

Repairing a Compromised Skin Barrier in Dermatitis: Leveraging the Skin's Ability to Heal Itself

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Abstract

Skin barrier defects play a major role in many dermatoses including irritant and allergic contact dermatitis, atopic dermatitis, dry skin, aged skin, xerosis, rosacea, acne and more. Skin barrier repair technology has heretofore focused on physiologic skin lipid replacement and skin protection without addressing the myriad other areas of compromise such as an elevated pH, balance of the microbiome, inflammation, susceptibility to infection, aberrant calcium gradients and the proclivity for contact sensitization. By changing the paradigm from physiologic skin lipid supplementation to that of supplementing the epidermis with lipids that have recently been found to be particularly deficient from the disrupted skin barrier, and by simultaneously addressing the many facets of vulnerability, the skin barrier can be effectively repaired. This model of advanced skin barrier repair wherein physiologic deficiencies are supplemented and/or augmented may be an effective method for restoring the ability of xerotic and dermatitic skin to heal itself.

Keywords: Skin barrier repair; Ceramide; Phytosphingosine; Cholesterol ester; 18- β Glycyrrhetic acid; Niacinamide; pH; Calcium chelation; Silicone; Paraffin

Abbreviations: ACD: Allergic Contact Dermatitis; AD: Atopic Dermatitis; AHAs: Alpha Hydroxy Acids; GLU: Gluconolactone; ICD: Irritant Contact Dermatitis; PPAR: Peroxisome Proliferator Activated Receptor; TEWL: Transepidermal Water Loss

Introduction

A compromised skin barrier plays a major role in many dermatoses including irritant and allergic contact dermatitis, atopic dermatitis, dry skin, aged skin, xerosis, rosacea, and acne [1–5]. Many of these conditions share common defects in the skin barrier and an association with inflammation [4,6]. The knowledge we have regarding specific lipid deficiencies, pH aberration, inflammation, irregular calcium gradients, and susceptibility to contact sensitization can be leveraged to address many aspects of the disrupted skin barrier. By addressing these major points of vulnerability the skin's inherent ability to heal itself can be optimized for skin barrier repair.

Dermatitis is a term that includes irritant and allergic contact dermatitis, atopic dermatitis and many other conditions that are explained by skin barrier disruption and dysfunction. An association with inflammation and, in many cases, exacerbation from chemical irritants and allergens is common (Figure 1). We will discuss the commonalities of skin barrier compromise in dermatitis and other forms of skin barrier disruption. We will discuss the role that skin barrier dysfunction plays in these conditions, how to leverage the strengths of the skin's barrier repair pathways to stimulate skin barrier repair, and the optimal features of skin barrier repair products.

ACD and ICD are associated with skin barrier defects that may be a result of exogenous (the nature of an irritant or allergen, exposure concentration, duration, chronicity, and other mechanical factors) and endogenous factors [7]. In atopic dermatitis, there are several known inherent skin barrier defects including specific lipid deficiencies and filaggrin null mutations [8–10]. Though the specific etiology of ACD, ICD and AD may be variable, all three conditions have similar deficiencies that drive the disease state. All three conditions are initiated as a result of skin barrier defects that lead to the activation of

inflammatory mediators such as IL-1 and TNF α [5,11,12]. These pro-inflammatory mediators set into motion inflammatory cascades in an effort to induce reparative processes and restore skin barrier function [13]. Unfortunately, the role of inflammation may overshoot the skin barrier repair mechanisms and result in dry, scaly, inflamed, and irritated skin.

For protection, the skin utilizes the following types of barriers: physical, biochemical, redox, and immune [4]. The epidermis makes up the physical barrier that is the first line of defense, mostly attributed to the protective effects of the stratum corneum which includes the lipid bilayer, the acid mantle (one contributor to the acidic pH of the epidermis), a calcium gradient which influences desquamation and cellular turnover and differentiation of the epidermis, and the many aspects of the cutaneous immune system [14]. The epidermis is able to provide protection from solids, liquids, and gases in addition to warding off attacks from viruses, bacteria, fungi, and other microbes [15].

Points of Vulnerability

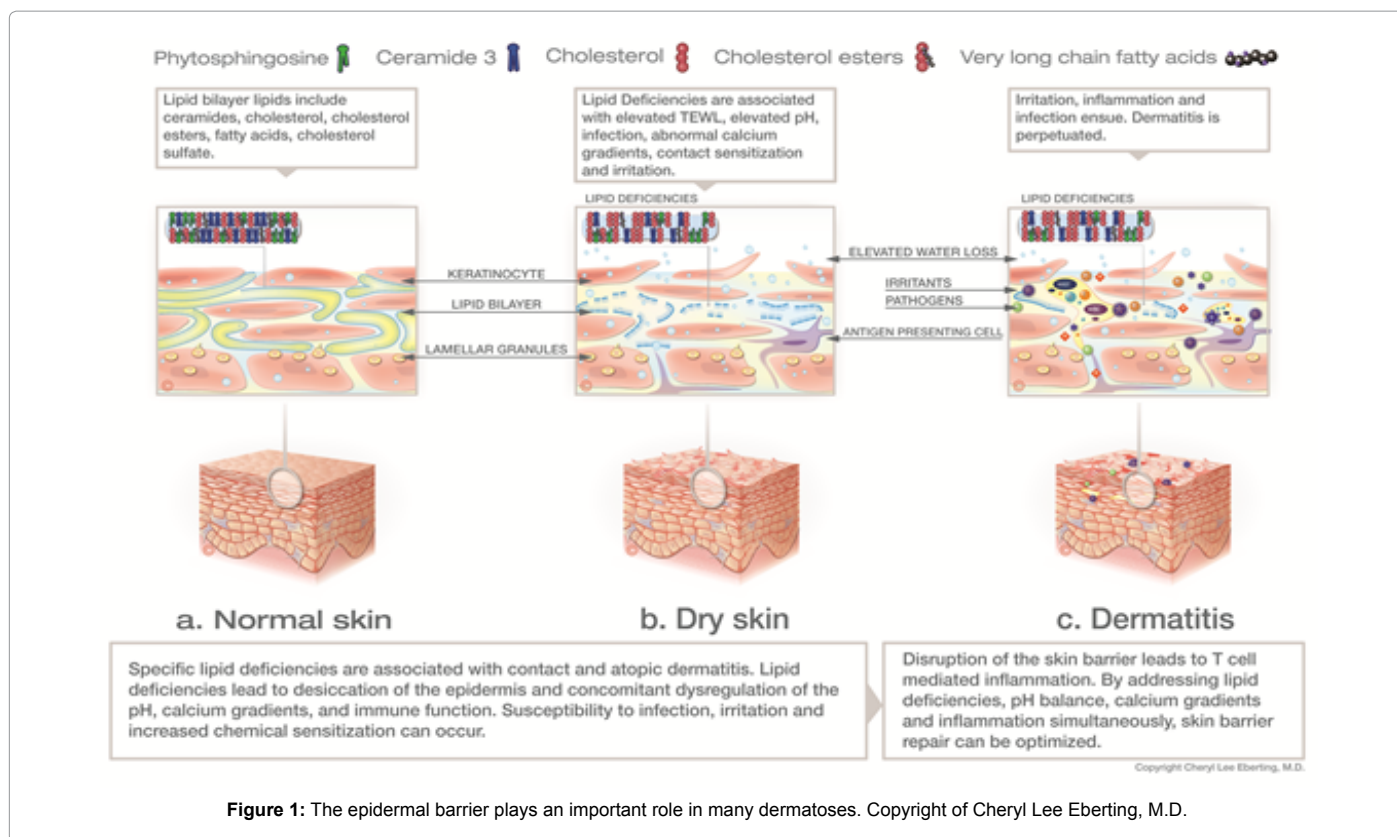
A disrupted skin barrier has many points of vulnerability including excessive water loss, slow/deficient lipid production, an imbalance in content and ratio of skin lipids, a dry skin barrier, an elevation of pH, susceptibility to infection and inflammation, and susceptibility to contact sensitization [16–19]. There have been many approaches to induce and enhance skin barrier repair in chronic dermatitis. Some products have focus on skin barrier protection or physiologic skin lipid replacement or inflammation. To effectively heal the skin barrier, trans-epidermal water loss (TEWL) must be minimized and the skin must be protected

