factor. Protein contact dermatitis, which presents on the hands with or without wheals or vesicles 30 minutes after protein

Table 3 Pathogenetic factors of hand dermatitis and differential diagnoses.

Causes of hand dermatitis
▶ Genetic factors (atopic skin diathesis or other genetic factors (Table 1))
▶ Irritant skin exposure (wet work, contact with chemicals, occlusion effects of gloves, mechanical stress)
▶ Contact allergens (occupational or recreational)
▶ Proteins (especially in the food-processing industry)
▶ Idiopathic (for example, idiopathic hyperkeratotic-rhagadiform hand dermatitis)
Differential diagnoses (especially in the absence of a response to graded anti-dermatitis treatment)
▶ <i>Common:</i> Mycosis (tinea manuum)
▶ <i>Common:</i> (eczematized) psoriasis, inverse psoriasis, palmoplantar pustular psoriasis (PPP)
▶ (eczematized) lichen planus
▶ Artifacts
▶ Chemotherapy-induced hand-foot syndrome (especially with arabinosyl cytosine (Ara-C), pegylated liposomal doxorubicin, capecitabine, 5-FU, and on targeted therapy with sorafenib and sunitinib)
▶ Mycid
▶ Hand-foot-and-mouth disease
▶ Scabies
▶ Mycobacteriosis
▶ Mycosis fungoides
▶ Bowen's disease
▶ Porphyria cutanea tarda
▶ Bullous pemphigoid
▶ Paraneoplastic acrokeratosis (Bazex syndrome)
▶ Malignant acanthosis nigricans (acral type)
▶ Hereditary palmoplantar keratosis

contact, is triggered by high-molecular-weight proteins [30]. In the vast majority of cases, exposure is occupational, for example, in the food-processing industry [30–32]. Unlike the general population, where the diagnosis of PCD is rare, it is a common disorder in individuals with hand dermatitis working in the food-processing industry (up to 21 %) [31, 32].

The characteristic eczematous appearance may provide a clue as to the leading etiological factor (Figure 1a–d). A recently developed diagnostic algorithm includes the most common etiological and morphological subtypes, and also reflects their various prevalences [33]: Using four criteria (irritation, contact allergy, atopy, foot involvement) and clinical morphology (hyperkeratotic-rhagadiform, dyshidrotic, or a mixture of both) as a basis for a binary decision-making model (yes/no), this algorithm distinguishes eight subtypes of chronic hand dermatitis.

Differential diagnoses

Table 3 summarizes frequent and rare differential diagnoses of hand dermatitis. Regarding their pathogenesis and treatment, the reader is referred to the relevant



Figure 1 Initial irritant hand dermatitis (a). Irritant hyperkeratotic hand dermatitis (b). Allergic contact dermatitis caused by type IV allergy to thiurams and carbamates (contained in the protective gloves used at the workplace) (c). Unilateral nummular hand dermatitis (idiopathic) (d).

In case of recalcitrant hand dermatitis on consistently conducted graded therapy, reconsidering the diagnosis is imperative.

The presence of psoriasis does not protect from acquiring contact allergy.

literature [34, 35]. Especially in case of recalcitrant hand dermatitis on consistently conducted graded therapy, reconsidering the diagnosis is imperative (Figure 2a–d).

In this context, whole-body inspection may yield crucial findings. At first presentation and in case of therapy-resistance, examination of the entire skin is therefore useful in addition to symptom-related examination of the hands.

The presence of psoriasis does not protect from acquiring contact allergy. On the hands, both diseases may overlap [36, 37]. In psoriasis patients, a delayed onset of positive patch test reactions has been observed (only after 7 days). Thus, besides usual readings after 48 and 72 hours, another patch test reading after 7 days appears necessary in this patient group [37].

Diagnosis

Patient history and exposure assessment

The diagnosis and differential diagnosis of hand dermatitis requires a detailed medical history of

- ▶ Existing occupational and recreational exposures,
 - ▶ Personal and family history of allergies and skin diseases (especially atopic disorders [38], psoriasis),
 - ▶ The duration and temporal course of hand dermatitis (in particular considering periods off work),
 - ▶ Underlying diseases and drug intake, and
 - ▶ Nicotine use.
- If contact sensitization has been identified, it is necessary – in the context of relevance assessment – to examine the presence of contact allergens in both the occupational and recreational realm [39].

