# Skin care products can aggravate epidermal function: studies in a murine model suggest a pathogenic role in sensitive skin

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## Summary

**Background.** Sensitive skin is defined as a spectrum of unpleasant sensations in response to a variety of stimuli. However, only some skin care products provoke cutaneous symptoms in individuals with sensitive skin. Hence, it would be useful to identify products that could provoke cutaneous symptoms in individuals with sensitive skin.

**Objective.** To assess whether vehicles, as well as certain branded skin care products, can alter epidermal function following topical applications to normal mouse skin.

**Methods.** Following topical applications of individual vehicle or skin care product to C57BL/6J mice twice daily for 4 days, transepidermal water loss (TEWL) rates, stratum corneum (SC) hydration and skin surface pH were measured on treated versus untreated mouse skin with an MPA5 device and pH 900 pH meter.

**Results.** Our results show that all tested products induced abnormalities in epidermal functions of varying severity, including elevations in TEWL and skin surface pH, and reduced SC hydration.

**Conclusions.** Our results suggest that mice can serve as a predictive model that could be used to evaluate the potential safety of skin care products in humans with sensitive skin.

**Key words:** adverse reactions; barrier function; contact dermatitis; epidermal function; hydration; pH; sensitive skin; skin care products.

Sensitive skin is defined as an occurrence of unpleasant sensations in response to a variety of stimuli that do not provoke comparable sensations in otherwise normal individuals (1). Clinical symptoms of sensitive skin include itching, stinging, burning, erythema, and dryness (2–6), and physiological signs of dysfunction include elevations in transepidermal water loss (TEWL) rates and skin surface pH, as well as decreased stratum corneum (SC) hydration (7). The prevalence of sensitive skin can be as high as 90% (8), with a higher frequency in females than in males (9–11), and it can negatively impact on the quality of patients' lives both physically and psychologically (11, 12). Although > 60% of subjects with a history of sensitive skin report sensitivity to certain skin care products, the development of these problems is usually attributed to a number of other factors, including environmental changes (wind, temperature, sun and humidity) and/or changes in psychological conditions, sex, age, ethnicity and a prior history of skin diseases, such as psoriasis and atopic dermatitis (2–7, 13).

Although the pathomechanisms of cutaneous symptoms in subjects with sensitive skin are not clear, a line of evidence points to the role of epidermal dysfunction in the development of cutaneous symptoms. First, there is a

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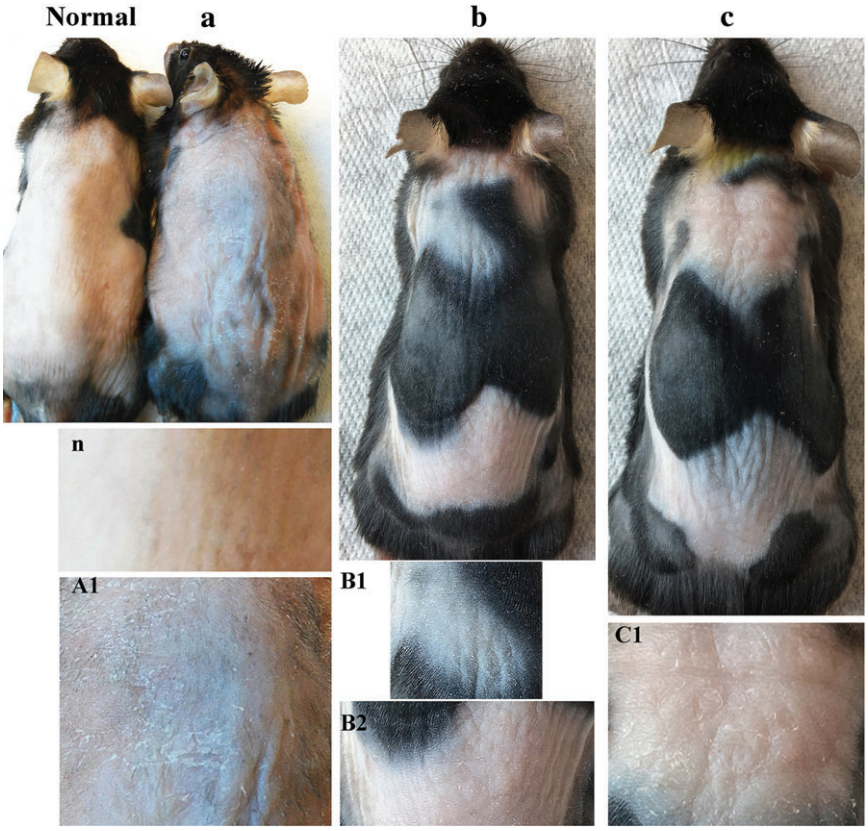


