Part IV

Skin Reactions

38 Sensitive Skin

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38.1 INTRODUCTION: DEFINITION OF SENSITIVE SKIN

Facial moisturizers frequently produce burning, stinging, itching, and suberythematous irritant dermatitis. Rates occasionally proximate 20%. The subjective symptoms are generally described by consumers as "sensitive skin."

The term "sensitive skin" has become ubiquitous in the world of cosmetology in recent years, yet no formal definition exists. Consumers use the term to describe a variety of adverse skin reactions to cosmetics and other topical products, as well as skin reactions triggered by environmental (e.g., temperature, wind, pollution), lifestyle (e.g., stress, emotion, diet), and hormonal factors (e.g., menstrual cycle).[1] This all-encompassing interpretation includes the spectrum of dry skin; oily or acne-prone skin; tendency to flushing; and nonspecific sensations of burning, stinging, and itching. Dermatologists and cosmetic chemists use the term to express both a situation of facial skin hyper-reactivity on contact with a variety of topical agents, as well as the occult dermatoses resulting

from or flaring up with topical applications and other exogenous factors.[1,2] Controversy exists over whether the term is reserved purely for visible hyper-reactive responses or for susceptibility to chemically induced stinging and other such sensations.[1] Contrary to consumer perception, few conventional medical assessments of sensitive skin take hormonal or lifestyle factors into account. Thus, sensitive skin remains an imprecise phenomenon. In broad terms, sensitive skin is largely agreed to be a lay term used by individuals who consider themselves more intolerant of topical preparations and environmental conditions than the general population. The onus on the medical practitioner, then, is not merely to label a patient as having sensitive skin, but to diagnose the underlying condition causing his or her symptoms.

Acne-prone skin is often classified under the sensitive skin category by cosmetic consumers. However, as many dermatologists consider it to be a separate clinical entity, acne-prone skin and acneiform eruptions will not be discussed here.

38.2 EPIDEMIOLOGY

Sensitive skin is largely believed to be a widespread phenomenon. Epidemiological studies have shown that the incidence of self-reported skin sensitivity is 51.4% in women and 38.2% in men. Studies also show that 10% of women and 5.8% of men consider themselves to have very sensitive skin.[3] However, consumer-perceived cutaneous reactions are usually scientifically unconfirmed; self-assessment is not an accurate parameter. Furthermore, estimates of the prevalence or incidence of sensitive skin are problematic as the term "sensitive skin" lacks a consistent definition.

The North American Contact Dermatitis Group has published data on a multicenter study of cosmetic reactions from 1977 to 1983 conducted by dermatologists with a special interest in contact dermatitis.[4,5] They identified patients with cosmetic dermatitis as 5.4% of 13,216 patients with contact dermatitis. Other studies have shown that cosmetic-induced subjective skin discomfort occurred more commonly in individuals with sensitive skin (53%) than in those individuals who did not consider themselves as having sensitive skin (17%).[3] The most frequent cause of cosmetic dermatitis was identified as allergic contact dermatitis, although this may have been a misrepresentation of the population due to the special interests of the dermatologists involved. Irritant dermatitis was thought to be under-reported, as it is a diagnosis of exclusion. We feel that although this study serves to alert physicians and consumers to suspect cosmetic reactions, it does not in any way represent the true prevalence of the problem. Individuals with sensitive skin may not have been identified as many experience sensory reactions with no visible inflammation. Frequently, consumers who experience a reaction to a cosmetic product will merely discontinue use of the suspected item, rather than consult a physician. While this action is certainly adequate in treating the symptoms at hand, it hinders both our ability to quantify the percentage of adverse reactions caused by cosmetics, as well as identification of the ingredients that cause these reactions.

In the previous study, 79% of the patients with cosmetic dermatitis were female and 85% were Caucasian. Correspondingly, in a series of skin reactivity studies, Frosch and Kligman concluded that the typical "hyper-reactor" had the following characteristics: white, fair skin, high susceptibility to sunburn and poor ability to tan (Fitzpatrick phototype I or II), and blond or red hair.[6] These features were most prominent in people of Celtic lineage. Accordingly, dark skin is commonly thought to resist chemical injury better, presumably because erythema is less discernible.[7] However, in light of recent studies, ethnic skin has been found to play a complex role in sensitive skin — this has been reviewed by Berardesca and Maibach.[7] Since ethnicity has been shown to play a role in an individuals skin sensitivity, one might also think that atopy would also contribute to the sensitivity of an individual's skin. Studies have shown that the incidence of atopy is higher in women with sensitive skin (49%) compared to those without sensitive skin (27%); however atopic diathesis does not appear to be a predictive factor for sensitive skin because the incidence of self-perceived sensitive skin was almost equal for atopics (49%) and nonatopics (51%).[3]

38.3 SYMPTOMATOLOGY

Although the differential diagnosis of sensitive skin encompasses a range of possible skin diseases, the types of complaints reported are very similar. Burning, itching, stinging, or a tight feeling (due to associated dry skin) are frequently reported symptoms.[2,8] These symptoms vary in intensity from mild to severe and may be intermittent or continuous throughout the day. Onset or exacerbation of symptoms correlates to application of the offending topical product(s). Clinical signs are usually minimal — even though erythema and edema may be evident, these inflammatory changes are often transient and have no long-term clinical sequelae. The lack of objective signs and overall similarity in clinical symptoms poses a challenge to the clinician's diagnostic acumen.

The face is the most common site for cosmetic reactions, particularly in the eyelid area.[4,5,9] Facial skin is highly permeable, due to a thinner stratum corneum and a greater density of appendages (e.g., sweat glands, hair follicles). Moreover, facial skin contains an elaborate network of sensory nerves. The frequency of cosmetic application is also increased at this body site. Although mild inflammatory changes are often masked on the face, in the event that eruptions do occur, they are readily noticed by the consumer.

38.4 CLASSIFICATION AND ETIOLOGY

Skin reaction to moisturizers and other cosmetic products have a varied differential diagnosis, challenging the clinician's ability to pinpoint the underlying cause. Indeed, sensitive skin is often regarded as a complex multifactorial syndrome, rather than a single entity. Maibach and Engasser coined the term "cosmetic intolerance syndrome" to describe this heterogeneous syndrome, whereby certain susceptible individuals cannot tolerate a wide range of cosmetic products.[9,10]

Fisher coined the term "status cosmeticus," a condition in which every cosmetic product applied to the face produces itching, burning, or stinging, rendering the sufferer incapable of using any cosmetic product.[11] The patient with status cosmeticus typically has a clinically unremarkable presentation. They may have a mild malar erythema with slight edema of the eyelids. Sometimes this is accompanied by a follicular eruption. The mild clinical picture usually contrasts vividly with the patients' bitter complaints of burning or stinging sensations. The history usually includes "sensitivity" to innumerable cosmetics, while patch test and "use" test results using various implicated products will be negative. Status cosmeticus may be considered to be at the extreme end of the spectrum of sensitive skin. In practice, the term "status cosmeticus" is only applied to a patient who has undergone a thorough workup and other diagnoses have been excluded.

When dealing with patients with sensitive skin, the following differential diagnoses have to be considered (see Table 38.1), thus permitting a rational approach.

38.4.1 Exogenous Causes

38.4.1.1 Subjective Irritation

Subjective or sensory irritation is defined as chemically induced burning, stinging, or itching sensations without detectable visible or microscopic changes.[2,9] This reaction commonly appears within an hour of application in certain susceptible individuals (known as "stingers") and is usually transient, lasting minutes. Ingredients that cause this reaction may not generally be considered objective irritants and will not cause abnormal responses in nonsusceptible persons (nonstingers). This nonspecific reaction is probably grossly under-reported, due to its transient nature. Furthermore, in specialized skin sites, such as the face and scalp, subtle inflammatory changes are often masked.

Subjective irritation is believed to be the most common cause of sensitive skin and cosmetic reactions.[2] Propylene glycol, butylene glycol, and hydroxy acids are examples of subjective irritants present in modern-day cosmetics.[2,12] Alcohol is also capable of causing subjective irritation, but is

TABLE 38.1
Etiology of Sensitive Skin: Differential Diagnosis[9]

Exogenous	
Subjective irritation	Common; acute onset; burning, stinging, itching within minutes of application
Objective irritation	Common; morphologically difficult to differentiate from ACD, diagnosis by exclusion
Suberythematous irritation	Burning, stinging, itching. Squamometry may show protein abnormality
Allergic contact dermatitis	Uncommon; diagnostic patch test essential
Photoallergic contact dermatitis	Uncommon; diagnosis by photopatch testing
Contact urticaria	Query patient about burning, stinging, itching. Diagnosis by immediate-type testing for wheal-and-flare reaction
Endogenous	
Seborrheic dermatitis	Rosacea Psoriasis
Atopic dermatitis	Common diagnoses, but small percentage have atypical morphology Æ difficult diagnosis
Dysmorphophobia	Rare; diagnosis of exclusion

not commonly known to cause objective irritation, whereas SLS, a strong objective irritant, does not usually cause stinging.[2] This suggests that subjective irritation is not just a mild form of objective irritation.