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from further contact with irritants, allergens, and infectious organisms [20]. Ideally, the skin pH would be optimized to encourage natural ceramide production and to discourage the growth of pathogens while encouraging the growth of a healthy microbiome [21,22]. Modulation of the disrupted calcium gradient may restore appropriate levels of desquamation [23]. Inflammation must also be minimized while all sensitizers, irritants and proinflammatory mediators should be avoided [24]. By addressing all of these points of vulnerability simultaneously, the skin's ability to itself may be optimized.

Skin Barrier Heal

Current medical and scientific literature provides insight to the characteristics, features, and classes of ingredients able to address the aforementioned vulnerabilities of the disrupted epidermis in chronic dermatitis.

Lipid Replacement

Close examination has revealed that much of the barrier protection from the epidermis comes from stratum corneum lipids. The lipids are arranged in a highly organized structure with controlled ratios. When these ratios or structure are interrupted or unbalanced, barrier function is compromised which gives microbes and allergens unencumbered entrance to the deeper layers of the skin where inflammatory pathways are triggered [15,25].

Current therapeutic options include products which address skin barrier repair by supplementing the skin with lipids in physiologic ratios, while other products have employed behentrimonium methosulfate, a cationic surfactant quaternary ammonium salt, as part of a dynamic lipid delivery system [20,26]. Several specific lipid deficiencies have been elucidated in many forms of chronic dermatitis.

Phytosphingosine-containing ceramides such as ceramide 3 [27–29], and possibly phytosphingosine itself are deficient in conditions such as dry skin, aged skin, and in atopic skin. In fact, as dryness levels of the skin increase, so does the degree of phytosphingosine-containing ceramide deficiency [27,30,31]. Marked deficiency in ceramide 3 (N-Acyl phytosphingosine) has also been well-documented in atopic skin and correlated to increased TEWL [32].

Cholesterol esters are deficient relative to cholesterol in xerotic skin [33] and in SDS-induced dry skin (Figure 2). The overall sterol content is preserved, but the ratio of cholesterol to cholesterol esters is increased with an excess relative concentration of cholesterol [27,33]. When SDS-induced dry skin treated with 1% cholesterol base was compared to 1% cholesterol ester base, the cholesterol ester treated skin showed improved conductance values while the cholesterol-treated skin did not [34]. Atopic skin has also been shown to have abnormally elevated levels of cholesterol [32]. Cholesterol esters are esterified to short, medium, long, and very long chain fatty acids. Based on these studies of chronic dermatitis conditions where the cholesterol:cholesterol ester ratio has been shown to be elevated as compared to normal skin, it may be optimal to supplement the skin with cholesterol esters rather than with cholesterol as has traditionally been done by many physiologic skin lipid replacement products. Indeed, it may not be necessary and may possibly be less efficacious, to supplement, xerotic, atopic, and SDS-induced dry skin with unesterified cholesterol, because the cholesterol:cholesterol ester ratios in these conditions have been shown to be abnormally elevated. (Figures 2-5) Of note however, cholesterol itself was shown to aid barrier recovery in a tape stripping model in aged skin, but not in young skin [35]. The aged skin in this study was not controlled for ingestion of cholesterol lowering medications. Of note, a disease of unknown etiology in aged skin, Grover's disease, is



Figure 2: Irritant "Lip-licker's Dermatitis" Before and eight hours after a single application of a preservative-free ointment that contains skin barrier lipids, isostearyl isostearate, petrolatum, paraffin wax and 18- β glycyrrhethinic acid. Photos copyright of Cheryl Lee Eberting, M.D.

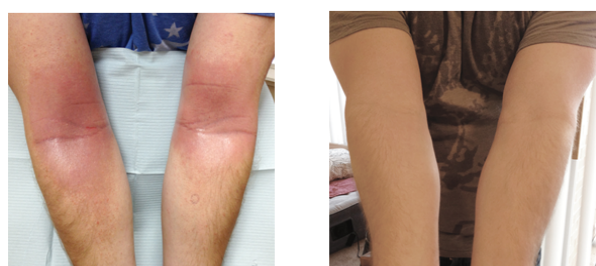


Figure 3: Atopic and allergic contact dermatitis due to lanolin. R. arm was treated with 0.1% Triamcinolone ointment and L. arm was treated with a preservative-free ointment that contains skin barrier lipids, isostearyl isostearate, petrolatum, paraffin wax and 18- β glycyrrhethinic acid. Photos copyright of Cheryl Lee Eberting, M.D.