If contact sensitization has been identified, it is necessary to examine the presence of contact allergens in both the occupational and recreational realm.



Figure 2 Histologically confirmed palmar psoriasis (a). Histologically confirmed mycosis fungoides (b). Unilateral trichophyton infection in a patient with previous hand dermatitis (c). Unilateral artifact in a patient with recognized occupational skin disease BK no. 5101 (d).

- ▶ In order to quantify wet work [21] as a risk factor for the development of hand dermatitis, detailed information is required regarding the duration of
 - Direct skin contact with water (> 2 hours/day?),
 - Wearing liquid-proof gloves (> 2 hours/day?),
 - Frequency and intensity of hand cleaning (hand washing frequency > 10 times/day, use of abrasive hand wash pastes?)
- ▶ It is also necessary to gather whether suitable occupational skin products [40, 41] and protective gloves (suitable for work requirements) [42, 43] are available, and also whether these are used.

Skin inspection

Besides examining the hands, whole-body skin inspection (including the feet) is useful in order to rule out differential diagnoses.

Atopy screening

To evaluate an existing atopic skin diathesis, it may be helpful to look for the presence of atopic stigmata and to record the Erlangen atopy score [38]. Prick testing or *in vitro* measurement of specific IgE antibodies against frequent airborne allergens as well as total IgE levels may be additionally useful to detect an atopic diathesis.

Patch testing

Patch testing with commercial test series and the patient's own materials

Allergy testing is required in all cases persisting for more than three months.

Contact with a contact allergen is co-responsible for triggering and maintaining one-half of all hand dermatitis cases [27–29]. Allergy testing is therefore required in all cases persisting for more than three months [44].

The following type IV sensitizations to standard-series contact allergens are associated with at least a twofold risk for occupational allergic contact dermatitis: thiuram mix (rubber accelerators), epoxy resin (plastic resin), mercaptobenzothiazole and derivatives (rubber accelerators), IPPD (rubber aging protection in black rubber [for example, car tires]), and biocides (MCI/MI, MDBGN, formaldehyde) [45].

Mere standard-series patch testing is insufficient in occupational hand dermatitis.

Mere standard-series patch testing is insufficient in those cases of hand dermatitis where there is a possibility of occupational causation or aggravation. Exposure-adapted supplementation of occupational test series is necessary in order to conclusively confirm or exclude the diagnosis of contact allergy. Test recommendations taking special occupational exposures into account have been published [46]. Besides testing with specific occupational test series, testing with the patient's own substances may be necessary to close the diagnostic gap [47].

The test concentration of a contact allergen in the finished product is not to exceed the recommended test concentration for that particular allergen [48, 49]. Patch test results may be false-negative if too little allergen is released onto the skin [48]. Synthetic and natural rubber gloves are a relevant example as the rubber accelerators they contain are often an allergen source for allergic contact dermatitis (Figure 1c). When patch testing with samples of nitrile gloves and nitrile-soaked cotton gloves, 70 % ethanol as test vehicle is superior to water in the detection of a type IV sensitization to rubber accelerators [50]. In case of a negative patch test result with the patient's own gloves but a positive test reaction to rubber accelerators used in the production of the patient's gloves (according to the manufacturer), avoidance of these gloves is still recommended; instead, gloves should be used that definitely do not contain any of these substances (according to the manufacturer) [51]. It is necessary to individually assess the relevance of confirmed contact sensitizations, identify occupational and recreational sources of exposure, and inform the patient about required avoidance measures [39].

Patch and prick testing with protein-containing native materials (for example, foods)

The diagnosis of protein contact dermatitis is in most cases based on positive prick test results.

In order to diagnose protein contact dermatitis, history-based prick and patch testing with protein-containing native material the affected individual has manual contact with is required. In addition, specific IgE measurement is necessary. Patch test results are usually negative as allergen penetration at the test site is too low. There is often prior atopic or irritant damage to the hands, the main site of manifestation, which facilitates protein penetration. Despite the eczematous appearance, diagnosis of PCD is in most cases based on positive immediate-type prick test reactions, positive *in vitro* IgE detection, and a positive history of (re-) exposure [30–32].