The precise mechanism of subjective irritation has yet to be determined. Insights concerning the mechanism of subjective irritation may be gleaned from the fact that local anesthetics block the response,[2] and stingers respond more vigorously to vasodilators.[13] The response of sensitive skin individuals was explored more in a study conducted by Issachar et al. This study examined the permeability of a vasodilator, methyl nicotinate, in sensitive and nonsensitive skin individuals specifically looking at its permeability. The study was designed to assess whether the barrier function of the skin is altered in sensitive skin. The study looked at 20 women divided into reactor and nonreactor groups based on their response to 10% aqueous solution of lactic acid. The vasodilatation of methyl nicotinate was measured by a laser Doppler perfusion imager (LDPI) every 5 min for 1 h after the methyl nicotinate was applied. This study revealed a significant difference between the reactor and nonreactor group. Reactors showed a significant increased intensity of response to the methyl nicotinate. This suggests that the correlation between increased penetration of methyl nicotinate and the skin response to lactic acid may be due to the increased penetration of water-soluble chemicals in individuals with sensitive skin.[14] Recent studies utilizing quantitative sensory testing methods, such as the thermal sensory analyzer (TSA), on antiinflammatory agents have provided insight into their action of cutaneous sensation.[15,16] Such studies with sensory irritants and their inhibitors may provide similar insight into the pathophysiology of subjective irritation.[2]

Before confirming a diagnosis of subjective irritation, patients must be patch tested and open tested to exclude allergic contact dermatitis and contact urticaria, respectively. Subclinical contact urticaria, in particular, mimics sensory irritation.

38.4.1.2 Objective Irritation and Nonerythematous Irritation

Objective irritation is defined as nonimmunologically mediated, localized inflammation of the skin, usually resulting from contact with a substance that chemically damages the skin.[2,9] The exact mechanism is unknown, and it is likely that both endogenous and exogenous factors are involved. *In vivo* predictive testing in animals (e.g., modified Draize test, repeated application patch tests,

guinea pig immersion test) and humans (e.g., cumulative irritation assay, chamber scarification test) can detect moderate to strong irritants, allowing manufacturers to eliminate these potential hazards prior to marketing a cosmetic.[17] Mild irritants, however, are more difficult to identify and are sometimes missed. Although irritation normally causes an erythematous reaction, dermatologists may have difficulty identifying low-grade inflammatory changes in the face. Careful examination of the facial area, aided by slight magnification, may be useful in unmasking the diagnosis. Patch testing to rule out allergic contact dermatitis is obligatory. Photoirritation or phototoxicity should also be considered. Some cosmetic products which cause irritant contact dermatitis are soaps and detergents, deodorants and antiperspirants, eye makeup, shampoo, permanent hair-waving products, and moisturizers.[9] It should be noted that many moisturizers contain surfactants and emulsifiers that are cumulative irritants, that is, mild irritants that produce inflammation only after repeated application.[9] This fact is frequently overlooked as moisturizers are commonly used in the treatment and prevention of irritant dermatitis.

Nonerythematous or suberythematous irritation is defined as a state in which the clinical observer sees no abnormality; the patient knows that there is something wrong and may describe it as burning, stinging, or itching. Charbonnier et al. have shown that objective alterations are present and are readily demonstrable by the technique of squamometry.[18] The latter utilizes protein staining and microscopic examination of stratum corneum tape strippings. The greater the protein abnormality, the greater the irritation. This is more discriminating than visual examination and current bioengineering technology.

Management of these patients is difficult as almost any chemical can be an irritant, depending on a host of factors, such as the concentration of the chemical, the mode of exposure, other chemicals in the formulation, and other environmental and constitutional factors.

38.4.1.3 Allergic Contact Dermatitis

Allergic contact dermatitis is dermatitis caused by prior exposure to an allergen leading to specific cell-mediated sensitization. It is classified as delayed-type hypersensitivity, as inflammation develops after a relatively long time interval following the exposure. Clinically, it manifests as a pruritic erythematous eruption, with papules and vesicles at the site of exposure. This is the simplest cause of sensitive skin, in terms of diagnosis and management. Patch testing is the diagnostic gold standard; all the patient's cosmetics and skin care items should be included in the patch testing procedure — it is not sufficient to patch test with the routine series.[9] As the most common cosmetic allergens are fragrances and preservatives, patch testing with the fragrance and preservatives series is imperative.[4,5] Lanolin, a naturally occurring wax emollient, is an uncommon albeit important cause of cosmetic allergy. In 2000, a study published suggested that sensitive skin was actually a subclinical expression of individuals contact allergy to nickel sulfate.[19] Note that many allergenic cosmetics are mild irritants under occlusion — this is a potential cause of false-positive patch test results.

Management of cosmetic allergy is relatively straightforward since the advent of cosmetic ingredient labeling. "Hypoallergenic" formulations of cosmetic products seem to be in vogue at present. Fragrance-free formulations are also available for the fragrance allergic — these are useful, as fragrance allergies are complex and difficult to isolate.

38.4.1.4 Contact Urticaria Syndrome

Most people think that the most common part of sensitive skin is sensory irritation. Contact urticaria syndrome (CUS) comprises a presumably smaller part and is a heterogeneous group of inflammatory reactions characterized by burning, tingling, itching, and a wheal-and-flare response that usually appear within minutes after contact with the eliciting substance.[20] These reactions are transient, disappearing within 24 h, with the majority fading within a few hours. In its more severe forms, generalized

urticaria and extracutaneous manifestations, such as respiratory or gastrointestinal symptoms and even anaphylaxis, may be experienced.[20]

Three mechanisms are implicated in CUS: immunologic (ICU), nonimmunologic (NICU), or uncertain mechanism.[20] ICU is a type I hypersensitivity reaction that is IgE mediated and is associated with atopy. NICU is the more common variety of CUS. NICU due to cosmetics is most commonly caused by fragrances (e.g., cinnamic aldehyde) and preservatives (e.g., benzoic acid and sorbic acid).[2] Parabens have been documented by passive transfer to cause ICU.[21]

Muizzuddin et al. recently studied contact urticaria in an attempt to define sensitive skin objectively.[22] Skin responsiveness was assessed using balsam of Peru, which induces NICU. They found that individuals with self-assessed sensitive skin were more susceptible to NICU. This group was also more susceptible to stinging induced by lactic acid and stratum corneum barrier removal using tape stripping.

Diagnosis of CUS involves a high index of suspicion and appropriate open testing for "immediate" onset lesions. These are easily missed on the face, and careful observation is required.

38.4.1.5 Photosensitivity Reactions

Photosensitivity reactions are adverse cutaneous responses to the synergistic actions of a chemical agent and ultraviolet light.[23] Photosensitivity reactions may be broadly categorized into phototoxic reactions and photoallergic reactions. Phototoxic reactions may be experienced by any individual under appropriate conditions (i.e., appropriate wavelength of ultraviolet radiation and sufficient concentration of phototoxic chemical), while photoallergic reactions are delayed-type immunologic reactions requiring a period of sensitization.[23,24] Photopatch testing is an invaluable diagnostic tool for photoallergic contact dermatitis. This is a modification of the basic patch test procedure — patch test sites of the suspected substance(s) are applied in duplicate; one site is irradiated with ultraviolet light, and the results are compared to the nonirradiated site. A stronger reaction in the irradiated site suggests photoallergy.

Cosmetic products that are photoallergenic include fragrances, such as musk ambrette and 6-methylcoumarin, and sunscreens (e.g., para-aminobenzoic acid and its derivatives, benzophenones, dibenzoylmethanes).[17] Oil of bergamot, previously a popular ingredient in fragrances, has now been eliminated from most perfumes due to its phototoxic properties.[24]

38.4.2 Endogenous Causes

These include atypical or subtle manifestations of dermatologic conditions such as seborrheic dermatitis, rosacea, psoriasis, atopic dermatitis, and ichthyosis. Classic manifestations of such diseases are diagnosed with relative ease. However, diagnostic difficulty arises in the presence of atypical morphology, lesions masked by topical therapy (e.g., corticosteroids), or exacerbations due to other topical agents (e.g., skin care products).[2,10]

A thorough clinical review sometimes directs the clinician to the correct diagnosis. In other cases, time is required for other stigmata to surface. Appropriate diagnostic testing and a prolonged cosmetic elimination program should be implemented in the first instance, but if all else fails, therapeutic trials may be indicated. Topical corticosteroids may sometimes prove useful to break a cycle of cosmetic intolerance syndrome.[10]

Another factor to consider is that patients with endogenous skin disease are frequently more susceptible to cosmetic reactions. One reason is that patients with preexisting skin disease may have skin barrier dysfunction, with consequent increased permeability. Skin hyper-reactivity in atopic patients, particularly, has been gathering interest in recent years. Epidemiologic associations between atopic dermatitis and irritant dermatitis are now supported by skin bioengineering data.[25]

Certain substances have been reported to affect eczematous skin, but not normal skin. One example is parabens, a popular preservative that may sensitize eczematous skin, but rarely causes

reactions in normal skin.[17] Fisher has termed this phenomenon the "paraben paradox."[11] Likewise, lanolin, a popular emollient, is an important sensitizer when applied to eczematous eruptions, particularly stasis dermatitis, but rarely affects individuals with normal skin.[17]

38.4.3 Dermatologic Nondisease

Cotterill used the term "dermatologic nondisease" to describe a group of patients who presented with significant skin symptomatology, but no significant objective skin pathology on examination.[26,27] In his experience, the majority of patients were females and middle-aged people. Burning, itching, or discomfort were the most frequent complaints, and these were most often experienced in the face, scalp, and perineum. Other features that may be present include a preoccupation with imagined excessive facial hair, imagined excessive hair loss, and orodynia. Cotterill found that these patients were commonly depressed, sometimes with suicidal ideation, and often suffered from dysmorphophobia or a disturbed psychological body image. Management of these patients is a delicate matter, as they often react badly to referral to a psychiatrist. These patients also largely fail to respond to any topical or oral therapy, and a placebo response is never seen. When associated with depression, systemic antidepressant treatment may be attempted, but is generally ineffective.