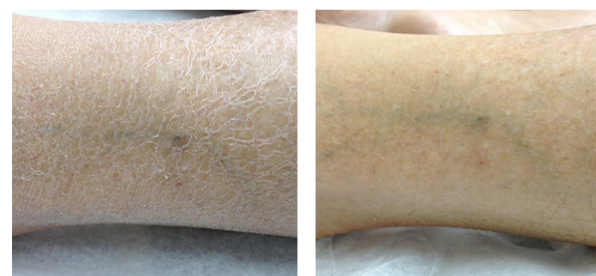


Figure 4: Severe Xerosis before and 30 seconds after application of a preservative-free ointment that contains skin barrier lipids, isostearyl isostearate, petrolatum, paraffin wax 18- β glycyrrhethinic acid. Photos copyright of Cheryl Lee Eberting, M.D.

frequently benefited from cholesterol ester-containing skin barrier repair products. Author's experience, CLE (Figure 6).

Fatty acid deficiency also contributes to a disrupted skin barrier. Long chain fatty acids like palmitic (C16) and stearic acids (C18) are known to be deficient in atopic skin [36], but more recent studies have shown a particular deficiency in the very long chain fatty acids cerotic (C26) montanic, (C28), and melissic (C30) acids [37]. Very long chain fatty acids are naturally occurring in candelilla wax. Candelilla wax is accessible, affordable, and has only one reported case of contact sensitization [38].

Inflammation

The use of molecules with inherent anti-inflammatory qualities has been shown to be effective in many forms of skin barrier disruption [39]. Glucocorticoids are most commonly prescribed for this purpose,

but non-glucocorticoid molecules also show anti-inflammatory qualities [40]. An over the counter petrolatum and lanolin-based product that employs bisabolol as an anti-inflammatory agent has shown comparable efficacy to a prescription medical device cream [41]. Increasing numbers of contact sensitization to this product are being reported in patients who are using it to treat dermatitis. Those who are sensitized to bisabolol should be counseled to avoid any bisabolol-containing products [42–44].

18 β -Glycyrrhethinic acid exhibits corticosteroid-like anti-inflammatory, anti-allergic activity, and many other benefits in contact dermatitis. In vitro, glycyrrhethinic acid is known to inhibit $\Delta 4\beta$ -reductase, an enzyme that competitively inactivates steroid hormones, and 11 β -hydroxysteroid dehydrogenase, an enzyme that deactivates cortisol [45]. Inhibiting the metabolism of naturally occurring cortisol enhances the body's natural anti-inflammatory capacity by potentiating the activity of endogenous (and possibly even exogenously applied) corticosteroids. When used in formulation by it or with a glucocorticoid, glycyrrhethinic acid may augment and extend the effectiveness of glucocorticoids, allowing the use of less-potent glucocorticoids and/or a shorter course of treatment. This could limit overall glucocorticoid exposure and associated side effects. When a metabolic precursor to 18 β -glycyrrhethinic acid was given intraperitoneally, it suppressed contact dermatitis in mice with higher efficacy than prednisolone. When administered orally, it was ineffective [46]; possibly highlighting the necessity to deliver the active molecule directly to the area of contact dermatitis. This same molecule is bactericidal to MRSA and has anti-candidal effects [47,48], a beneficial characteristic when treating disrupted skin that particularly is susceptible to these organisms. This molecule has skin brightening and lightening effects [49] and thus may have additional benefits for dermatitis associated with

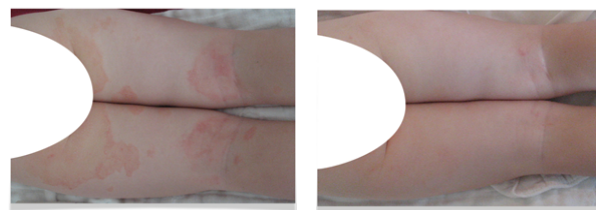


Figure 5: Atopic Dermatitis before and after ten days twice daily application of a hypoallergenic skin barrier repair cream that contains skin barrier lipids, isostearyl isostearate, petrolatum, niacinamide, gluconolactone, 18- β glycyrrhethinic acid, gluconolactone and EDTA. Photos copyright of Cheryl Lee Eberting, M.D.

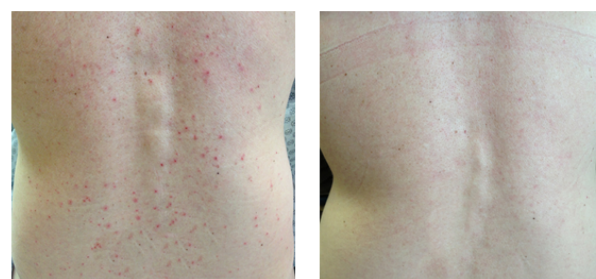


Figure 6: Grover's Disease before and after ten days of twice daily application of a preservative-free ointment that contains skin barrier lipids, isostearyl isostearate, petrolatum, paraffin wax and 18- β glycyrrhethinic acid. Photos copyright of Cheryl Lee Eberting, M.D.

post-inflammatory hyperpigmentation in light and darker-skinned individuals [49]. This molecule also has photoprotective benefits. After UV exposure, it reduced ROS, NF-KB, cytochrome c, and caspase 3 levels and inhibited hyaluronidase, possibly by inhibition of MMP1 activation by modulating NF-KB signaling [50]. Feeding mice with this molecule prior to UVB radiation caused delays in tumor appearance, multiplicity, and size [51]. This molecule also offers protection from UVB radiation damage in humans [52].