Standardization and optimization of diagnostic methods to detect protein contact dermatitis are the subject of ongoing studies [31].

Nickel detection test (dimethylglyoxime test), cobalt detection test (disodium-1-nitroso-2-naphthol-3,6-disulfonate test)

Although nickel has been described as a risk factor for hand dermatitis, among all patients with hand dermatitis and confirmed type IV sensitization to nickel treated within the Information Network of Dermatology Departments (IVDK) between 2009 and 20113, tools were assumed to be a possible source of exposure in only 0.7 % of cases [52]. However, the rare nickel release rate of only 5 % of 200 hand-held work tools observed in Denmark [53] cannot be applied to Germany. A recent study performed in Germany on a similar range of 600 new tools using the dimethylglyoxime test recently showed nickel release from 32.5 % of examined tools. In 22.9 % of cases, nickel was released from the handle region or the entire tool [52]; in 9.7 %, only from the functional part, which less in contact with the hands. These results are in keeping with the initial nickel release study from Sweden, which found nickel release in 27 % of 565 investigated tools [54]. Tools and keys are not subject to the EU nickel directive or REACH regulation (REACH [Annex XVII], see above). Keys for door locks often release nickel as well [55].

In patients with chronic hand dermatitis and nickel sensitization, it is reasonable to check for nickel release from tools and keys – if there is such exposure – using the dimethylglyoxime test.

In patients with chronic hand dermatitis and nickel sensitization, it is reasonable to check for these sources of exposure, of which the patient is usually unaware, using the dimethylglyoxime test.

Test kits for the detection of nickel (with dimethylglyoxime) and cobalt (with disodium-1-nitroso-2-naphthol-3,6-disulfonate) release, indicated by a color reaction, are commercially available and easy to use. Cobalt release from keys and tools is only rarely detectable [52, 55].

Further diagnostic workup

Under special conditions and with standardization of room temperature and humidity, diminished skin resilience may be demonstrated – despite the absence of clinical symptoms – using the differential irritation test, which is the measurement of transepidermal water loss after standardized parallel exposure to normal saline and 0.5 M NaOH solution on the ventral aspect of the forearm and the back of the hand [56]. With respect to recognized occupational diseases, this may be important in the assessment of the reduction in earning capacity. Measurement of transepidermal water loss (TEWL) and many other methods aimed at examining physiological parameters of the skin are characterized by large individual variations, the absence of robust normal values, and partly by the dependence on climatic factors, which is why they do not play a role in routine diagnostics [57]. Skin irritability and skin function tests geared towards detecting irritant skin damage but not suitable for routine diagnostics (according to scientific assessment) have been summarized in a “negative list” [57].

At the onset of the disease, mycological workup to rule out tinea manuum is required.

At the onset of the disease, mycological workup to rule out tinea manuum is required. If there is evidence for one of the differential diagnoses (Table 3), histological examination of a biopsy may help confirm the diagnosis.

Treatment

Testing of substitute material and optimization of suitable preventive measures

Treatment of hand dermatitis starts with the identification and elimination of individual triggers. This involves testing of substitutes of identified contact allergens

Different glove materials have distinct penetration times for different chemicals.

If there is a possibility that occupational factors play a part in triggering or maintaining hand dermatitis, the accident insurer in charge shall be informed early on by means of a dermatologist's report, in order to initiate preventive measures.

Dermatological treatment of hand dermatitis shall be graded and guided by the severity and clinical appearance.

and irritants, as well as optimization of suitable preventive measures. Apart from using (preferably fragrance-free) skin products (skin protection, moisturizing, and cleansing agents) [40, 41], this also includes suitable protective gloves.

Provision of suitable gloves must take individual work materials and work requirements into account [42, 43]. Different glove materials have distinct penetration times for different chemicals [43]. Penetration time is defined as the interval between first contact of the glove material with a chemical until its leakage on the inside of the glove. Thus, the penetration time is the time within which a glove provides protection from skin contact with the chemical in question. For example, medical examination gloves are not suitable for handling surface disinfectants [58]. Information on suitable glove materials and the thickness of various layers of material can be obtained from the safety data sheet of the chemical.