38.5 DIAGNOSTIC TESTS FOR SENSITIVE SKIN

Measurement of differences in skin reactivity or "sensitivity" among individuals plays an important role in the workplace, as well as in the manufacture of safe topical therapeutics and cosmetics. Outlined in the following sections are objective and subjective methods of quantifying the reactivity of human skin to chemicals, which are potential irritants.[6] The experimental basis of such testing is to quantify the differences among individuals to chemicals that produce characteristic responses using a standard reproducible procedure. Individuals classified as hyper-reactors (sensitive skin) and hyporeactors can then be identified.

38.5.1 Objective Methods

1. Ammonium hydroxide blistering time[6] — This test measures the permeability of the stratum corneum barrier, the rationale being that the time taken to raise a blister is a function of the number of cell layers in the horny layer. An aqueous dilution of concentrated ammonium hydroxide is placed in a small plastic well, which is subsequently covered with a glass slip. Careful observation using a magnifying lens is then carried out until a tense blister forms in the well. Tiny vesicles initially appear, and formation of a full blister usually takes a few minutes; the time taken for the full blister to form is known as minimal blistering time (MBT). Lower values of MBT correspond to skin that is more reactive.
2. Dimethyl sulfoxide (DMSO) test[6] — This test measures the diffusional resistance of the horny layer. Equal quantities of three different concentrations of DMSO are applied to three plastic wells for 5 min. DMSO provokes wheeling in human skin. The wheals are scored 10 min after removal of the test fluid using a scale. Individuals with high reactivity are those susceptible to wheeling with the lowest concentration of DMSO.
3. Sodium lauryl sulfate (SLS) test[6] — The SLS attacks the horny layer, making it more penetrable to chemicals and also causing inflammation. Thus, it measures both the horny layer barrier and tissue reactivity to toxic substances. Aluminum chambers are filled with 0.1 ml of 1 and 2.5% aqueous solutions of SLS. The chambers are then applied to the ventral forearm for 24 h. The reactions are scored 3 h after removal of the chambers on a scale. Those reacting strongly to the lower concentration of SLS are deemed more reactive or sensitive.

38.5.2 Subjective Methods

Subjective responses are nerve-mediated sensory responses such as burning, stinging, itching, or pain that may be experienced in varying intensities, but do not induce visible changes that can be perceived by an outside observer. Semiquantitative methods of assessment have been devised to measure such responses.

1. Chloroform–methanol pain threshold[6] — A 0.1 ml solution of equal parts chloroform and methanol (CM) is placed in a plastic well. This mixture rapidly induces sharp pain. As soon as the subject perceives this pain, the fluid is removed and the elapsed time is recorded. Highly sensitive individuals experience pain induced by CM more rapidly than less sensitive individuals.
2. Lactic acid sting test[6] — This test, devised by Frosch and Kligman in 1977,[28] utilizes the subjective irritant, lactic acid, and remains the most popular test for subjective irritation. Lactic acid, as well as a number of other substances, will induce a sharp stinging sensation without overt inflammation in a number of susceptible individuals, known as stingers. Stinging potential of a substance is not strictly related to its objective irritancy. The subject is placed in a hot, humid environmental chamber until profuse sweating is achieved. Then a 5% solution of lactic acid is rubbed over the nasolabial folds and cheeks with a cotton-tipped applicator. The stinging sensation is scored on a scale at 10 sec, 2.5 min, and 5 min.

The methods for assessing reactivity previously outlined are simple, convenient, inexpensive, and noninvasive or minimally invasive.[6] However, cutaneous reactivity depends on many factors. None of the previous methods give a full picture of the characteristics of sensitive skin, only susceptibility of skin to irritants. Subtle manifestations of endogenous cutaneous conditions must still be clinically excluded. Exclusion of allergic contact dermatitis must still be performed by patch testing, exclusion of contact urticaria by open tests or PUT/ROAT, and exclusion of photoallergy by photopatch testing.

One experiment conducted by Giacomoni et al. used the lactic acid sting test on two different cohorts divided into a sensitive and nonsensitive skin group. Volunteers were asked to grade the intensity of their irritation as nil, mild, moderate, or severe (scored as 0, 1, 2, or 3). For more than 80% of the nonsensitive skin volunteers, the score of intensity was a 0 or 1. In the sensitive skin group, 75% of volunteers scored their intensity as a 2 or above 2.[30]

38.6 PATHOPHYSIOLOGY

As the definition of sensitive skin is controversial and its etiology is thought to be heterogeneous, it follows that the pathophysiology of sensitive skin is thus far incompletely defined and probably embraces an array of mechanisms. Clinical manifestations such as contact dermatitis in a hyper-reactor probably have the same mechanisms as in a "normal" person with the same dermatoses. However, some general features causing enhanced reactivity have been identified in individuals with sensitive skin. Increased susceptibility to irritation from exogenous substances may be due to inherent structural features of the skin, for instance, hyper-reactors may have a thinner stratum corneum with a reduced corneocyte area,[31] thus allowing a higher transcutaneous penetration of water-soluble chemicals.[32] A heightened neurosensory input in subjects with sensitive skin, corresponding to an augmented response to cutaneous stimulation, may also lower the threshold to irritant stimuli.[33] Release of a different makeup of inflammatory mediators, which may alter the inflammatory response, has also been implicated in individuals with sensitive skin.[34]

Evidence to support the idea that sensitive skin has a thinner stratum corneum is an experiment using stripping and TEWL. Stripping of the stratum corneum was done by the application of sticky tape and its removal. Sticky tape was applied and removed, taking the upper layers of the stratum corneum. Each time this was done, the TEWL was measured. The average number of tape

strippings necessary for doubling the TEWL was about 10 for sensitive skin while it took about 20 for nonsensitive skin.[30]

One study examining the inflammatory mediators revealed that compared with normal skin, prostaglandin E_2 was increased approximately 3.8-fold ($p < .0002$) in sensitive skin compared to normal skin. Leukotriene B_4 and interleukin-1* showed no differences between normal and sensitive skin individuals.[35] Progress has been made in establishing the pathophysiology of sensitive skin; however, a great deal of work remains to be done in this field.

38.7 SKIN BIOENGINEERING AND SENSITIVE SKIN

Studies on sensitive skin are often performed using subjective self-assessment — this naturally yields results of variable reliability. The current trend is striving toward identification of more objective biophysiological measures of skin sensitivity. Today, skin bioengineering studies are employed to investigate the correlation of various biophysiological parameters with skin reactivity, thereby also conveying some insight into its mechanisms.[29] The advantages of bioengineering instruments are that they are quantitative, noninvasive, and detect subtle changes that would otherwise be undetectable to the naked eye.[36] Examples of bioengineering techniques used to evaluate the pathophysiology of skin reactivity include transepidermal water loss (TEWL), skin conductance, resistance, impedance, blood flow velocity, and skin pH (Table 38.2).[17] Descriptions of these methods may be found in the textbooks of Berardesca et al.[37] and Elsner et al.[38]

Determination of basal biophysiological parameters may identify subjects with sensitive skin. Earlier studies have shown that increased skin susceptibility has been correlated with an increased basal TEWL,[39–41] skin surface pH,[42] and fair skin complexion (measured by chromametric L* values),[43] whereas no relationship was shown for basal skin thickness, skin blood flow, sebum excretion, and skin hydration.[29] However, a recent study by Seidenari et al. utilizing multiple bioengineering techniques showed significant correlations only for capacitance and colorimetric a* values.[44]

Individuals with sensitive skin often have associated dry skin. In a recent study of subjects with sensitive hands, no difference in skin hydration was seen macroscopically between normal subjects and sensitive hand subjects (who had self-perceived dry skin). However, measurement with the corneometer confirmed reduced skin surface moisture in the group with sensitive hands, and D-squame analysis showed greater loss of cohesiveness between corneocytes harvested from the

TABLE 38.2
Bioengineering Methods and Biophysiological Parameters in Sensitive Skin Research[30]

Method	Biophysiological parameter
Evaporimetry	Transepidermal water loss (TEWL)
Colorimetry/chromametry (CIE system)	L*: skin reflectance
	a*: red/green axis
	b*: blue/yellow axis
Laser doppler velocimetry	Skin blood flow
Ultrasound	Skin thickness (edema formation)
pH meter	Skin pH
Corneometer (electric capacitance)	Stratum corneum hydration
Sebumeter	Sebum excretion

sensitive hands group.[45] In this study, no correlation was found between sensitive hands and TEWL or skin redness.

The results of the latter two studies described contradict earlier data. Up to this point, an elevated TEWL had been the most widely accepted biophysiological parameter associated with sensitive skin, due to impairment of the skin barrier function or composition. That further studies are imperative to create a consistent and objective operational definition for "sensitive skin" is affirmed by these conflicting results.