Niacinamide, a B vitamin and possible Peroxisome Proliferator-Activated Receptor (PPAR) ligand, has been shown to up regulate fillagrin and involucrin synthesis [53]. It has been proven effective in the treatment of many forms of a disrupted skin barrier [54-56]. Niacinamide also suppresses antigen-induced lymphocytic transformation, an added benefit that may minimize rates of contact sensitization. Niacinamide also inhibits 3'-5' cyclic AMP phosphodiesterase, and blocks the inflammatory actions of iodides [57]. Niacinamide increases the thickness of the epidermis [58] while inducing de novo ceramide production through up-regulated expression of serine palmitoyltransferase, the rate-limiting enzyme in sphingolipid synthesis [59]. Ceramides are effective in blocking the reduction, and even stimulating the synthesis, of collagen after UV irradiation [60]. Niacinamide shows improved facial wrinkle appearance and tolerability compared to tretinoin [61]. Additionally, a niacinamide-containing moisturizer applied with tretinoin therapy enhanced the response to tretinoin, improved the stratum corneum, and decreased tretinoin-associated side-effects [62]. Niacinamide is well tolerated by the skin and provided significant improvements versus control in fine lines/wrinkles, hyperpigmentation spots, texture, red blotchiness, elasticity, and skin yellowing versus an oil in water moisturizer control [63,64]. Both niacinamide and 18- β glycyrrhetic acid are optimal anti-inflammatory molecules for optimizing repair of the compromised skin barrier.

pH Modulation

The pH of the epidermis becomes abnormally elevated in the setting of dermatitis, infection, or from contact with alkaline substances such as soap, bleach, solvents and even tap water [65]. The optimal pH of the skin is between 4.6 and 5.6 which is ideal for ceramide production. The skin lipid-producing enzymes β -glucocerebrosidase and acid sphingomyelinase both have optimal levels of activity within this pH range [21,22]. When the skin is overly alkaline, both serine protease-mediated inactivation and metabolism of the β -glucocerebrosidase and acid sphingomyelinase enzymes take place. Ceramide and lipid production slows or comes to a halt [66]. The disrupted and alkaline skin barrier is unable to support a healthy microbiome. *Staphylococcus aureus*, *Candida*, and *Propionibacterium* acnes all grow more effectively in an alkaline environment. Natural skin flora also become compromised at an elevated pH [67,68]. This shift in the microbiome of the skin may lead to a cycle of increased alkalinity, infection, and a disrupted epidermal barrier. Additionally, as the pH reaches and exceeds 5.7, there is inhibition of lamellar body secretion and corneodesmosome-constituent proteins can be degraded [66].

Acidification and even hyper-acidification of the epidermis has been shown to decrease TEWL [69]. In fact, a common technique for acidifying topical skin care formulations is the addition of acidic salts, such as citric or lactic acids. These acids are uncommon sensitizers, but are prone to crystallization, which can result in irritation of the skin. Alpha Hydroxyacids (AHAs) are also used to modulate the pH of the skin and to enhance stratum corneum desquamation and improve skin appearance. Unfortunately, AHAs result in sunburn cell

formation and increase the risk of skin cancer. The FDA now requires a sun-burn warning on products containing AHAs [70]. A natural polyhydroxy acid, Gluconolactone (GLU) is a free radical scavenger and is a superior TEWL inhibitor when compared to several other acids [69,71]. Additionally, GLU is known to enhance stratum corneum desquamation, improve skin appearance, prevent skin irritation, and is protective against UV radiation-induced elastin promoter activation [71]. GLU treatment does not result in a significant increase in sunburn cells. UV absorption of GLU is low, so the UV protective effect must be due to other mechanisms, such as its ability to function as a chelating agent and free radical scavenger [71]. Additionally, GLU does not crystallize and become an irritant to the skin as easily as citric and lactic acid, making it an optimal epidermal acidifier (CLE, unpublished author observation).

Skin Barrier Protection

Effective transepidermal water loss inhibition

TEWL measurements can be used as a marker for skin barrier integrity. Improvements in TEWL have been tied to improvements in SCORAD scores in atopic dermatitis and are considered a marker for stratum corneum integrity and hydration [20]. In addition to the TEWL lowering benefits of sphingolipid and cholesterol ester fractions, TEWL inhibitors like petrolatum, dimethicone and other lipid fractions are commonly used as skin protectants. Petrolatum is considered to be the gold standard TEWL inhibitor [72]. In an effort to explore possible alternatives to petrolatum, the author subjectively tested countless plant-based petrolatum substitutes and was unable to find one that matched the characteristics of petrolatum including: hypoallergenicity, hydration, taste, viscosity, melting temperature, and non-desiccating effects on palmar and lip skin (as these areas tend to become most-easily irritated/tight when they are desiccated). Petrolatum is a complex semi-solid combination of paraffin wax, microcrystalline wax and white mineral oil. Paraffin wax is even more impermeable to water than petrolatum and when combined with petrolatum, is also an extremely efficient TEWL inhibitor.

Dimethicone, a man-made polymer of the naturally occurring element silica or silicon, is a very common skin protectant. Silicon is naturally present in very small amounts in the human body and may be associated with bone health [73]. Silicone and dimethicone are manufactured by polymerizing silicon with carbon, hydrogen and oxygen. The human body does not have the ability to metabolize these polymers and in fact, when human monocytes were incubated on dimethicone, they secreted variable levels of IL-1 beta, IL-6 and TNF-alpha [24]. Furthermore, dimethicone has the potential to cause an inflammatory reaction when implanted [74]. When five different silicone materials were tested for skin sensitization potential, the murine local lymph node assay showed weak to moderate skin sensitization potential for four of the five materials. Sensitization via cutaneous contact or via injection or implantation is increasingly reported in the literature. Reactions include allergic contact dermatitis, granuloma formation, systemic sclerosis, and a psoriasiform eruption, among others [75-78]. Rates of sensitization to silicone and silicone polymers are increasing in both topical and implanted exposures [79-81].

While it is technically difficult to objectively study a skin protectant's ability to prevent penetration of allergens, irritants, and microbes into the skin, there are three objective measures that may be used to determine a product's or ingredient's effectiveness in these areas: 1) if a product or molecule has superior hydrophobicity; 2) lower water solubility; and 3) a higher melting point than another, it may be more

difficult to wash off and therefore more efficient at preventing contact with irritants, allergens and pathogens. Solvent permeability and penetration characteristics are also to be considered.