**Fig. 1**. Topical applications of in-house-prepared vehicles irritate mouse skin. Both flanks of 14-week-old mice were treated topically with the respective vehicle twice daily for 4 days. Untreated normal mice served as controls. Pictures were taken on day 5. **(a)** In-house vehicle A-treated mouse; (n) shows a higher magnification of normal mouse skin, and (A1) is in-house vehicle A-treated mouse skin at a higher magnification. **(b)** In-house vehicle B-treated mouse; (B1) and (B2) are in-house vehicle B-treated mouse skin at a higher magnification. **(c)** In-house vehicle C-treated mouse; (C1) in-house vehicle C-treated mouse skin at a higher magnification.

higher prevalence of sensitive skin in subjects with skin disorders that are known to be accompanied by altered epidermal permeability barrier function, such as atopic dermatitis, psoriasis, acne, and/or a prior history of atopic dermatitis (5, 9, 14, 15). Second, improvements in epidermal permeability barrier function alleviate cutaneous symptoms and reduce lactic acid stinging test scores in subjects with sensitive skin (16–18). Third, lactic acid stinging test scores correlate positively with TEWL (19). Together, these observations suggest that the development of cutaneous symptoms in subjects with sensitive skin could be attributable, at least in part, to an underlying skin condition. Therefore, it is generally assumed that it is the patient's suboptimal skin condition, rather than topical skin care products, that account for the development or exacerbation of cutaneous symptoms. However, not all skin care products trigger cutaneous symptoms in subjects with sensitive skin, and nor are subjects with sensitive skin necessarily sensitive to all skin care products.

We hypothesized that the cutaneous symptoms in individuals with sensitive skin could be attributable to the use of potentially unsuitable skin care products. Although skin care products can cause few or no adverse reactions in normal human skin, they could still provoke cutaneous symptoms in subjects with sensitive skin. Accordingly, in the present study, we assessed the impact of several vehicles and branded skin care products on epidermal functions in normal mice, whose skin is more permeable than human skin (20, 21). This model could serve as a useful analogue of sensitive skin in humans.

## Materials and Methods

### Materials

Female C57BL/6J mice aged 10–14 weeks were purchased from Jackson Laboratory (Bar Harbor, MA, USA), and fed with mouse diet (Ralston-Purina, St Louis, MO, USA) and water *ad libitum*. Vehicles that were either commercially available, or made in-house and widely used, were gifted by the respective companies. Skin care products were purchased from a local department store. According to the label, product A was claimed to benefit 'dry and damaged skin', whereas product B was designed for 'hypersensitive and irritable skin'. Product C was recommended for application to 'very dry sensitive and irritated skin'. All vehicles and skin care products were used in original formulations, except for commercial vehicle B, which was used at a 10% concentration in aq.

Ingredients in vehicles and skin care products are listed in Table S1.

### Experimental protocols and functional studies

All animal procedures were approved by the Animal Studies Subcommittee (IACUC) of the San Francisco Veterans Administration Medical Center, and performed in accordance with their guidelines. Twenty four hours prior to experiments, both flanks of mice were shaved with an electric clipper, and then with an electric shaver (Remington WDF-5000). The respective vehicle or skin care product was applied topically to both flanks of mice twice daily for 4 days. At each time point, ~50 mg of product was spread evenly on an approximately 18–20-$cm^2$ area on the back and flanks of mouse skin with a finger covered with a latex glove. Because there was no visible residue of the product on the skin by the time of the second application, no washing or rinsing of mouse skin was performed prior to subsequent applications. Untreated normal mice served as control. On day 5, 18 h after the last vehicle or skin care product application, basal SC biophysical properties were assessed by measuring TEWL rates and SC hydration with respective probes (TM300 for TEWL and CM825 for hydration) connected to an MPA5 device (Courage & Khazaka, Cologne, Germany) (22). A pH 900 pH meter was used to measure skin surface pH (Courage & Khazaka) (22). Data are presented as percentage change from untreated normal controls, according to the formula: (treated – untreated normal controls)/untreated normal controls × 100.