38.8 MANAGEMENT OPTIONS

The first step in management is to identify the causative ingredient(s), as well as the causative mechanism, if possible. As sensitive skin is often multifactorial, the approach to the patient should cover the range of differential diagnoses. Thus, starting with a complete history and examination, clues derived from clinical suspicion should aid in devising a plan for diagnostic testing (Table 38.3).

A thorough history for burning, stinging, and itching identifies sensory irritation and possible CUS. The history should include careful questioning of all topical products applied, as well as the time of onset in relation to exposure. Personal and family history of atopy should be actively sought, as should other skin conditions such as psoriasis and rosacea. A meticulous physical examination may identify other stigmata of atopic dermatitis, psoriasis, or other skin disease.

Patch testing (and photopatch testing) should document the few cases due to allergic contact dermatitis. Apart from the routine battery, testing should be performed with the fragrance and preservative series, as well as any cosmetic or skin care product that the patient uses. Immediate-type testing should be performed if indicated by the history. If systemic symptoms were present, perform only in the presence of emergency resuscitative facilities.

If an ingredient is identified as the causative agent, then avoidance of the ingredient is advised. If, however, no substance is identified or the patient reacts to a wide range of substances, then a prolonged cosmetic elimination program may be considered.[9,10] The patient will be barred from using most cosmetic products for a period of 6 to 12 months. For the duration of the cosmetic elimination program, no soaps or detergents or moisturizers are allowed. Glycerin and rose water may function as a substitute for commercial moisturizers. Lip and eye cosmetics may be used freely if no problems are identified in these areas. Face powder may also be used. After the allotted time,

TABLE 38.3
Management of Sensitive Skin[9]

1. Clinical review: history and physical examination
2. Examine every cosmetic and skin care product
3. Patch test and photopatch test — to rule out contact and photocontact allergy
   Immediate-type testing — to rule out contact urticaria
4. Avoid causative ingredient, if identified by testing.
5. Treat any endogenous inflammatory disease.
6. Cosmetic elimination program — 6 to 12 months.
   Avoid all cosmetics apart from:
   - Lip cosmetics
   - Eye cosmetics
   - Face powder
   - Glycerin and rose water

   After 6 to 12 months, gradually reintroduce one product every one to two weeks
7. Be alert to depression and other neuropsychiatric conditions

gradual reintroduction of one cosmetic product will be instituted periodically, for instance, one product every 2 weeks, so that in the end, a simple skin care regime is devised for the patient.

One study conducted by Hawkins et al. looked at the benefits of mild cleansing, moisturizing, and sun protection as a way to improve skin health and quality. In three groups, those with normal skin, sensitive skin, or dermatologist-assessed highly sensitive skin (mostly rosacea with atopic background in some cases) this skin care regiment showed significant improvements in skin health and quality assessed by expert assessments, instrumental evaluations, and subjective self-assessment.[46] Proper skin care may help some individuals with sensitive skin; however, the lack of a control group in this study makes the results vulnerable to interpretation. In another noncontrolled study, it was concluded that adequately formulated cosmetics (sterile preservative, emulsifier, and perfume-free) may reduce both irritation and sensitive skin. It is also felt that this type of cosmetic could also clinically improve dryness, erythema, and stinging.[47]

Another study conducted looking at menopausal women on or without HRT therapy examined the response if the individuals stratum corneum to variations in environmental humidity, either in air or in response to an emollient. Data showed that the baseline stratum corneum hydration is decreased by a low dew point; however, both HRT and emollients improves the functional properties of menopausal women's skin and can counteract some of the deleterious effects of cold and dry weather.[48]

38.8.1 Hypoallergenicity

Because up to 40% of the population claim to possess sensitive skin,[49] numerous cosmetic and skin care items have been formulated to be "hypoallergenic" or literally "reduced allergy." These are products designed for an individual with sensitive skin. Marketing claims for hypoallergenicity are based on objective tests performed on these products, such as the guinea pig maximization test, repeat insult patch test, cumulative irritancy test, chamber scarification test, photopatch test, and facial sting test (lactic acid test), as well as postmarketing surveillance programs.[50] However, no formal criteria exist for evaluation of hypoallergenic products. Draelos and Rietschel demonstrated the ambiguity of the term "hypoallergenicity" in a recent study.[50] Although 75% of dermatologists believed that the concept was relevant to their clinical practice, dermatologist's perceptions of the hypoallergenicity claim was varied. Most believed that hypoallergenicity embodied skin irritation (72.6%) and contact allergy (87.9%), while opinions were divided over subjective irritation (59.8%), contact urticaria (46.4%), photomediated responses (31.5%), and acne (23.4%). A similar ambiguity exists among cosmetic manufacturers: some hypoallergenic products are low in certain allergens, others are low in certain irritants; some are preservative free; some are fragrance free — the diversity is potentially endless. This is an issue that clearly needs to be addressed.

38.8.2 Antiirritants

Goldenberg and Safrin suggested that the sensory effects of topical irritants may be neutralized by "antiirritants."[51] They proposed three possible mechanisms of action of antiirritants: complexing of the irritant, blocking the reactive sites in the skin, and preventing physical contact with the skin. The main antiirritant cosmetic chemicals are imidazole, hydroxy, and carboxyl compounds. Studies of the safety and efficacy of these antiirritants in cosmetics are ongoing.[11]

38.9 SUMMARY

Sensitive skin is not a single entity, but a heterogeneous syndrome, puzzling both consumer and clinician alike. The definition remains obscure, and so it follows that prevalence and pathophysiology are as yet undetermined. Innovative skin bioengineering techniques have opened up new avenues for

sensitive skin research. Such studies are still in their infancy and continue to be published — this will undoubtedly shed new light on the topic.

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39 Stinging and Irritating Substances: Their Identification and Assessment

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CONTENTS

39.1 INTRODUCTION

This chapter explores the assessment of the irritant potential of cosmetic ingredients and products and details a number of methodologies available, chiefly in human volunteers. The practicalities associated with conducting studies using human volunteers are also examined. To try to increase

the practical utility of the material, rather than present a generic review, focus is on the general strategy and methods employed in our own laboratory. It should be made clear at the beginning that all assessments should be made on a case by case basis; the methods are not to be slavishly applied to the safety assessment of all new moisturizers.

There are two main aspects associated with skin irritation, the physical manifestation resulting from damage or perturbation to the skin barrier, for example, erythema and dryness and that which cannot be seen, but is sensory in nature, for example, stinging and itching. Generally, skin irritation is a transient response and once the irritant stimulus has been removed the skin repairs very swiftly and normal condition restored within a few days. Human volunteers are generally used in skin irritation studies on formulated products, but a sound safety assessment must be performed to ensure that there is sufficient knowledge and assurance on the ingredients for the key toxicological endpoints of concern. Testing in humans allows both the physical and sensory aspects of skin irritation to be examined simultaneously in the species of interest; a significant advantage over animal testing.

39.2 REGULATORY REQUIREMENTS FOR TOXICOLOGICAL TESTING

The majority of moisturizers are manufactured with a view to providing cosmetic benefits, chiefly to maintain the skin in good condition and sometimes also to perfume it. The primary objective of cosmetic product safety legislation is to safeguard consumer safety. In the European Economic Community in the 1970s it was evident that there were considerable differences in the requirements amongst the Member States. In 1976, Council Directive 76/768/EEC,[1] on the approximation of the laws of the Member States relating to cosmetic products, introduced harmonized cosmetic safety legislation into the European Community. Article 2 states that "a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use." Article 7a states that "the manufacturer shall take into consideration the general toxicological profile of the ingredient, their chemical structure and their level of exposure."

The directive does not provide any detail about the types of methodologies that may be used to assess the toxicological profile of the ingredient. In this respect, the Commission's Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) guidance notes,[2] provide some assistance on the testing and safety evaluation of cosmetic ingredients. The 7th amendment to the Directive (2003/15/EC),[3] introduced an animal testing ban on finished products and prototypes from September 2004 and on cosmetic ingredients no later than March 2009. The ban covers animal testing for the majority of toxicological endpoints, including skin irritation.

Irrespective of the intended use of a chemical, be it cosmetic or otherwise, European legislation[4] governing the safe use of chemicals requires a "base set" of toxicity data for any chemical.[5] This directive is designed to guarantee adequate protection for humans and the environment against the potential risks of chemical substances. For the endpoint of skin irritation, traditionally the rabbit[6] has been used to determine whether a material should be classified as R38 Irritant. To date, there are no validated *in vitro* methods for the assessment of skin irritation, but for the purposes of making a judgement on the irritant potential of cosmetic ingredients and formulations there are a number of non-animal methods that may be used as part of a tiered testing strategy.

39.3 SOURCES OF SKIN IRRITATION DATA

Before any practical work is carried out, all possible sources of information on skin irritation should be tapped, including manufacturers data on raw materials. However, this is often no more than basic Draize data from a regulatory rabbit study and is unlikely to be of great utility for safety assessment. In addition, the safety assessor must be aware that the skin irritation potential of a formulation is not

a direct summation of the irritation potential of the ingredients. Other sources of information on the skin irritation potential of individual chemicals include the following.

39.3.1 In *Silico* Models

Only a handful of (Quantitative) Structure Activity Relationship ((Q)SAR) models have been developed in recent years to predict the skin irritant potential of chemicals. The most extensive work appears to be that by Enslein[7], other workers have focused on smaller datasets comprising specific chemical classes such as esters, alcohols, or acids. The real predictivity of all these tools is not fully characterized. Further discussion/details have been published elsewhere.[8,9]

DEREK (deductive estimation of risk from existing knowledge) for Windows contains 25 chemical structural alerts associated with skin irritation.