Hydrophobicity

Hydrophobicity is the measure of a product or ingredient's degree of repellency from a mass of water. Hydrophobic molecules are non-polar and prefer other neutral molecules. The hydrophobicity of a skin barrier product or ingredient can be objectively measured by determining the contact angle, or the angle measured through the liquid where a liquid/vapor interface meets a solid surface, of a drop of water applied to the product in question. The contact angle is also directly correlated with a molecule's ability to adhere to a surface. While there are many variables that can alter the contact angle of a molecule, hydrophobicity can be subjectively measured by observing how easily water will bead and roll off of the skin. A product that is very hydrophobic will have a high contact angle, causing water to bead more efficiently [82]. The higher the contact angle, the more hydrophobic and adherent to the skin the molecule is. The largest contact angles measured between water and a smooth surface are with paraffin. Paraffin is a mixture of saturated aliphatic hydrocarbons and is considered to be the most hydrophobic water-repelling agent [83]. By comparison, to reach this range of hydrophobicity, dimethicone must be applied to a smooth surface such as glass and then must be baked on [84]. The contact angle of paraffin is between 106 and 112 degrees and is dependent on the texture of the surface and the purity of the paraffin [83]. Paraffin is composed of non-polar alkane chains that, like the methyl groups in silicone fluid, have hydrophobic properties. They interact very weakly with water molecules so water stays in a drop and does not wet the paraffin wax.

Melting point

The melting points of skin protectant molecules may be another indicator of their persistence on the skin after washing and effectiveness. The melting point of paraffin wax ranges from 47°C up to 65°C depending on which grade of wax is used [85]. The melting point of dimethicone is generally below 50°C (depending on which polymer is used) [86].

Water solubility

Water solubility is an objective variable that can be used to assess the effectiveness of a skin protectant. The water solubility of an ingredient is an important indicator of its ability to protect the skin from water, allergens and irritants. The water solubility of dimethicone is 33-77 g/l, while paraffin wax is insoluble in water [87].

In addition to petrolatum, paraffin wax, and dimethicone, many lipid-based TEWL inhibitors have also been investigated. These lipids include glyceryl monoisostearate, isopropyl isostearate, isostearyl isostearate, cetyl alcohol, potassium cetyl phosphate, cetyl behenate and behenic acid [88,89]. Isostearyl Isostearate has been proven to be the most effective lipid-based TEWL inhibitor in these studies [88].

Calcium chelation

Forslin et al. were able to use a scanning nuclear microprobe to map calcium distribution in cross sections of normal, atopic, and psoriatic skin. In normal skin, calcium localizes to the uppermost granular layer of the epidermis as well as to the basal and spinous layers. Forslin et al. found that psoriatic and dry atopic skin had an epidermal calcium gradient higher than normal skin [90]. Calcium is a necessary part of the apoptotic process, and increased intracellular calcium may induce the activation of endonuclease, transglutaminase, and morphological

changes [90]. Lee et. al., showed that removal of extracellular calcium stimulates both lamellar body secretion and lipid synthesis, while also blunting those responses when extracellular calcium concentration was raised for hairless mice [91]. Calcium also seems to impair corneodesmin hydrolysis with incomplete desquamation at alkaline pH and without the presence of EDTA [23]. The final step appears to be inhibited by calcium, resulting in incomplete desquamation and residual intercorneocyte cohesion in cases of skin barrier disruption. The skin's naturally occurring chelating agent is unknown, but calcium chelation in a lower pH environment and in the presence of EDTA allows this step to proceed [92]. Therefore, weak calcium chelation may benefit a disrupted skin barrier by improving desquamation. Gluconolactone and EDTA are both mild chelating agents that can safely be used in skin barrier repair formulations to help optimize desquamation.

Susceptibility to contact sensitization

Those with fillagrin null mutations have been found to have increased rates of ACD particularly to lanolin and p-tert-butylphenol-formaldehyde resin [93]. Research regarding the relevance of ACD in atopic dermatitis is emerging [17,94,95]. Those with atopic dermatitis are more likely to develop contact sensitization to certain chemicals relative to non-atopics. Formaldehyde-releasers [18], cocamidopropylbetaine [96] nickel, cobalt, chromium [16], Kathon CG, fragrance, neomycin [97], and propolis (from beeswax but found in cough syrup, pills, cosmetics, and vitamins) are advisably avoided in atopic dermatitis in the setting of contact dermatitis as atopics are possibly more likely to develop contact dermatitis [96].

Discussion

Techniques that optimize skin barrier repair include skin lipid replacement, pH modulation/optimization, the use of anti-inflammatory molecules, the use of mild calcium chelation, and the overt avoidance of known skin irritants and allergens in formulation. The effectiveness of a skin barrier repair and protectant product may also be determined by its ability to adhere to the skin and its ability to prevent the contact of water, irritants, allergens, and solvents from coming in contact with the skin. These qualities may be a function of a product's hydrophobicity, melting point, and water solubility.

Conclusion

A healthy skin barrier protects from pathogens, allergens, toxins, and irritants. When the skin's leading physical barrier, the stratum corneum, is damaged as a result of disease or acute destruction, the deeper layers of the epidermis and dermis are vulnerable to further irritation and sensitization. Finding ways to protect the skin and repair its natural barrier qualities is a major goal in reducing the incidence of chronic dermatitis. Utilizing the large amount of existing and recent data on different chemicals' interaction with the stratum corneum and the skin barrier to create novel products based on evidence-based medicine is essential to improving treatment outcomes. Further research and investigation into the skin's barrier function and our ability to enhance its protective qualities is paramount to the future treatment of these patients.

References

1. Jarmuda S, McMahon F, Zaba R (2014) Correlation between serum reactivity to Demodex-associated *Bacillus oleronius* proteins, and altered sebum levels and Demodex populations in erythematotelangiectatic rosacea patients. *J Med Microbiol* 63: 258-262. doi:10.1099/jmm.0.065136-0.