### Statistics

GRAPHPAD PRISM 4 software was used for all statistical analyses. The Mann–Whitney test was used for comparisons between two groups. One-way ANOVA with Tukey's multiple comparison *post hoc* test was used to determine the differences between three or more groups. Data are expressed as mean ± standard error of the mean.

## Results

We first assessed the effect of in-house-prepared vehicles, as used in numerous skin care products, on epidermal functions in mice. After 1 day of treatment with the vehicle, erythema appeared on the mouse skin. After 4 days of treatment, mouse skin became dry, scaling, and rough (Fig. 1). In parallel with these macroscopic changes, significant increases in both TEWL rates and skin surface pH were observed following 4 days of treatment with topical vehicle (Fig. 2a,b). In parallel, topical

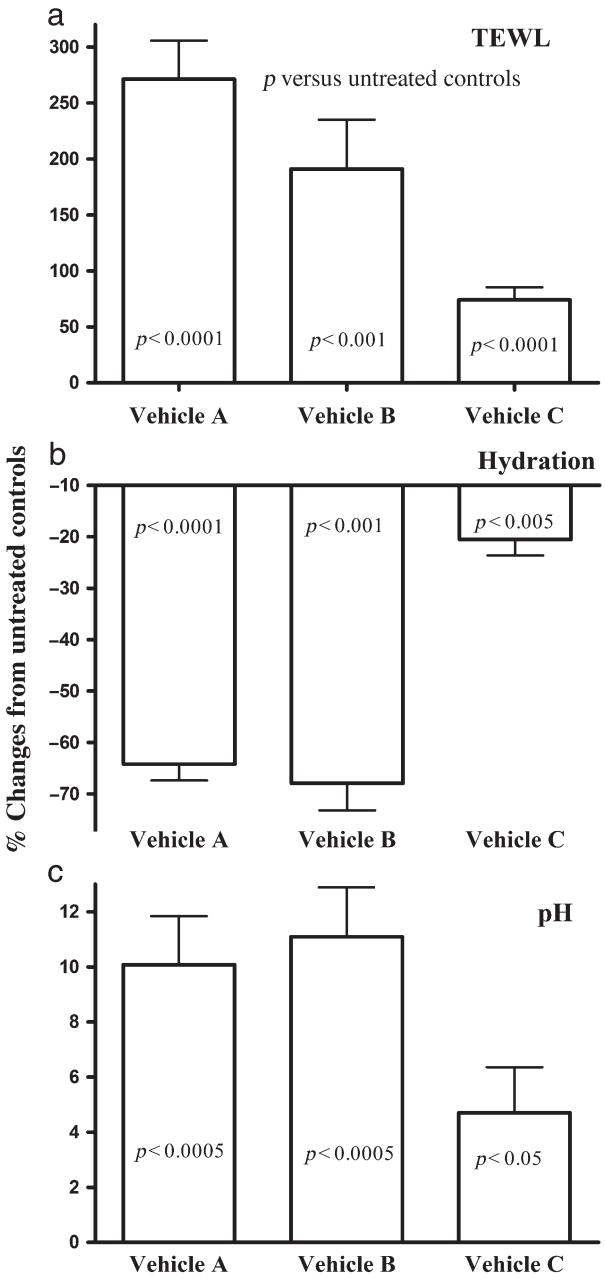


**Fig. 2.** Topical applications of in-house-prepared vehicles compromise epidermal function in mouse skin. Both flanks of 14-week-old mice were treated topically with the respective vehicle or skin care product twice daily for 4 days. Untreated normal mice served as controls. On day 5, 18 h after the last vehicle application, basal stratum corneum biophysical properties were assessed as detailed in Materials and Methods. **(a–c)** Changes in transepidermal water loss (TEWL), stratum corneum hydration, and skin surface pH, respectively. Data are expressed as percentage changes from untreated normal mice. *p*-Values are versus untreated controls. n = 10 for all groups.