If there is a possibility that occupational factors play a part in triggering or maintaining hand dermatitis, the respective accident insurer in charge shall be informed early on by means of a dermatologist's report, in order to initiate preventive measures [23].

It has been shown that specific preventive services provided by accident insurers at the level of secondary individual prevention (SIP; ambulatory training seminars) and tertiary individual prevention (TIP; modified inpatient/outpatient treatment methods) enable the majority of patients to remain in their jobs, while simultaneously achieving marked clinical improvement and an increase in their quality of life [59]. This also holds true for patients with advanced occupational diseases refractory to outpatient treatment [59].

Topical dermatological treatments

Dermatological treatment shall be guided by the severity and appearance of hand dermatitis [27, 40] (Table 4). The general principles of graded dermatitis therapy apply [34].

Combined with corticosteroid-free basic therapy, topical corticosteroids of different strength classes (I–IV) [60] are the treatment of first choice in graded therapy [40, 44]. Based on their ratio of desired and adverse effects, topical corticosteroids with a high therapeutic index ($\text{TIX} = 2$) are preferable [40], and were used in 45 % of 9,784 hand dermatitis patients treated by office-based dermatologists, according to an analysis published in 2012 [61]. Topical corticosteroids have antiinflammatory effects but impair regeneration of the stratum corneum, which is essential for intact skin barrier function [62]. Short-term use of a potent corticosteroid is considered more beneficial than protracted use of too weak a corticosteroid [40].

Beneficial effects on prolonging recurrence-free intervals have been demonstrated (randomized studies) for intermittent use (Sunday/Tuesday/Thursday) of mometasone furoate cream in hand dermatitis as well as proactive use (2–4 times per week, depending on the study) of topical agents containing tacrolimus, fluticasone propionate, and methylprednisolone aceponate in the prophylaxis of atopic dermatitis recurrence [63, 64].

The use of calcineurin inhibitors (pimecrolimus, tacrolimus) is possible within the approved indication of atopic hand dermatitis. In licensing studies, 0.1 % tacrolimus ointment was more effective and 1 % pimecrolimus cream was less effective than the comparator class I corticosteroids (used on the face) and class II corticosteroids (on the trunk) [65, 66].

Depending on the characteristics of hand dermatitis, other substances are also used: antiseptic agents (clioquinol, chlorhexidine, triclosan, polyhexanide, silver sulfadiazine) in case of superinfection, astringent tanning agents in case of vesicular lesions, keratolytic and antiproliferative substances (including salicylic acid,

Table 4 Graded treatment options according to the severity of hand dermatitis, modified from [40, 44].

Basic therapy (dry skin of the hands)	▶ Reduction/avoidance of causative factors ▶ Use of skin-protective measures ▶ Skin hydration
Treatment level I (mild hand dermatitis)	<i>In addition to basic therapy:</i> ▶ Topical corticosteroids (potency class 1 and 2 according to Niedner) ▶ Topical calcineurin inhibitors (approved only for hand dermatitis of atopic origin) ▶ Antipruritic agents ▶ Antiseptic agents ▶ Iontophoresis
Treatment level II (moderate and severe hand dermatitis)	<i>In addition to level I measures:</i> ▶ Topical corticosteroids (potency class 3 and 4) ▶ UV therapy ▶ Systemic alitretinoin (off-label for moderate hand dermatitis)
Treatment level III (chronic recurrent and persistent hand dermatitis)	<i>In addition to level I and II measures:</i> Systemic immunomodulatory therapy ▶ Alitretinoin ▶ Cyclosporine (licensed only for hand dermatitis of atopic origin) ▶ Systemic corticosteroids (short-term for acute flare-ups) ▶ If necessary, other systemic therapeutic agents (if approved first- and second-line treatments are insufficiently effective or contraindicated)

urea, dithranol) in case of hyperkeratosis, as well as coal tar, polidocanol, and ichthyol as antipruritic and antiinflammatory agents. Besides the known antipruritic, antiproliferative, and antiinflammatory effects, it has recently been shown that coal tar increases filaggrin expression in skin equivalent models of atopic dermatitis [67]. Tap water iontophoresis is another level I treatment option for vesicular hand dermatitis in conjunction with hyperhidrosis [40, 68].