2. Purohit P, Chandar P, Vilinska A, Ananthapadmanabhan KP, Somasundaran P (2014) Effect of mixed surfactants on stratum corneum: a drying stress and Raman spectroscopy study. *Int J Cosmet Sci*.
3. Zouboulis CC, Jourdan E, Picardo M (2014) Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *J Eur Acad Dermatol Venereol* 28: 527-532.
4. Proksch E, Brasch J (2012) Abnormal epidermal barrier in the pathogenesis of contact dermatitis. *Clin Dermatol* 30: 335-344.
5. Czarnowicki T, Krueger JG, Guttman-Yassky E2 (2014) Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. *J Allergy Clin Immunol Pract* 2: 371-379.
6. Proksch E, Brandner JM, Jensen JM (2008) The skin: an indispensable barrier. *Exp Dermatol* 17: 1063-1072.
7. Lee HY, Stieger M, Yawalkar N, Kakeda M (2013) Cytokines and chemokines in irritant contact dermatitis. *Mediators Inflamm* 2013: 916497.
8. Kezic S, O'Regan GM, Lutter R, Jakasa I, Koster ES, et al. (2012) Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol* 129: 1031-1039.
9. Vávrová K, Henkes D, Strüver K, Sochorová M, Skolová B, et al. (2014) Filaggrin deficiency leads to impaired lipid profile and altered acidification pathways in a 3D skin construct. *J Invest Dermatol* 134: 746-753.
10. Agrawal R, Woodfolk JA (2014) Skin barrier defects in atopic dermatitis. *Curr Allergy Asthma Rep* 14: 433.
11. Lisby S, Baadsgaard O (2006) Mechanisms of Irritant Contact Dermatitis. In: Frosch P, Menné T, Lepoittevin J-P (Eds.) *Contact Dermatitis*. Springer Berlin-Heidelberg, Germany
12. Smith HR, Basketter DA, McFadden JP (2002) Irritant dermatitis, irritancy and its role in allergic contact dermatitis. *Clin Exp Dermatol* 27: 138-146.
13. Feingold KR, Schmuth M, Elias PM (2007) The regulation of permeability barrier homeostasis. *J Invest Dermatol* 127: 1574-1576.
14. Watt FM (1989) Terminal differentiation of epidermal keratinocytes. *Curr Opin Cell Biol* 1: 1107-1115.
15. Madison KC (2003) Barrier function of the skin: "la raison d'être" of the epidermis. *J Invest Dermatol* 121: 231-241.
16. Malajian D, Belsito DV (2013) Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. *J Am Acad Dermatol* 69: 232-237.
17. Fonacier LS, Aquino MR (2010) The role of contact allergy in atopic dermatitis. *Immunol Allergy Clin North Am* 30: 337-350.
18. Shaughnessy CN, Malajian D, Belsito DV3 (2014) Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: reactivity to topical preservatives. *J Am Acad Dermatol* 70: 102-107.
19. Herro EM, Matiz C, Sullivan K, Hamann C, Jacob SE (2011) Frequency of contact allergens in pediatric patients with atopic dermatitis. *J Clin Aesthetic Dermatol* 4: 39-41
20. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, et al. (2002) Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 47: 198-208.
21. Holleran WM, Takagi Y, Imokawa G, Jackson S, Lee JM, et al. (1992) beta-Glucocerebrosidase activity in murine epidermis: characterization and localization in relation to differentiation. *J Lipid Res* 33: 1201-1209.
22. Bowser PA, Gray GM (1978) Sphingomyelinase in pig and human epidermis. *J Invest Dermatol* 70: 331-335.
23. Egelrud T, Lundström A (1990) The dependence of detergent-induced cell dissociation in non-palmo-plantar stratum corneum on endogenous proteolysis. *J Invest Dermatol* 95: 456-459.
24. Anderson JM, Ziats NP, Azeez A, Brunstedt MR, Stack S, et al. (1995) Protein adsorption and macrophage activation on polydimethylsiloxane and silicone rubber. *J Biomater Sci Polym Ed* 7: 159-169.
25. Wollenberg A, Kraft S, Hanau D, Bieber T (1996) Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. *J Invest Dermatol* 106: 446-453
26. Draeels ZD (2008) The effect of ceramide-containing skin care products on eczema resolution duration. *Cutis* 81: 87-91.
27. Fulmer AW, Kramer GJ (1986) Stratum corneum lipid abnormalities in surfactant-induced dry scaly skin. *J Invest Dermatol* 86: 598-602.
28. Wu JQ, Kilpatrick-Liverman L (2011) Characterizing the composition of underarm and forearm skin using confocal raman spectroscopy. *Int J Cosmet Sci* 33: 257-262.
29. Macheleidt O, Kaiser HW, Sandhoff K (2002) Deficiency of epidermal protein-bound omega-hydroxyceramides in atopic dermatitis. *J Invest Dermatol* 119: 166-173.
30. Van Overloop L, Declercq L, Maes D (2001) JOURNAL OF INVESTIGATIVE DERMATOLOGY. In: Visual scaliness of human skin correlates to decreased ceramide levels and decreased stratum corneum protease activity. (Edn.), BLACKWELL SCIENCE INC, USA
31. Chopart M, Castiel-Higounenc I, Arbey E (2001) Quantitative and qualitative analysis of ceramides in the stratum corneum of normal and dry skin. *Poster Strat Corneum III Bâ*
32. Di Nardo A, Wertz P, Giannetti A, Seidenari S (1998) Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol* 78: 27-30.
33. Saint-Léger D, François AM, Lévêque JL, Stoudemayer TJ, Kligman AM, et al. (1989) Stratum corneum lipids in skin xerosis. *Dermatologica* 178: 151-155.
34. Imokawa G, Akasaki S, Minematsu Y, Kawai M (1989) Importance of intercellular lipids in water-retention properties of the stratum corneum: induction and recovery study of surfactant dry skin. *Arch Dermatol Res* 281: 45-51.
35. Hamanaka S, Asagami C, Suzuki M, Inagaki F, Suzuki A (1989) Structure determination of glucosyl beta 1-N-(omega-O-linoleoyl)-acylsphingosines of human epidermis. *J Biochem* 105: 684-690.
36. Yamamoto A, Serizawa S, Ito M, Sato Y (1991) Stratum corneum lipid abnormalities in atopic dermatitis. *Arch Dermatol Res* 283: 219-223.
37. van Smeden J, Janssens M, Kaye EC, Caspers PJ, Lavrijsen AP, et al. (2014) The importance of free fatty acid chain length for the skin barrier function in atopic eczema patients. *Exp Dermatol* 23: 45-52.
38. Barrientos N, Abajo P, Moreno de Vega M, Dominguez J (2013) Contact cheilitis caused by candelilla wax contained in lipstick. *Contact Dermatitis* 69: 126-127.
39. Hoare C, Li Wan Po A, Williams H (2000) Systematic review of treatments for atopic eczema. *Health Technol Assess* 4: 1-191.
40. Saeedi M, Morteza-Semnani K, Ghoreishi MR (2003) The treatment of atopic dermatitis with licorice gel. *J Dermatolog Treat* 14: 153-157.
41. Miller DW, Koch SB, Yentzer BA (2011) An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. *J Drugs Dermatol JDD* 10: 531-537
42. Jacob SE, Matiz C, Herro EM (2011) Compositae-associated allergic contact dermatitis from bisabolol. *Dermatitis* 22: 102-105.
43. Jacob SE, Hsu JW (2010) Reactions to Aquaphor: is bisabolol the culprit? *Pediatr Dermatol* 27: 103-104.
44. Russell K, Jacob SE (2010) Bisabolol. *Dermatitis* 21: 57-58.
45. Hikino H (1985) Recent research on oriental medicinal plants. *Econ Med Plant Res H Wagner Hiroshi Hikino Norman R Farnsworth*
46. Bradley PR (1992) *British Herbal Compendium. Volume 1. A Handbook of Scientific Information on Widely Used Plant Drugs. Companion to Volume 1 of the British Herbal Pharmacopoeia.* British Herbal Medicine Association
47. Messier C, Grenier D (2011) Effect of licorice compounds licochalcone A, glabridin and glycyrrhizic acid on growth and virulence properties of *Candida albicans*. *Mycoses* 54: e801-806.
48. Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM (2013) 18β-Glycyrrhetic acid inhibits methicillin-resistant *Staphylococcus aureus* survival and attenuates virulence gene expression. *Antimicrob Agents Chemother* 57: 241-247. doi:10.1128/AAC.01023-12.
49. Fisk WA, Agbai O2, Lev-Tov HA3, Sivamani RK4 (2014) The use of botanically derived agents for hyperpigmentation: a systematic review. *J Am Acad Dermatol* 70: 352-365.