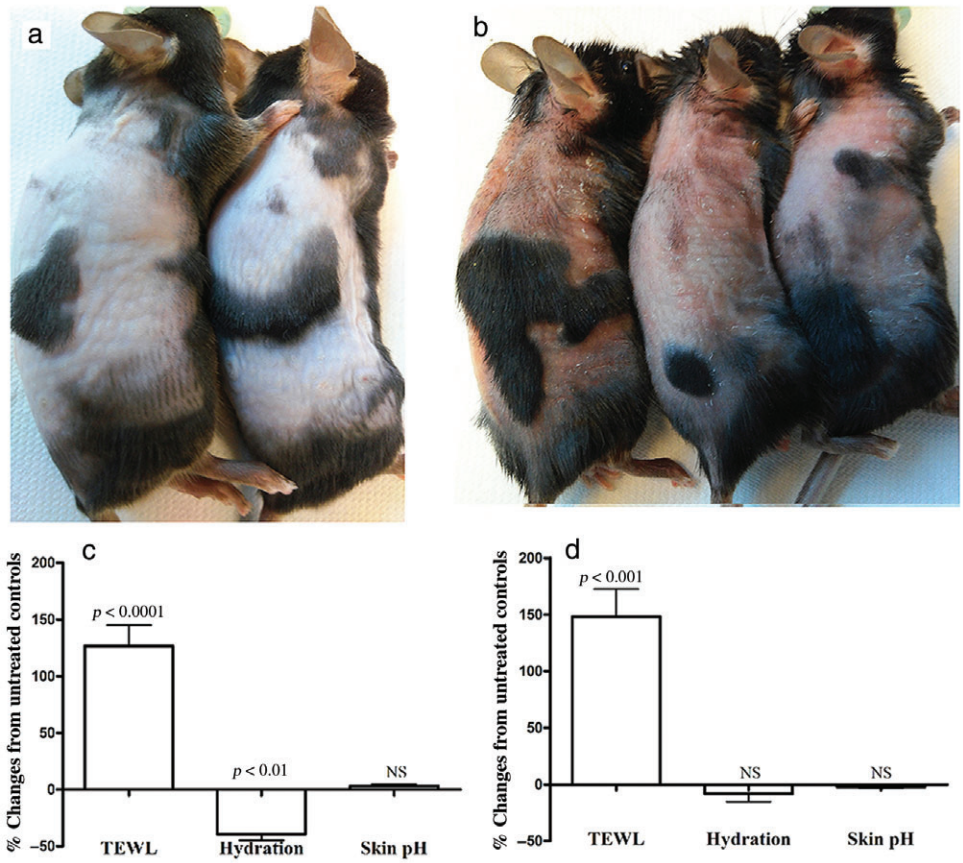


**Fig. 3**. Topical applications of commercial vehicles alter epidermal function in a murine model. Both flanks of 10–12-week-old mice were treated topically with the respective vehicle twice daily for 4 days. Untreated normal mice served as control. On day 5, 18 h after the last vehicle or skin care product application, basal stratum corneum biophysical properties were assessed as detailed in Materials and Methods. **(a, b)** Commercial vehicle A-treated and commercial vehicle B-treated mice, respectively. **(c)** Changes in epidermal function following 4-day treatments with commercial vehicle A. **(d)** Changes in epidermal function in mice treated with commercial vehicle B. Data are expressed as percentage changes from untreated normal mice. *p*-Values are versus untreated controls. n = 10 for vehicle A, and n = 8 for vehicle B. NS, not significant; TEWL, transepidermal water loss.