Hazard Expert contains a number of alerts for skin irritation.

TOPKAT comprises 13 QSAR models and data from which these models are derived (rabbit skin irritation). Compounds and data were collected from national and international journals as well as U.S. government sources and total some 1258 compounds. The chemicals are grouped into five class specific models, heteroaromatic and multiple benzenes, alicylics, single benzenes, and two classes of acrylics. Each model applies to a specific class of chemicals and is further subdivided into two or three groups based on severity.

BgVV The BgVV database has been used to develop specific SAR models for predicting skin irritation and corrosion. These models have been incorporated into a decision support system (DSS). The DSS is mainly a rule based approach, the rules being developed are not only based on substructural features but additionally incorporate specific physicochemical properties such as Log P, molecular weight, and aqueous solubility. The rules have been developed and validated on a total of 1508 compounds of which 199 are classified as hazardous. The DSS is designed to predict EU risk phrases.

39.3.2 *In Vitro* Methodologies

There is currently very little information in the literature regarding the mechanisms of skin irritation. Work performed in-house has investigated the genomic and proteomic profiles of known skin irritants (SLS, benzalkonium chloride, and phenol) applied to EpiDerm™ (3D human skin model supplied by MatTek).[10] These investigations have indicated that signaling pathways are upregulated at an early stage upon treatment with an irritant and thus genes within these pathways could be utilized as potential (early) biomarkers. Different irritants upregulated different genes within an individual pathway. Proteomic analysis of the different irritants have indicated that they appear to operate via different mechanisms of action as there were a very limited number of proteins, which were changed with all the irritants.[11,12] These technologies provide a method of obtaining a global view of the changes, which occur within a given cell or tissue making them very useful for investigating mechanisms of action, which could be combined with the use of 3D human skin models and human volunteer studies.

Currently there are a number of 3D human skin models commercially available, for example, EpiDerm™ (MatTek Corporation, USA), EPISKIN™ (EPISKIN SNC, France), and SkinEthic™ (SkinEthic Laboratories, France). These models have been validated (or are undergoing validation) for the identification of potential skin corrosivity of test materials (EU Annex V method B40 and OECD guideline 431).[13] All the manufacturers provide suggested protocols for the identification of skin irritants, but at present there are no *validated* protocols or prediction models for skin irritation. However, an ECVAM skin irritation validation trial, including the EpiDerm™ and EPISKIN™ models, has recently started (completion due end 2005). The protocols being assessed use a short exposure period to test material (15 min), followed by a model-dependent recovery incubation in the absence of test material. An in-house protocol using EpiDerm™ (similar to that being used in the validation trial) was previously identified and the in-house performance assessed by comparison

with the results of human 4 h occluded patch tests. Irritant materials could be identified, but there was over prediction of borderline materials. Although these assays are primarily being examined for hazard identification, they have the potential for looking at potency as dose-responses can be examined. These assays currently rely on cytotoxicity (MTT assay) as the major end-point (although SkinEthic™ recommend morphology and cytokine measurement as well). In future, skin model assays will need to benefit from the identification of more meaningful endpoints (such as may be identified by studies of skin irritation mechanisms described earlier) to enhance their sensitivity. Further development of the skin models to include all relevant cells is also required; the current models consist of a keratinized epidermis only, although MatTek are piloting a so-called full-thickness model with a dermal-like layer containing fibroblasts.

39.4 HUMAN VOLUNTEER TESTS

Prior to embarking on a skin irritation study in the human volunteer, a full safety assessment must be conducted by a suitably qualified and experienced individual on all ingredients and formulations to be tested.[14] This is of paramount importance to safeguard the health of the participating volunteers through avoidance of adverse health effects. The study must also receive the approval from an Ethical Review Committee and the study must be conducted in accordance with the Declaration of Helsinki (1964) and subsequent revisions.[15]

As part of the safety assessment the assessor must consider the chemical structure and all the available information regarding the toxicological profile of the material. The decision to proceed with human testing should only be made if the information available provides sufficient confidence that the volunteer will not be exposed to undue risk. Key toxicological endpoints of concern for moisturizing products include skin corrosivity, percutaneous absorption, genotoxicity, skin sensitization, skin irritation, systemic toxicity, reproductive toxicity, and phototoxicity.

At the very least, to support limited topical exposure, for example, single application patch test in the human, genotoxicity data are required (*and a favourable judgement on the sensitization and corrosive potential of the material*). The following types of study may be performed using human volunteers.

39.4.1 Acute Skin Irritation

Many of the methodologies involve the assessment of visible signs of irritation, for example, erythema and dryness following a short topical exposure to a material. The assessment may be subjective, made by a trained skin assessor, or quantitative using one of the many bioengineering tools available. For example, damage to the stratum corneum may be assessed using a transepidermal water loss (TEWL) meter and skin dryness by measuring electrical capacitance. However, dermatopathological signs may be useful prequels to visible irritation. A number of cytokines (IL-1$\propto$, IL-1RA) and chemokines (IL-8) are upregulated early in skin inflammation. *Cytokine profiling* may therefore be used to gain useful information on the potential of a material to cause skin irritation. Punch biopsy and blister formation techniques may be used to sample skin for inflammatory mediators; however, both are invasive, with the procedures themselves inducing cytokine production. Tape stripping an area of skin previously exposed to test material and extracting cytokines from the tape has also shown upregulation of inflammatory mediators and is a simple, noninvasive procedure.[16]

Metabonomics (the quantitative measurement of time-related responses to stimuli within the body)[17,18] may prove to be of some use to assess the potential of a material to elicit an irritant response following topical application. The concept being that certain stimuli change the metabolite profile in intermediate biochemical pathways. Analysis of body fluids such as urine, saliva, plasma, biopsy material, etc. produces a "fingerprint" of biochemical changes characteristic of the nature or site of a toxic (or other) effect.

The *4 h occluded patch test* was developed in an effort to reduce animal testing and to obtain more relevant acute skin irritation data. The test is designed to evaluate the potential irritancy of undiluted materials such as detergents, as required by the laws governing labelling of such materials. It is based on the four hour rabbit patch test defined by Annex V of the EEC Dangerous Preparations Directive (DPD ref. 88/397/EEC).[19–21] In April 1997, the OECD issued a draft guideline based on this methodology, but it is yet to be accepted.

A small area of the outer surface of the upper arm is exposed to test and control materials under occlusive cover. The test and control materials are applied to round chambers and taped to the arm with surgical tape. A standard irritant (20% sodium dodecyl sulphate [SDS]) is used as the positive control. Each panellist has up to four patches applied, each patch being applied for an increased duration. Due to the potential irritancy of the test materials a cautious approach is used. The first patch is applied for one hour, the second, third, and fourth patches for two, three, and four hours, respectively. Each patch is applied to a different site on consecutive weeks. This approach allows any unexpected or unacceptable reactions to be limited to a minimum.

Any panellist that develops a positive reaction (defined by an in-house scoring system) to any material, is not retreated with that material at the following exposure(s). All other materials are tested for up to 4 h. If the number of skin reactions to the test material is similar or greater than the control material, then this would indicate that the material should be classified as R38-Irritant.

A *covered patch test (*2×23 *h)* may be conducted to generate information on the skin irritant potential of the test material (as a single ingredient or in formulation) against a control material(s), which when appropriate might be a marketed formulation whose acceptability in the market place is well established. Patch testing, the diagnostic version of which dates back to the late 19th century, is a scientific procedure now widely used by dermatologists to identify materials causing allergic contact dermatitis in a patient. The method can also be used in a predictive capacity to investigate the potential of a product or ingredient to cause irritant contact dermatitis. Although there are a number of variations on a general theme, one typical approach uses a small area of the outer surface of the upper arm, which is exposed to test and control materials under occlusive cover. 50 μl of the test or control materials are applied onto chambers mounted on tape and placed on the upper outer arm. A standard irritant, for example, 0.3% sodium dodecyl sulphate is used as the positive control and water as the negative control. For comparative purposes, a product with a similar formulation and with a satisfactory market history is normally included in the test. Twenty-three hours after application the patches are removed. If no significant irritation is apparent, identical and freshly prepared patches are then reapplied to the sites, removed 23 h later and assessed again one hour later for irritation. A further assessment is taken 24 h after this assessment to monitor recovery.

Patch testing is an artificial procedure, which ensures that the product is in close and constant contact with the skin for approximately 48 h and simulates a worse case exposure scenario. Using the information from the patch test on the new product's irritation potential, a risk assessment for the product can be made; this will take into consideration its intended use at realistic levels and times of exposure. Additional tests that more closely simulate the intended use of the product may be required to confirm the risk assessment.

39.4.2 Cumulative Skin Irritation

Simulated use tests

These are conducted to gain information on the cumulative irritancy of a product. This type of test is designed to mirror the intended use of the product, but exposure may also be exaggerated, to provide a greater margin of safety in the risk assessment on the product and also to provide information on problems that may be encountered should the product be misused. Some methods are designed to simulate the normal use of products, with controlled exposure. The skin irritation is monitored and comparisons made between the test and control product in the same panellist. The controls are

usually similar products that are already marketed and have an acceptable market history. A risk assessment can then be made, which can be extrapolated to support the market place.