50. Afnan Q, Adil MD, Nissar-UI A (2012) Glycyrrhizic acid (GA), a triterpenoid saponin glycoside alleviates ultraviolet-B irradiation-induced photoaging in human dermal fibroblasts. *Phytomedicine Int J Phytother Phytopharm* 19: 658-664. doi:10.1016/j.phymed.2012.03.007.
51. Cherng J-M, Tsai K-D, Yu Y-W, Lin J-C (2011) Molecular mechanisms underlying chemopreventive activities of glycyrrhizic acid against UVB-radiation-induced carcinogenesis in SKH-1 hairless mouse epidermis. *Radiat Res* 176: 177-186
52. Rossi T, Benassi L, Magnoni C, Ruberto AI, Coppi A, et al. (2005) Effects of glycyrrhizin on UVB-irradiated melanoma cells. *In Vivo* 19: 319-322.
53. Oblong J, Bissett D, Ritter J, Kurtz K, Schnicker M (2001) Niacinamide stimulates collagen synthesis from human dermal fibroblasts and differentiation marker in normal human epidermal keratinocytes: potential of niacinamide to normalize aged skin cells to correct homeostatic balance. In: 59th Annual Meeting American Academy of Dermatology, Washington
54. Soma Y, Kashima M, Imaizumi A, Takahama H, Kawakami T, et al. (2005) Moisturizing effects of topical nicotinamide on atopic dry skin. *Int J Dermatol* 44: 197-202.
55. Niren NM, Torok HM (2006) The Nicamide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. *Cutis* 77: 17-28.
56. Draelos ZD, Ertel K, Berge C (2005) Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. *Cutis* 76: 135-141.
57. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK (1995) Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 34: 434-437.
58. Mohammed D, Crowther JM, Matts PJ, Hadgraft J, Lane ME. Influence of niacinamide containing formulations on the molecular and biophysical properties of the stratum corneum. *Int J Pharm* 441: 192-201. doi:10.1016/j.ijpharm.2012.11.043.
59. Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S (2000) Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 143: 524-531.
60. Grether-Beck S, Mühlberg K, Brenden H, Krutmann J. [Topical application of vitamins, phytosterols and ceramides. Protection against increased expression of interstitial collagenase and reduced collagen-I expression after single exposure to UVA irradiation]. *Hautarzt Z Für Dermatol Venerol Verwandte Geb.* 2008;59(7):557-562. doi:10.1007/s00105-008-1554-7.
61. Fu JJJ, Hillebrand GG, Raleigh P, et al. A randomized, controlled comparative study of the wrinkle reduction benefits of a cosmetic niacinamide/peptide/retinyl propionate product regimen vs. a prescription 0.02% tretinoin product regimen. *Br J Dermatol.* 2010;162(3):647-654. doi:10.1111/j.1365-2133.2009.09436.x.
62. Draelos ZD, Ertel KD, Berge CA (2006) Facilitating facial retinization through barrier improvement. *Cutis* 78: 275-281.
63. Bissett DL, Miyamoto K, Sun P, Li J, Berge CA (2004) Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci* 26: 231-238.
64. Bissett DL, Oblong JE, Berge CA (2005) Niacinamide: A B vitamin that improves aging facial skin appearance. *Dermatol Surg* 31: 860-865.
65. Kawai E, Kohno Y, Ogawa K, Sakuma K, Yoshikawa N, Aso D (2005) Can inorganic powders provide any biological benefit in stratum corneum, while residing on skin surface. *IFSCC Mag* 5: 269-275
66. Hachem J-P, Roelandt T, Schürer N (2010) Acute acidification of stratum corneum membrane domains using polyhydroxyl acids improves lipid processing and inhibits degradation of corneodesmosomes. *J Invest Dermatol* 130: 500-510. doi:10.1038/ijd.2009.249.
67. Korting HC, Kober M, Mueller M, Braun-Falco O (1987) Influence of repeated washings with soap and synthetic detergents on pH and resident flora of the skin of forehead and forearm. Results of a cross-over trial in health probationers. *Acta Derm Venereol* 67: 41-47.
68. Korting H, Greiner K, Hubner K, Hamm G (1991) Changes in skin pH and resident flora by washing with synthetic detergent preparations at pH 5.5 and 8.5. *J Soc Cosmet Chem* 42: 147-158
69. Berardesca E, Distanto F, Vignoli GP, Oresajo C, Green B (1997) Alpha hydroxyacids modulate stratum corneum barrier function. *Br J Dermatol* 137: 934-938.
70. US Food and Drug Administration. Guidance for Industry: Labeling for Cosmetics Containing Alpha Hydroxy Acids.
71. Bernstein EF, Brown DB, Schwartz MD, Kaidbey K, Ksenzenko SM (2004) The polyhydroxy acid gluconolactone protects against ultraviolet radiation in an in vitro model of cutaneous photoaging. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al.* 30: 189-195
72. Patzelt A, Lademann J, Richter H (2012) In vivo investigations on the penetration of various oils and their influence on the skin barrier. *Skin Res Technol Off J Int Soc Bioeng Skin ISBS Int Soc Digit Imaging Skin ISDIS Int Soc Skin Imaging ISSI* 18: 364-369. doi:10.1111/j.1600-0846.2011.00578.x.