treatment with these vehicles markedly reduced SC hydration (Fig. 2c). Notably, vehicle C induced less extensive changes in both TEWL rates (Fig. 2a; $p < 0.05$ for vehicle C versus both vehicle A and vehicle B) and SC hydration (Fig. 1b; $p < 0.001$ for vehicle C versus both vehicle A and vehicle B). Similarly, vehicle C also induced significantly less extensive changes in skin surface pH than vehicle B (Fig. 2c; $p < 0.05$ for vehicle B versus vehicle C). These results show that commonly used in-house-prepared vehicles alter epidermal functions in mice. Because all three in-house-prepared vehicles caused adverse reactions, we next determined whether commercial vehicles also negatively affect epidermal functions in mice. Indeed, both tested commercial vehicles also induced severe irritation in mouse skin (Fig. 3a,b). Again, these macroscopic changes were accompanied by striking increases in TEWL rates (Fig. 3c,d). Vehicle A also dramatically reduced SC hydration (Fig. 3c). However, in contrast to the in-house-prepared vehicles, neither of these commercial vehicles significantly altered skin surface pH (Fig. 3c,d). Together, these results show that vehicles in skin care products can cause adverse reactions in mouse skin, which is a model for sensitive skin.

Although skin care products generally undergo rigorous safety testing before being placed on the market, > 60% of subjects with sensitive skin still experience cutaneous symptoms after applications of skin care products (12, 13), suggesting that at least some skin care products are not safe for these individuals. We next evaluated the changes in epidermal functions in mice following 4 days of topical treatment with several branded skin care products that have been claimed to benefit human

skin. As seen in Fig. 4a–c, all three of the tested skin care products caused severe skin scaling and dryness, accompanied by a marked increase in skin surface pH (Fig. 4f), whereas SC hydration declined significantly (Fig. 4e). Among these three tested products, product A appeared to induce more profound alterations in epidermal functions (Fig. 4d–f). Although Product C induced only an approximately 6% increase in skin surface pH (Fig. 4f), this still amounted to a substantial increase in pH (~0.4 pH units over normal controls). Moreover, treated mouse skin became rough after 4 days of treatment with these products (Fig 4a1–c1). Collectively, these results indicate that certain widely used skin care products, marketed for supposed beneficial effects on skin, can cause irritation and alter epidermal functions in mouse skin.

## Discussion

The pathomechanisms of cutaneous symptoms in subjects with sensitive skin have not been well established. However, it is well known that certain skin care products can trigger cutaneous symptoms in these individuals, which are generally attributed to the impaired skin, rather than the skin care products – in view of these products having passed safety tests before being deployed in the marketplace. Indeed, these commercially available products usually appear to be safe when tested in normal human skin, which can better tolerate product-induced perturbations; the adverse effects may become evident only when the individual's skin is sensitive.

Our prior studies clearly showed that topical applications of several branded skin care products, marketed as 'barrier repair' formulations, instead negatively impacted on permeability barrier homeostasis in both inflamed mouse and normal human skin (Figure S1) (23, 24). However, it is not clear which ingredient(s) induce these functional abnormalities. We show here that both commonly deployed vehicles and skin care products induce inflammation, paralleled by abnormalities in epidermal function, including elevations in TEWL rates and skin surface pH, as well as reductions in SC hydration in normal mouse skin, all of which can predispose to the development of cutaneous symptoms in subjects with sensitive skin. Disruption of the epidermal permeability barrier alone stimulates the production and release of proinflammatory cytokines in the epidermis, in addition to inducing dermal inflammation (25–31). Likewise, reductions in SC hydration also induce the release of both cutaneous cytokines and histamine, both of which are mediators of pruritus (32, 33). Moreover, several studies have shown that elevations in SC pH can compromise epidermal permeability barrier homeostasis (34–36), and provoke pruritus via activating type 2 protease activated receptor (37, 38). Furthermore, either reduced SC hydration or permeability barrier disruption induces pruritus in mice (39, 40). Conversely, improvements in epidermal function can prevent/relieve both cutaneous inflammation and pruritus (41–47). Accordingly, improvements in epidermal function alleviate the cutaneous symptoms of sensitive skin (16, 17). Coupled with the fact that epidermal permeability barrier function and cutaneous reactions to irritants in normal individuals are similar to those in individuals with sensitive skin following the treatment of sensitive skin with products containing minimal preservatives and no surfactants (48), skin care products, at least in certain cases, could contribute to the development of cutaneous symptoms of sensitive skin. Accordingly, strategies to improve epidermal function could, in theory, alleviate the propensity to develop cutaneous symptoms in these subjects with sensitive skin. Clearly, improvements in the safety of skin care products would be crucial to reduce the risk of development of cutaneous symptoms of sensitive skin.