UV light therapy

UV therapy is useful as stage II treatment in adults.

If the disease takes a chronic and recurrent course using the treatment of first choice, UV therapy (UVB, cream or bath PUVA) is useful as level II treatment in adults, depending on skin type.

In most studies, PUVA was superior to UVB broadband therapy [68]. In a comparison using UVB (311 nm) therapy on the one side and topical PUVA therapy with 0.1 % 8-MOP cream on the other, there was marked improvement of hand dermatitis in both treatment arms, without a statistically significant difference [68].

Systemic dermatological therapy

Should consistently conducted graded level I and II topical therapy, including preventive measures for occupational and recreational skin protection, not lead to resolution or improvement of hand dermatitis, reconsidering the diagnosis and differential diagnoses is reasonable.

If the diagnosis of chronic hand dermatitis refractory to exhaustive graded topical treatment applied for weeks is confirmed (Table 4), there is little benefit to be expected from protracted use of this treatment level. In this case, early therapy adjustment and increase – in accordance with guidelines – is required, if necessary on an (intensified) inpatient basis and/or using systemic therapy.

Alitretinoin (9-*cis*-retinoic acid; 9-*cis*-RA) is licensed in adults for the treatment of severe chronic hand dermatitis unresponsive to treatment with potent topical corticosteroids.

As a vitamin A derivative, alitretinoin is teratogenic.

Alitretinoin

Since 2008, alitretinoin (9-*cis*-retinoic acid; 9-*cis*-RA) has been licensed in adults for the treatment of with severe chronic hand dermatitis unresponsive to treatment with potent topical corticosteroids (second-line therapy).

While clinical licensing studies showed positive effects on all morphological subtypes, patients with predominantly hyperkeratotic forms of hand dermatitis responded best [69]. The standard dose is 30 mg po every day. Depending on the response, a treatment cycle with alitretinoin usually lasts 12 to 24 weeks. In case of a relapse, patients may benefit from another treatment cycle. Should management of side effects be insufficient, the dose may be tentatively decreased to 10 mg po every day. As regards contraindications and special warnings and precautions, please refer to the prescribing summary of product characteristics [Toctino SmPC; date of information: August 2014/1]. As a vitamin A derivative, alitretinoin is teratogenic. Women of child-bearing age must therefore follow a pregnancy prevention program with reliable contraception for a month prior to the start of treatment, during treatment, and up to one month after treatment discontinuation [69].

The mechanism of action of alitretinoin includes several pathophysiological points of action in the differentiation, proliferation, and migration of T and B lymphocytes [70]. Decreased T cell-dependent interleukin-17 production and a reduction of plasmablasts and immunoglobulins IgE, IgA, and IgM have been found in the serum of hand dermatitis patients on systemic therapy [70], indicating that 9-*cis*-RA has a disease-modifying effect.

A recent analysis of drugs prescribed by office-based dermatologists showed that, of 9,784 hand dermatitis patients treated, 1.2 % received alitretinoin and 0.2 % were given cyclosporine (CsA) [61]. By contrast, the selected CARPE hand dermatitis registry, whose inclusion criteria only allow chronic and refractory cases, revealed that 19.7 % of patients were treated with alitretinoin and 1.9 % received cyclosporine [26].

Other systemic therapies

According to evidence-based medicine (EBM) criteria, there is a moderate evidence level for cyclosporine, which is licensed exclusively for the treatment of dermatitis of atopic origin, and a low evidence level for acitretin with respect to beneficial effects in the treatment of hand dermatitis. As a vitamin A derivative, acitretin is teratogenic. Women of child-bearing age must therefore follow a pregnancy prevention program with reliable contraception for a month prior to the start of treatment, during treatment, and up to two years after treatment discontinuation. For all other systemic agents (corticosteroids, methotrexate, azathioprine), there are no controlled scientific studies on the treatment of hand dermatitis [44]. Taking into account their contraindications, special warnings, and precautions (refer to the respective summary of product characteristics), these therapeutic options may be considered as third-line therapy in patients who require long-term therapy but in whom the aforementioned treatments of first and second choice are insufficiently effective or contraindicated [44].

Unsuitable for longer-term treatment due to their side effect profile, systemic corticosteroids (0.5–1 mg/kg of prednisolone equivalent every day) may be used short-term for the treatment of severe acute flare-ups of hand dermatitis [44].