73. Jugdaohsingh R (2007) Silicon and bone health. *J Nutr Health Aging* 11: 99-110.
74. Bélanger MC, Marois Y (2001) Hemocompatibility, biocompatibility, inflammatory and in vivo studies of primary reference materials low-density polyethylene and polydimethylsiloxane: a review. *J Biomed Mater Res* 58: 467-477
75. Dospinescu P, Jones GT, Basu N (2013) Environmental risk factors in systemic sclerosis. *Curr Opin Rheumatol* 25: 179-183.
76. Schmutz JL, Trechot P (2013) [Psoriasisform eruption and silicone injection in a male HIV patient]. *Ann Dermatol Venereol* 140: 494.
77. Petry T, Bosch A, Coste X, Dupuis V, Eigler D et al. (2012) An assessment of the skin sensitisation hazard of a group of polyfunctional silicones using a weight of evidence approach. *Regul Toxicol Pharmacol RTP* 64: 305-314. doi:10.1016/j.yrtph.2012.08.021.
78. Chen Y-C, Chen M-L, Chiu Y-M (2011) A case of mimicking angioedema: chin silicone granulomatous reaction spreading all over the face after receiving liquid silicone injection forty years previously. *Chin Med J (Engl)* 124: 1747-1750
79. Oprea ML, Schnöring H, Sachweh JS, Ott H, Biertz J, et al. (2009) Allergy to pacemaker silicone compounds: recognition and surgical management. *Ann Thorac Surg* 87: 1275-1277.
80. Rubio A, Ponvert C, Goulet O, Scheinmann P, de Blic J (2009) Allergic and nonallergic hypersensitivity reactions to silicone: a report of one case. *Allergy* 64: 1555.
81. Williams PJ, King C, Arslanian V (2012) Allergic contact dermatitis caused by a cell phone cover. *Australas J Dermatol* 53: 76-77.
82. Yuan Y, Lee TR. Contact angle and wetting properties. In: *Surface Science Techniques*. Springer; 2013:3-34
83. Ray BR, Bartell FE (1953) Hysteresis of contact angle of water on paraffin. Effect of surface roughness and of purity of paraffin. *J Colloid Sci* 8: 214-223. doi:10.1016/0095-8522(53)90040-3
84. Noll W. *Chemistry and Technology of Silicones*. Elsevier; 1968.
85. Paraffin wax (8002-74-2).
86. Material: PDMS (polydimethylsiloxane)
87. Seager SL, Slabaugh M. Alkane reactions. *Chem Today Gen Org Biochem*.364.
88. Pennick G, Harrison S, Jones D, Rawlings AV (2010) Superior effect of isostearyl isostearate on improvement in stratum corneum water permeability barrier function as examined by the plastic occlusion stress test. *Int J Cosmet Sci* 32: 304-312. doi:10.1111/j.1468-2494.2010.00604.x.
89. Pennick G, Chavan B, Summers B, Rawlings AV (2012) The effect of an amphiphilic self-assembled lipid lamellar phase on the relief of dry skin. *Int J Cosmet Sci* 34: 567-574.
90. Forslind B, Werner-Linde Y, Lindberg M, Pallon J (1999) Elemental analysis mirrors epidermal differentiation. *Acta Derm Venereol* 79: 12-17.
91. Lee SH, Elias PM, Feingold KR, Mauro T (1994) A role for ions in barrier recovery after acute perturbation. *J Invest Dermatol* 102: 976-979.
92. Simon M, Jonca N, Guerrin M, Haftek M, Bernard D, et al. (2001) Refined characterization of corneodesmosin proteolysis during terminal differentiation of human epidermis and its relationship to desquamation. *J Biol Chem* 276: 20292-20299.
93. Landeck L, Visser M, Skudlik C, Brans R, Kezic S, et al. (2014) No remarkable differences in rates of sensitization to common type I and IV allergens between FLG loss-of-function mutation carriers and wild-type subjects. *Contact Dermatitis* 70: 27-34.

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94. Landeck L, Schalock P, Baden L, González E (2011) Contact sensitization pattern in 172 atopic subjects. *Int J Dermatol* 50: 806-810.
95. Heine G, Schnuch A, Uter W, Worm M, Information Network of Departments of Dermatology (IVDK), German Contact Dermatitis Research Group (DKG) (2006) Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). *Allergy*. 61: 611-616. doi:[10.1111/j.1398-9995.2006.01029.x](https://doi.org/10.1111/j.1398-9995.2006.01029.x).
96. Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R (2011) The most important contact sensitizers in Polish children and adolescents with atopy and chronic recurrent eczema as detected with the extended European Baseline Series. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol*. 22: 252-256. doi:[10.1111/j.1399-3038.2010.01075.x](https://doi.org/10.1111/j.1399-3038.2010.01075.x).
97. Schena D, Papagrigoraki A, Tessari G, Peroni A, Sabbadini C, et al. (2012) Allergic contact dermatitis in children with and without atopic dermatitis. *Dermatitis* 23: 275-280.