The *elbow test* involves applying products to the inside of the elbow up to six times per day for three weeks. This is a sensitive area of skin, and easily defined, which is important since this is a self-application test. This test is useful for products such as body lotions, etc., and also as a preliminary to a face test, where the skin is more sensitive. Each panellist serves as their own control; the test material is applied to one elbow and the control material applied to the other. The panel is balanced according to sex, hand dominance, and initial skin grades of reaction. One half of the panel has the dominant hand allocated to the test material, and the other half has their dominant hand allocated to the control material. The levels of irritation elicited by the test and control treatments are compared. Subjective comments are also taken into consideration. At intervals throughout the treatment period, each site is assessed for visible signs of irritation, for example, erythema and dryness.

The *volar forearm* is a fairly sensitive area of the body as it does not receive a great deal of exposure to the sun. Up to three different products can be tested on each arm and are applied up to six times per day for three consecutive weeks, with the sites assessed at regular intervals by trained skin assessors.

In use tests represent a very valuable tool in the assessment armory. Many personal care products are designed for frequent skin contact, often with very sensitive areas of skin (e.g., the face or underarm). Materials such as face creams and deodorants, etc. must therefore be evaluated for their irritation potential to ensure that they are safe for normal use. A use or exaggerated use test provides data on which a safety assessment can be made. A test material is compared with a control, usually a material of similar formulation that is already marketed, and has an acceptable market history. The frequency of exposure may be exaggerated to maximize the sensitivity of the test. For the duration of the test, panellists are provided with test and control materials and a treatment card to record the daily use of each material. The materials issued at the start of the test are weighed before and after the test, so that the amount of material used can be calculated.

Full-face test. A panel of 60 healthy adults is recruited. 20 panellists are provided with the test material, 20 with control material, and 20 act as untreated controls. The 60 panellists are balanced according to sex, hand dominance, and initial skin grades of reaction. Panellists are asked to apply the materials to their forehead, cheeks, nose, chin, and neck after washing at least twice a day for 21 days. The levels of irritation in each of the three panels are compared to assess the irritancy of the test material relative to the control and the untreated groups. Subjective comments are also taken into consideration. At intervals throughout the study, the face is assessed for the standard parameters, primarily for erythema and dryness at six sites (forehead, right cheek, left cheek, nose, chin, and neck). All relevant panellists comments are recorded and considered in the final evaluation.

Half-face test. A panel of 24 healthy adults is recruited. The panel is balanced according to sex, hand dominance, and initial skin grades of reaction. Twelve panellists apply the test material to the right side of the face and 12 apply control to the right side of the face. The test material is applied to one half of the face and neck and the control material is applied to the opposite side of the face and neck at least twice a day for 21 days. The levels of irritation elicited by the test and control treatments are compared to assess the irritancy of the test material relative to the standard. Subjective comments are also taken into consideration. At intervals throughout the study, the face is assessed for the standard parameters, primarily for erythema and dryness at ten sites (left and right sides of the forehead, cheek, nose, chin, and neck). All relevant panellists comments are recorded and considered in the final evaluation.

39.4.3 Sensory Irritation

Cosmetic and detergent-based materials such as face creams, shower gels, deodorants, etc. are specifically designed for frequent skin contact, even to very sensitive areas of the body. An individual may experience a wide variety of skin reactions to a topically applied material. These reactions are not always visible, for example, erythema or dryness and may be subjective reactions such as stinging,

burning, or itching. Visible signs of skin irritation may not always parallel the subjective effects of a material. It is therefore important that the sensory effects of new or modified materials can be assessed to ensure that they are acceptable for use in the market place.

Stinging is a problem that occurs primarily (but not uniquely) on the face, particularly on the nasolabial folds. The extreme sensitivity of this region is a reflection of its microanatomy, including a more permeable horny layer, a high density of sweat glands and hair follicles, and an elaborate network of sensory nerves. The sensory perception test is designed to detect materials, which cause adverse sensory effects (primarily stinging) within minutes of application, and is similar to that described by Frosch and Kligman.[21] The test involves applying small quantities of material to the nasolabial folds and surrounding area. This site is chosen partly due to its sensitivity, but also because any responses obtained almost invariably remain mild and transient, with little or no visual effects. This latter point is of obvious importance when conducting tests on the face.

Individuals are classified as "stingers," "nonstingers," and "inconsistent," according to whether they are consistently sensitive, consistently insensitive, or inconsistently responsive to the application of 10% aqueous lactic acid to the nasolabial fold. A panel of 24 healthy adults are recruited for each test, consisting of approximately eight panellists from each sting category, the males and females being grouped within the categories. The side allocated for application of the test material is then alternated for each panellist, so that half the panel has the test material applied to one side of the nose and the remaining half on the opposite side. Test and control materials are applied once to the nasolabial folds and surrounding area with cotton wool buds (one material to each side of the face). Panellists are asked to wash off the materials with damp tissues 8 min later. At intervals during the 8 min panellists are asked whether they experience stinging or other sensory effects by means of a questionnaire. The visible condition of the application sites is also recorded, along with any spontaneous comments. Panellists are also followed up 24 h later, to check on any effects after the treatment period. The levels of irritation caused by test and control treatments are compared to assess the irritancy of the test material relative to the standard. Subjective comments are also taken into consideration. Stinging reactions are classified on a scale of 0 (none) to 3 (severe). The total of the scores obtained over the test period then provides an indication to whether the material causes stinging in that individual. Subjective effects other than stinging (e.g., itching), along with visual assessments (erythema) are compared.

39.5 PRACTICALITIES ASSOCIATED WITH HUMAN VOLUNTEER TESTING

39.5.1 Study Design

One of the practicalities which must be considered early in designing a study, is the most appropriate size of the panel. Obviously this will impact on the cost of the study, the statistical power of the study, the number of trained staff needed to conduct the study and the time it will take to execute and report the study.

39.5.2 Description of Study/Informed Consent

It is important when recruiting volunteers onto a study that they are fully informed, both verbally and in writing, about what is required of them. They must be provided with information about the product being tested and the methodology being used, and of any possible risks associated with taking part in the study. It is also important that they understand that they may not fulfil the inclusion/exclusion criteria and are ineligible to take part in the study. It must also be made clear to the individual that they are free to withdraw from the study or that they may be withdrawn from the study if they do not adhere to the required schedule/study requirements. Volunteers must confirm their agreement to take part in the study by giving written consent and responding to any questions posed, which may affect panel selection.

39.5.3 Panel Selection

Under the Declaration of Helsinki, when conducting safety testing, one must always consider the health and welfare of the volunteers and ensure the method is designed such that the volunteers health will not be compromised during a study. Part of ensuring that this occurs is at the volunteer selection phase, when it is good practice to complete an initial review of their general health prior to their being accepted onto a study. This information can be gained by asking the volunteers a number of questions, for example, their age, current skin condition, history of skin disease, and details of any medication that they may be taking. Not all medication will necessarily exclude the individual from participating in a study, but it is generally accepted that has taking medication that has an anti-inflammatory effect or may affect the immune system, should not be included in the panel, as the medication could suppress the inflammatory response, thereby producing false negative results. In addition, women that are knowingly pregnant or mothers that are still nursing are also generally excluded, as are individuals wish a known history of allergic or irritant reactivity to similar product types that are already in the market place.

It is also good practice to ensure that volunteers only participate in one study at a time and if they have recently completed another skin irritation study, the skin must be checked to ensure it has returned to normal condition before they are selected for another study (a gap of 1 month is recommended between studies).

39.6 ASSESSMENT OF SKIN IRRITATION

39.6.1 Visual Assessment

Core to all these methodologies to assess skin irritation, is the assessment of visible effects by experienced skin assessors. Erythema and dryness are often the primary parameters for assessment, but other effects, which may be present and can be assessed as individual assessment parameters include wrinkling, glazing, oedema, and vesicles. The grading scheme that is used in-house is shown in Table 39.1. Experienced skin assessors are able to assess these reactions in a highly reproducible fashion[22] and are able to identify very subtle changes in skin reactivity, beyond that which a consumer may see or consider as being of any relevance.

In order to ensure that the visual assessment captures all irritant responses, it may be necessary to record more than one assessment for any given skin site. This is particularly true for use tests, where topical application is likely to cover a large area of skin. The area of application may need to be divided into several discrete sites, which are assessed separately. For example, the axilla may be split into three sites; the “peak” (generally identified as the mounded area in the centre of the axilla, where the majority of hair growth occurs), the “around” (skin around the peak which usually receives some treatment) and the “creases” (creases that are found crossing through the axilla). Treatment may be discontinued due to a reaction (e.g. well-developed erythema) in any of the three sites.

39.6.2 Bioengineering Equipment

There is a number of bioengineering tools used to complement visual assessment, for example, a transepidermal water loss (TEWL) meter can be used to detect early changes in the integrity of the stratum corneum, prior to the mainfestation of readily visible signs of irritation. The readout from bioengineering equipment is quantitative, and the use of these tools is easily transferable between laboratories, whereas visual assessment is subjective and requires an experienced skin assessor to produce accurate, reproducible data. Bioengineering methods commonly used to assess skin irritation include the following.