Ex vivo studies have recently shown that low-dose CsA therapy (1–2 mg/kg every day), unlike high-dose therapy with CsA (3–5 mg/kg every day), leads to partial inhibition of interleukin-2 production. The desired induction and expansion of regulatory T cells in patients with atopic dermatitis on low-dose CsA therapy is attributed to this effect [71].

Table 5 Validated instruments for assessing the severity of hand dermatitis and disease-related impairment of quality of life.

Acronym	Instrument	Description	Reference
–	Clinical Photo Guide	Comparison and evaluation using four series of photos of hand dermatitis of increasing severity. Score: 0–4 Hand dermatitis severity: 0 = healed, 1 = nearly healed, 2 = moderate, 3 = severe, 4 = very severe	[73, 74]
PGA	Physicians global assessment	Score: 0–4 Hand dermatitis severity: 0 = healed, 1 = nearly healed, 2 = mild, 3 = moderate, 4 = severe	[75]
HECSI	The hand eczema severity index	The severity of six morphologic criteria (erythema, scaling, infiltrate, edema, fissures, and vesicles) as well as the extent are evaluated. Score: 0–360	[76]
OHSI	Osnabrück Hand Dermatitis Severity Index	The severity of six morphologic criteria (erythema, scaling, papules, infiltrate, fissures, and vesicles) as well as the extent are evaluated. Score: 0–18	[77, 78]
ODDI	Occupational Contact Dermatitis Disease Severity Index	Two areas are evaluated: (1) Disease course, treatment, and clinical findings; (2) workplace-related activity. Evaluation: 1–5 points per area Total score: 2–10 (a higher score indicates greater impairment)	[79, 80]
DLQI	Dermatologic Quality of Life Index	Ten questions about the impact of the skin disease on physical, social, and functional aspects of life in the past week. Score: 0 (best quality of life), 30 (poorest quality of life)	[81]
–	Skindex-29	30 questions on emotionality, skin symptoms, and "functional capacity" in daily life. Question 18 (side effect of treatment) is not included in the score. Each question is assessed on a 5-point Likert scale (never, rarely, sometimes, often, always), and all answers are transferred to a linear scale from 0–100. The total score is the average value of all answers.	[82]

As to other topical and systemic therapeutic approaches in hand dermatitis, please refer to the recently published guidelines of the European Society of Contact Dermatitis (ESCD) on the management of hand dermatitis, which provide further consensus recommendations based on an as yet unpublished systematic Cochrane review [44, 72]. Based on this, revision and updating of the German AWMF guidelines [40], whose period of validity has expired, have been announced.

Validated instruments for assessing severity and quality of life in hand dermatitis

Numerous different validated instruments are available for the standardized assessment of the severity of hand dermatitis and its effects on quality of life. A selection of instruments frequently used in studies [73–82] is summarized in Table 5.

In the self-assessment of the severity of hand dermatitis using visual analogue scales, patients significantly more often rate their disease as severe, compared to the physicians' assessment [83]. With increasing improvement of their hand dermatitis, patients' recollection of the worst-ever disease severity shifts towards less severe [84]. Not only are these findings important for the evaluation of questionnaire-based study results but also for the management of patients in everyday clinical practice.

Standardized severity assessment enables monitoring of graded, severity-related therapy of hand dermatitis and quantification of therapeutic effects.

Treatment satisfaction in hand dermatitis patients is not ensured if treatment is only geared towards the management of visible disease manifestations.

The results obtained with various instruments (PGA and HECSI by the treating physicians and using clinical photo guide and DLQI by patients) largely correlate with each other [85]. In the German CARPE hand dermatitis registry, which includes a patient population with severe hand dermatitis, the median DLQI in 992 patients was eight points, which corresponds to moderate impairment of quality of life [26]. The clinical morphological disease severity impacts the treatment concept to a greater extent than the disease duration, and has a significant impact on the quality of life [27]. Standardized severity assessment enables monitoring of graded, severity-related therapy of hand dermatitis and quantification of therapeutic effects not only in clinical studies but also in routine clinical practice [85].