Although our results show the potential adverse cutaneous effects of certain skin care products, it is not clear how these products cause adverse reactions. Clearly, one culprit could be the vehicle in which the products is formulated. Certain ingredients can potentially induce abnormal epidermal function and/or inflammation if their concentrations are sufficiently high. For example, jojoba oil, which is enriched in eicosadienoic acid, can increase the production of prostaglandin E2 and tumour necrosis factor-$\alpha$, which are both proinflammatory mediators (49). Similarly, stearic acid, ceteareth 20, PEG-40 castor oil and PEG-100 stearate can induce inflammation (50–53).

Because the maintenance of optimal epidermal permeability barrier function requires a proper ratio of the three key SC lipids, namely cholesterol, fatty acids, and ceramides, excessive amounts, or a lack of any one or more, of these lipids could disturb lipid ratios, thereby compromising permeability barrier function (54, 55). It is important to note that triglycerides and certain vegetable oils (jojoba, borage seed, and sunflower oil) can contribute high amounts of free fatty acid levels to the SC, resulting in alterations in critical lipid ratios, leading to disruption of the epidermal permeability barrier. Regardless of the pathomechanisms responsible for sensitive skin, the results of the present study suggest that caution should be used when skin care products are formulated.

We have shown here that both vehicles and branded skin care products can induce severe adverse reactions in normal mouse skin, which is much thinner (~15 μm)