TABLE 39.1 Description of Grades Used in Skin Condition Assessment

Grade	Erythema (R)	Dryness (D)	Edema (E)	Vesicles (V)	Wrinkling (W)	Glazing (G)
No reactions:						
0	Nothing visible					
1	A marginal reaction that is detectable, but is not sufficient to be classed as "slight"					
Slight reactions						
2	Perceptible erythema	Perceptible dryness	Perceptible swelling	One or two small vesicles	Perceptible surface wrinkling	Perceptible shiny surface
3	A higher grade reaction than another "slight" reaction, which is not sufficient to be classed as "distinct"					
Distinct reactions (obvious to the eye)						
4	Distinct erythema	Distinct dryness	Distinct swelling	Several small vesicles	Distinct surface wrinkling	Distinct shiny surface
5	A higher grade reaction than another "distinct" reaction, which is not sufficient to be classed as "well developed"					
Well-developed reactions (very obvious to the eye)						
6	Well-developed erythema; may extend beyond site	Well-developed dryness with possible flaking	Well-developed swelling; may extend beyond site	Vesicles covering approximately 50% of site	Well-developed defined wrinkling	Well-developed shiny surface with possible cracking
7	A higher grade reaction than another "well-developed" reaction, which is not sufficient to be classed as "strong"					
Strong reactions (outstanding)						
8	Strong, deep erythema; may extend beyond site	Strong dryness with flaking and possible cracking	Strong "blister like" swelling; may extend beyond site	Vesicles covering most or the entire site	Strong deep wrinkling	Strong refractive surface with possible cracking
9	**and above Open ended scale as necessary**					

Each grade of reaction is for the *whole* of the site, **OR** the subsequent grade on *part* of the site, for example, R1 = perceptible erythema on the whole site, or distinct erythema on part of the site. Reactions of 6 and above are considered too great for further treatment.

39.6.2.1 Evaporimeter

The measurement of TEWL is used to evaluate the barrier function of the stratum corneum. TEWL may be assessed using an open chamber system, in which the water vapor pressure gradient produced above the skin surface is measured. This method allows continuous TEWL measurement, as it does not occlude the skin, making it more suitable for the assessment of patch test reactions.[23] Alternatively, a closed chamber system may be used, which estimates TEWL from the gradual increase in relative humidity inside the closed chamber caused by evaporation of water from the skin surface under the chamber.[24] Probably the biggest limitations of most TEWL meters is the need for a temperature and humidity controlled environment and the necessity for the individual to acclimatize for 10 to 15 min prior to taking readings. It should be noted however, that substantial progress is being made to resolve such practical issues associated with the use of this type of equipment.

39.6.2.2 Colorimeter/Erythema Meter

Colorimeters tend to work by measuring the average colour of the skin over a site. Skin contact is necessary for such measurements, however this can cause variation in readings, as the pressure placed on the skin can alter the skin colour, as can the intensity of light at the site being measured. Another factor that should be taken into consideration, is that the colorimeter produces an average color measurement based on the area surrounding the probe, and this could be misleading if the area to be assessed is smaller or composed of different colors. A more sophisticated instrument is the imaging colorimeter that requires no contact with the skin. The combination of imaging and colorimetry provides a more accurate and reproducible measurement.[25]

39.6.2.3 Capacitance

Equipment is available that is based on the capacitance measurement of a dielectric medium. Any change in the dielectric constant due to skin surface hydration verification alters the capacitance of the measuring capacitor.

39.6.2.4 Laser Doppler Perfusion Imaging

This technique involves the creation of a two-dimensional image of skin perfusion. It operates by emitting laser light on to the skin tissue, which upon partial absorption and diffuse scattering, is then reflected with doppler shifted frequencies from blood cells and with unshifted frequencies from stationary tissue. It is a popular method, as it is easy to use and non-invasive, however subjects must refrain from smoking for 4 h prior to measurements and no caffeine intake is permitted 1 h prior to measurements.[26]

Although such tools aid assessment, rarely will they provide data beyond that which can be obtained with thorough visual assessment of the sites at appropriate time points during a study (e.g., no single bioengineering tool is currently more sensitive than visual assessment techniques when conducted by experienced skin assessors, using sensitive scoring schemes).

39.6.3 Interpretation of Results/Evaluation

The results from each study are considered on a case by case basis and the subsequent analysis and interpretation will be dependent on the type of study and the data collected. Generally, data comparison is made between test and control substances. Standard analysis for the majority of skin irritation studies includes a breakdown of the range of assessment grades elicited by each substance tested, a summary of subjective comments and some form of statistical analysis.

39.6.4 Considerations for Statistical Analysis

This must be decided before the study commences, to avoid biasing the interpretation of the results, and to ensure that a suitable number of volunteers are included in the study to provide a sufficiently powerful test.

A common statistical comparison, is between the test material(s) and the control material(s), to detect any differences beyond those that would occur as a consequence of random probability. In general, the smaller the size of the panel, the lower power the test will have, i.e. it will be less likely to identify genuine differences should they exist. Whether this is an issue hinges on the size of difference that the investigator would like to detect, with the optimum panel size determined by the anticipated variability of the results, which may not be known. A pragmatic approach should be taken toward panel size selection, with a sufficient number to allow some meaningful analysis, but that is not unwieldy in terms of running the study or that is prohibitively costly.

39.7 OTHER FACTORS THAT CAN IMPACT ON SKIN IRRITATION

There are numerous factors that can impact on the irritation seen in any given study and it may be necessary to consider these when interpreting results. It is well documented that, particularly in terms of visible skin irritation, reactivity varies according to the skin site, for example, the forearm is known to be more sensitive than the back. This difference is also seen in terms of sensory effects. The influence of the vagus and trigeminal nerves is evident when testing products on the face, as it is much more sensitive than the upper arm or back. Differences in skin physiology between anatomical sites are also known to contribute to differences in skin sensitivity and consequently reactivity. This is perhaps best illustrated in the axilla, which unique, in that it is a partially occluded site, populated with a number of different types of gland (sebaceous, eccrine, and apocrine). Consequently, the irritation profile at this site is often quite complex, with sensory effects, erythema, dryness, and on occasion folliculitis.

It is well documented that seasonal variation produces changes in skin reactivity. Stronger visible reactions are produced during the colder winter months, often increasing the number of pronounced reactions within a panel quite significantly.[27] In contrast, during the summer, skin that is exposed to sunlight is often more robust and therefore generally less reactive to chemical insult. The effects of seasonal variation on reactivity can be interpreted meaningfully by simply including a positive control such as 0.3% Sodium dodecyl sulphate (SDS) to gauge the level of sensitivity. It is also of use to include a marketed control, with a known history of use in the market place, which can be used to benchmark new products.

Age effects are thought to exist, with skin sensitivity becoming less pronounced from 30 years of age. The density of epidermal nerve fibers is also thought to decrease with age.[28]

39.8 IRRITATION TESTING STRATEGY

General strategies for the assessment of skin irritation potential have been available for many years.[29–31] They are rarely absolute, both in the sense that they neither insist on very specific protocols, nor do they generally try to identify the skin effects of a product in isolation. Typically, the approach that is used is to compare a prototype formulation with appropriate benchmarks, which might be a defined dose of a standard irritant such as SDS, or a safely marketed product of the same type (and which for example can be used in a similar manner in an exaggerated use test). Currently, information gained from *in vitro* methods and *in silico* models are sufficient to allow limited exposure in man, that is, a single topical application to a small area of skin, from which a judgement can be made on the irritant potential of the material for use in the internal risk assessment on the material in

formulation. The real problem lies in the fact that unless the material has been proven to be an irritant by a validated QSAR models, or corrosive by a validated *in vitro* method, only *in vivo* methods are accepted by regulatory authorities for the purposes of hazard identification. However, at the moment, there are no validated *in vitro* methodologies to assess skin irritation, although this may change subject to the results of the ECVAM validation trial (due end 2005). There is also a paucity in knowledge surrounding the mechanisms by which materials cause skin irritation. Investment in the following areas may therefore be helpful in developing robust nonanimal alternatives to assess skin irritation:

- Improve the utility of QSARs to accurately predict the skin irritant potential of materials.
- Conduct research into the mechanisms involved in skin irritation across a range of different chemical classes both *in vitro* and in man, using proteomics, genomics, and metabonomics.
- Develop new, robust biomarkers to assess irritation, compare *in vitro* profiles with those *in vivo*.
- Further develop skin models to include all relevant cell types.

39.9 RISK ASSESSMENT

Information on each of these endpoints is used in the risk assessment of the finished product:

$$\text{Risk} = \text{Hazard} \times \text{Exposure},$$

where hazard stands for the inherent property of a material, exposure stands for the consumer contact with hazard and, risk stands for the probability of adverse event in contact with hazard.

In practice, safety assessment of a product potential skin irritative effect considers various factors:

1. Hazard data on the individual ingredients.
2. Dose response data on the individual ingredients.
3. Any historical data on the general formulation type.
4. *In vitro* irritation data on the formulation.
5. Human skin test data on the formulation compared to market benchmarks.
6. Consumer test data (e.g., feedback from efficacy/preference studies).
7. Ongoing monitoring of marketplace feedback.