A single-center cross-sectional study has recently shown that treatment satisfaction in hand dermatitis patients is not ensured if treatment is only geared towards the disappearance of visible disease manifestations [86]. Besides physician-related factors such as competence and empathy, disease severity and competence in self-treatment, stress caused by the disease has been identified as a significant factor impacting patient satisfaction. Thus, assessment of the quality of life also appears to be an important follow-up parameter.

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Fragen zur Zertifizierung durch die DDA

1. Welche Aussage zum Handekzem trifft **nicht** zu?

- a) Die Punktprävalenz von Handekzemen in der Allgemeinbevölkerung beträgt ca. 4 %.
- b) Die Inzidenz von Handekzemen ist bei Frauen höher als bei Männern.
- c) Eine hohe Inzidenzrate von Handekzemen ist assoziiert mit atopischer Dermatitis.
- d) Eine hohe Inzidenzrate von Handekzemen ist assoziiert mit Haustierhaltung.
- e) Eine ausgeprägte Ausdehnung von Handekzemen ist ein Risikofaktor für die Persistenz der Handekzeme.

2. Welche Aussage zu Filaggrin trifft **nicht** zu?

- a) Filaggrin spielt eine zentrale Rolle in der terminalen Differenzierung der Kerneozyten.
- b) Filaggrin trägt zur mechanischen Belastbarkeit der Hautbarriere bei.
- c) Filaggrin ist Ausgangsprodukt für die Bildung des körpereigenen *natural moisturizing factor*.
- d) Bei heterozygoten FLG-Mutationsträgern können strukturelle Alterationen der Haut festgestellt werden.
- e) Loss-of-Function-Mutationen im Filaggrin-Gen sind protektiv gegen Nickelsensibilisierung

3. Welche Aussage zu beruflichen Einflüssen trifft **nicht** zu?

- a) Feuchtarbeitsplätze gehen mit einem erhöhten Handekzemrisiko einher.
- b) Besteht die Möglichkeit, dass berufliche Einflüsse an der Entstehung oder Unterhaltung der Handekzeme beteiligt sind, soll frühzeitig eine Information des Unfallversicherungsträgers mittels Berufskrankheitenanzeige (BK-Anzeige) erfolgen.
- c) Kriterien eines Feuchtarbeitsplatzes liegen vor, wenn ein Beschäftigter

mehr als zwei Stunden pro Tag mit den Händen Arbeiten in in feuchtem Milieu ausführt.

- d) Kriterien eines Feuchtarbeitsplatzes liegen vor, wenn ein Beschäftigter bei seiner Arbeitstätigkeit häufig die Hände reinigen muss.
- e) Kriterien eines Feuchtarbeitsplatzes liegen vor, wenn ein Beschäftigter mehr als zwei Stunden pro Tag bei seiner Arbeitstätigkeit feuchtigkeitsdichte (okklusive) Schutzschuhe tragen muss.

4. Welche Aussage zur diagnostischen Abklärung von Handekzemen trifft zu?

- a) Handekzeme sind in der Mehrheit der Fälle monokausal verursacht.
- b) Das Vorliegen einer Psoriasis der Hände schließt das Auftreten einer Kontaktallergie an den Händen aus.
- c) Bei allen länger als drei Monate bestehenden Handekzemen wird eine expositionsadaptierte Epikutantestung empfohlen.
- d) Eine mykologische Diagnostik zum sicheren Ausschluss einer Tinea manuum ist bei Handekzemen aufgrund der bestehenden verlässlichen klinisch-morphologischen Aspekte entbehrlich.
- e) Der Farbumschlag im Dimethylglyoxim-Test zeigt eine Freisetzung von Kobalt an.

5. Welche Aussage zur Therapie von Handekzemen trifft **nicht** zu?

- a) Die Therapie eines Handekzems beginnt mit der Identifikation der individuellen Auslöser und der Einleitung von entsprechenden Karenzmaßnahmen.
- b) Die Versorgung mit Schutzhandschuhen muss die individuellen Arbeitsstoffe und Durchbruchzeiten unterschiedlicher Chemikalien berücksichtigen.