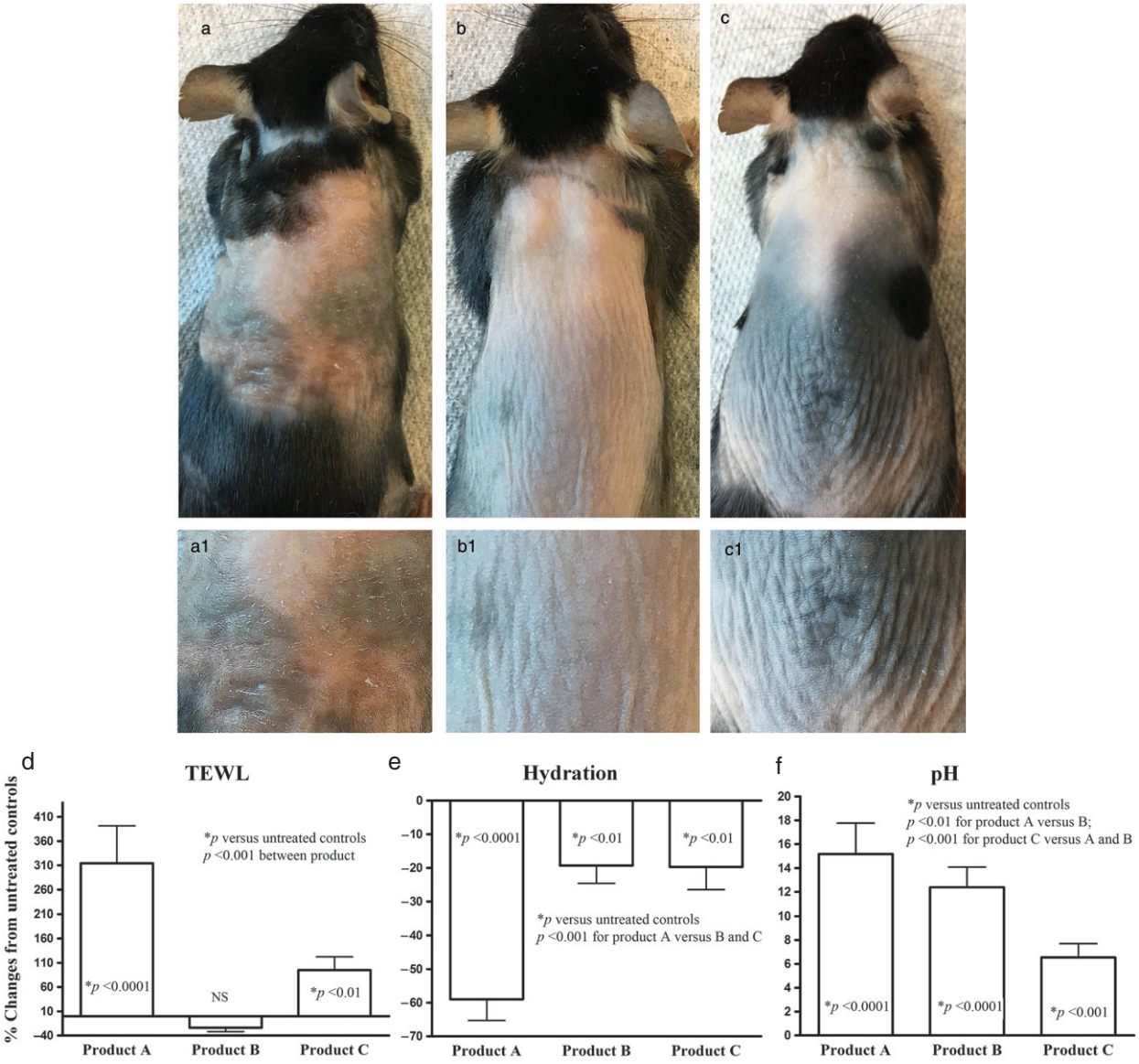


**Fig. 4**. Topical skin care products induce functional abnormalities in murine skin. Both flanks of 10–12-week-old mice were treated topically with the respective product twice daily for 4 days. Untreated normal mice served as controls. On day 5, 18 h after the last vehicle or skin care product application, basal stratum corneum biophysical properties were assessed as detailed in Materials and Methods. **(a–c)** Mice treated with products A–C, respectively; **(a1–c1)** mouse skin treated with products A to C-treated, respectively, at high magnification. **(d)** Changes in transepidermal water loss (TEWL) following 4-day treatments with products. **(e, f)** Changes in stratum corneum hydration and pH, respectively, following 4-day treatments with products. Data are expressed as percentage changes from untreated normal mice. *p*-Values are versus untreated controls. n = 11 for product A, n = 14 for product B, and n = 9 for product C. NS, not significant.

(56) and more permeable (20, 21) than human skin (~ 75–96 μm) (57), making it more susceptible to stimuli than normal human skin. Therefore, depending on regulatory issues related to the testing of such products in animals, mouse skin could serve as a useful model with which to evaluate the safety of over-the-counter skin care products and cosmetics. Our results not only raise safety concerns about skin care products currently on the market, but also point to a potential pathogenic role of skin care products in the development or exacerbation of cutaneous symptoms in subjects with underlying skin disorders, such as atopic dermatitis and other inflammatory dermatoses, characterized by abnormalities in epidermal function.

In summary, the present study shows that both vehicles and branded skin care products can induce adverse reactions in terms of irritation, suggesting a pathogenic role of skin care products in the development of cutaneous symptoms in individuals with irritable skin. As mouse skin is thinner and more sensitive to stimuli, it could serve as a suitable model with which to evaluate the safety of skin care products.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Topical skin care products delay barrier recovery in murine skin. (**a–c**) The negative effects of topical skin care products on permeability barrier homeostasis in inflamed mouse skin. Both flanks of 10–12-week-old hairless mice were treated topically with oxazolone once every other day for 10 days. Eighteen hours after the last oxazolone application, both flanks of mice were tape-stripped until transepidermal water loss rates were at least five times over the baseline, and each product was applied immediately to the taped site once. Transepidermal water loss rates were measured 2 and 4 h after tape-stripping. (**d**) The negative effects of topical skin care products on permeability barrier homeostasis in normal human skin. Nine (aged 22–62 years, 7 females and 2 males) non-atopic human volunteers were enrolled in this study. Creams (n = 3–4subjects each) were applied to 3 × 3-cm areas (of previously untreated skin sites) on the flexural surface of the forearm twice daily for 4 days. Two sites, 12–14 cm apart, were selected on each forearm. Untreated sites on contralateral forearms served as normal controls. On day 5, transepidermal water loss rates were measured with a Tewameter®. Barrier recovery rates were assessed 3 h following barrier disruption by repeated tape-stripping until transepidermal water loss levels were $\geq 5\ mg/cm^2/h$. Data are expressed as mean ± SEM (23, 24).

**Table S1.** Ingredients in vehicles for skin care products and branded skin care products.

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