- c) Die Durchbruchzeit ist die Zeitspanne, innerhalb derer ein Handschuh Schutz gegen Hautkontakt mit einer bestimmten Chemikalie bietet.
- d) Medizinische Einmalhandschuhe sind zur Flächendesinfektion geeignet.
- e) Berufsgruppenspezifische individuelle Präventionsangebote (ambulante Schulungsseminare und stationär-ambulant vernetzte Heilverfahren) erzielen bei der Mehrheit der Patienten mit therapieresistenten Handekzemen eine wesentliche Verbesserung des Hautbefundes und der Lebensqualität.

6. Welche Aussage zur topischen Therapie von Handekzemen trifft **nicht** zu?

- a) Topische Steroide mit hohem therapeutischen Index (TIX = 2) sind aufgrund ihrer Ratio von erwünschter zu unerwünschter Wirkung bei der Behandlung von Handekzemen vorzuziehen.
- b) Topische Steroide fördern die Regeneration des Stratum corneum.
- c) Steinkohleteer hat eine steigernde Wirkung auf die Filaggrinexpression.
- d) Ein intermittierender oder proaktiver Einsatz von topischen Steroiden oder Calcineurininhibitoren kann zur Verlängerung von Ekzemrezidiv-freien Intervallen beitragen.
- e) Der Einsatz von Calcineurininhibitoren (Pimecrolimus, Tacrolimus) innerhalb der zugelassenen Indikation ist nur bei Handekzemen atopischer Genese möglich.

7. Welche Aussage zur Systemtherapie von Handekzemen trifft **nicht** zu?

- a) Zur Behandlung von schweren, chronischen Handekzemen, die therapierefraktär auf potente topische Steroide sind, ist als Systemtherapie 9-*cis*-Retinsäure (Alitretinoin) zugelassen.

- b) Die Standarddosierung von Alitretinoin beträgt 30 mg/Tag p.o.
- c) Im Falle von nicht ausreichend kontrollierten Nebenwirkungen kann die Alitretinoin-Dosierung versuchsweise auf 10 mg/Tag p.o. reduziert werden.
- d) Als Vitamin-A-Säure-Derivat ist Alitretinoin teratogen.
- e) Systemische Glukokortikosteroide sind Therapie der zweiten Wahl zur langfristigen Behandlung von schweren, chronischen Handekzemen, die therapierefraktär auf potente topische Steroide sind.

8. Welche Aussage zum Umgang mit hautbelastenden Stoffen trifft nicht zu?

- a) R- und S-Sätze (Risiko- und Sicherheitssätze) charakterisieren Gefahrenmerkmale von Gefahrstoffen.
- b) Die R-Sätze R38, R43 und R66 weisen auf Gefahren für die Atemwege hin.

- c) REACH beinhaltet Grenzwerte für die Nickelfreisetzung aus Schmuck und anderen Produkten, die direkten und längeren Hautkontakt haben.
- d) Die TRGS 401 beinhaltet gesicherte Erkenntnisse für Tätigkeiten mit Gefährdung durch Hautkontakt.
- e) Nach SGB VII ist es Aufgabe der gesetzlichen Unfallversicherungsträger, mit allen geeigneten Mitteln Arbeitsunfälle und Berufskrankheiten sowie arbeitsbedingte Gesundheitsgefahren zu verhüten.

9. Bei Nichtansprechen auf eine stadiengerechte anti-ekzematöse Handekzem-Therapie ist differenzialdiagnostisch als Erkrankung am wenigsten zu berücksichtigen:

- a) Tinea manuum
- b) Histaminintoleranz
- c) Psoriasis vulgaris
- d) Mycosis fungoides
- e) Artefakte

10. Welche der aufgeführten Testsubstanzen aus der Standardreihe geht nicht mit einer Risikoverdoppelung für ein berufliches allergisches Kontaktekzem einher?

- a) Natriumlaurylsulfat (Detergens)
- b) Thiuram-Mix (Gummiakzeleratoren)
- c) Epoxidharz (Kunstharz)
- d) Mercaptobenzothiazol (Gummiakzelerator)
- e) IPPD (Gummialterungsschutz in Schwarzgummi)

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 17.Feb 2016. Die richtige Lösung zum Thema „Pain and pain management in dermatology“ in Heft 10 (October 2015) ist: (1b, 2c, 3b, 4d, 5a, 6c, 7d, 8b, 9b, 10d).

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