Normally, sufficient data will be available for point 1, but generally will not be of much value for the safety assessment, particularly since data from point 2 are rarely available. However, since the skin irritating effects of a formulation are a complex function of the ingredients,[32] the most valuable information is derived from the other five points. Of most note are data from point 5, particularly exaggerated exposure studies where a test product is applied to a defined skin site many times a day and is compared to a marketed product known to have an extensive history of safe use. Valuable information often comes also from more extended consumer use tests, perhaps undertaken in a number of locations to allow for differences in use habits. Ultimately it is not possible to do predictive studies (clinical or *in vitro*) which will predict the market place perfectly, particularly low level complaint rates — which means that point 7, monitoring feedback from the market, is always of importance.

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40 Sensitizing Substances

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CONTENTS

40.1 INTRODUCTION

The most important sensitizing culprits in cosmetics, including skin care products, are perfume components, preservative agents, and also certainly excipients and emulsifiers.[1,2] Perfume components have been attracting more attention recently since reactions to them seem to be increasing over the years, and the literature indicates that routine patch testing of markers in addition to the fragrance mix is required to detect fragrance allergy. With preservatives, important shifts in allergenicity have occurred over the years, and their spectrum varies considerably from country to country. With regard to excipients and emulsifiers, many reports have recently appeared in the literature on both moisturizing preparations — also those intended for "sensitive skin" — and lip-care products. Among the other potential cosmetic sensitizers are antioxidants, natural ingredients, such as herbal extracts and vitamins, and also sunscreens, which are nowadays often being added to skin-care products and are responsible mainly for photoallergic contact dermatitis.

40.2 THE NATURE OF COSMETIC ALLERGENS IN MOISTURIZERS

40.2.1 Fragrance Ingredients

Fragrance ingredients are, in general, the most frequent culprits in cosmetic allergies.[2–7] Katsarar et al.,[8] who investigated the results of patch testing over a 12-year period, found an increasing trend in sensitivity to fragrance compounds, which reflects the effectiveness of the advertising of perfumed products. Sensitization is most often induced by highly perfumed products, such as toilet waters, after-shave lotions, and deodorants,[9] but fragrance-containing skin-care products may also cause contact allergic reactions.[1]

The literature confirms that the fragrance mix remains the best screening agent for contact allergy to perfumes because it can detect some 70 to 80% of all perfume allergies.[10,11] However,

the literature also insists on the need to test with additional perfume allergens. Indeed, testing with additional markers, for example, the individual components hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), farnesol, and citral, as well as with complex natural mixtures[12–16] increases the sensitivity of testing. In the near future, a new fragrance mix (II) will be introduced into the standard series.[17] Because of the increasing importance of fragrance allergy and to ensure that sensitized consumers are adequately informed, 26 fragrance components will have to be labeled as cosmetic ingredients on the packaging (Annex 3 of the Cosmetic Directive[18]). Positive patch-test reactions are frequently associated with a fragrance allergy and often indicate the presence of common or cross-reacting ingredients in natural products, the occurrence of cross-reactions between simple fragrance chemicals, or a concomitant sensitivity.

40.2.2 Preservatives

Preservatives are important allergens in skin-care products alongside cleansers and makeup.[1,2] However, within this class, important shifts have occurred over the years.[2,19] The methyl (chloro)isothiazolinone mixture was commonly used in the 1980s and was then a frequent cause of contact allergies. This frequency has declined considerably in recent years.[4] Since then, formaldehyde and its releasers, particularly methyldibromo glutaronitrile — as used in a mixture with phenoxyethanol, better known as Euxyl K400 — did gain importance in this regard,[1,2,4,19–22] although the frequency of positive reactions observed seems to be influenced by the patch-test concentration.[21,22] Both the methyl(chloro)isothiazolinone and methyldibromo glutaronitrile mixtures are now recommended to be used only in rinse-off products, and they still can be found in some of the leave on products in the market.

The spectrum of the allergenic preservatives also varies from country to country. For example, in contrast to continental Europe where reactions to the methyl(chloro)-isothiazolinone mixture and more recently methyldibromo glutaronitrile have been the most frequent,[2,4,5,19,23] formaldehyde and its releasers have always been much more important, particularly as concerns quaternium-15[2] in the United Kingdom, although its incidence seems to have slightly declined recently.[24] Parabens are rare causes of cosmetic dermatitis. When a paraben allergy does occur, the sensitization source is most often a topical pharmaceutical product, although its presence in other products can be sensitizing as well.[1,25] This is often the case also for other ingredients, such as chlorphenesin,[26] which cross-reacts with mephenesin, which is used in pharmaceuticals. Another recently introduced preservative is iodopropynyl butylcarbamate, which was first reported as a cosmetic allergen by Pazaglia and Tosti in 1999[27] and for which the test concentration seems critical.[28] Its presence in cosmetics is being discussed, not because of its potentially allergenic properties but because of its iodine content (Ian White, personal communication).

40.2.3 Excipients, Emulsifiers, and Humectants

Many excipients, emulsifiers, and humectants are common ingredients in topical pharmaceutical products, which are likely to induce sensitization, and cosmetic products. The classical examples are wool alcohols, fatty alcohols (e.g., cetyl alcohol), and propylene glycol.[1,2] Emulsifiers, in particular, have long been regarded as irritants, but their sensitization capacities should not be overlooked. It is imperative, of course, that patch testing be properly performed to avoid irritancy and that the relevance of the positive reactions be determined. A large number of emulsifiers, emollients, excipients, and humectants have been reported to be contact allergens in moisturizers,[1] including preparations to treat dry lips[29,30] for which pigmented contact cheilitis has also been described.[31]

Table 40.1 lists the emulsifiers, excipients, and humectants that have been reported to be contact allergens in moisturizers over the last five years. For the allergens previously identified, see de Groot.[1]

Some of these substances, because of their low irritancy potential and "skin-mildness," are often incorporated in skin-care products "recommended by dermatologists," "for use on intolerant skin"

TABLE 40.1
Emulsifiers, Excipients, and Humectants Reported as Contact Allergens in Skin and Lip Moisturizers from 1999 to 2004 (NonExhaustive List)

Substances	Literature references
Butylene glycol	1, 32–35
Castor oil and derivatives:	1, 36
glyceryl ricinoleate	1, 37
propylene glycol ricinoleate	38
ricinoleic acid	31
Ceramide (hydrophilized)	39
Cetearyl isononanoate	40
Di-isostearyl maleate	41, 42
Ethylhexylglycerin	43
Glycerin	44
Glycerylisostearate	45
Glycerylmonoisostearate monomyristate	46
Hexyldecanoic acid (isopalmitate)	47
Isopalmityl diglyceryl sebacate	48–51
Laureth-9	52
Maleated soybean oil	53
Methoxy PEG-17 dodecylglycol polymer	54, 55
Methoxy PEG-22 dodecylglycol polymer	55
Pentaerythritol rosinate	50, 56
Pentylene glycol	57
Polyquaternium-7	52
Sodium dihydroxycetyl phosphate	58
Triglycerides: caprylic/capric and synthetic triglycerides	59, 60
VP/eicosene copolymer (already reported previously as allergen in sunscreen products)	61–63

or "for sensitive skin" that have become very popular in recent years. A low irritant potential, however, does not preclude the occurrence of allergic contact dermatitis. Examples of this are butylene glycol[33] and pentylene glycol,[57] that is, aliphatic alcohols with similar uses (solvent, humectant, and antibacterial) to those of propylene glycol, which is considered to be more irritant and allergenic, ethylhexylglycerin (syn.: octoxyglycerin), a skin conditioning agent,[43] and methoxy PEG-17 and PEG-22/dodecyl glycol copolymers, which are alkoxylated alcohols and synthetic polymers used as emulsion stabilizers and suspending and viscosity-increasing agents, and also as skin-conditioning agents.[54,55] Alkyl glucosides, which are condensation products of fatty alcohols with glucose such as coco and lauryl glucosides[64] are often used as mild surfactants and cleansing agents and also as emulsifiers, particularly decyl- and cetearyl-glucoside, and may be hidden allergens in sunscreens.[65]

40.2.4 Antioxidants

Antioxidants form only a minor group of cosmetic allergens. Examples are propyl gallate, octyl gallate,[66] which may cross-react with other gallates and are also used as food additives, and t-butyl hydroquinone, a well-known allergen in the United Kingdom but not in continental Europe.[2]

Some antioxidants are used more specifically in sunscreen products and also in moisturizing products to prevent aging but are rare causes of allergic contact dermatitis in such preparations, for example, tocopherol (vitamin E) acetate, retinol palmitate,[67] and ascorbic acid (vitamin C).[68]

40.2.5 Natural Ingredients

In addition to the vitamins already mentioned as antioxidants, panthenol, a vitamin B derivative[69] and its derivative panthotenyl ether[70] may exceptionally cause contact allergy due to their presence in moisturizers.

Plant extracts and herbal remedies have become very popular in recent years. For example, resveratrol (a phenolic phytoalexin produced naturally in red grape skin and in leaf epidermis of various plants) was recently reported as an allergen in a moisturizer.[57] Protein-derived ingredients, in particular, are often used in skin-care products, especially in those for treating dry skin in atopic subjects (often children). Contact dermatitis (sometimes located mainly on the eyelids[71]) may develop occasionally from oat or *Avena* extract,[72] hydrolyzed wheat protein,[73] and soybean extract.[74] Not only contact dermatitis but also contact urticarial[75] reactions to protein-derived products, sometimes severe,[76] have occurred. Although such reactions seem to be rare and may sometimes be irritant in nature, especially when patch testing atopic subjects,[77] their use has given rise to controversy since subjects (also children) may become sensitized through topical preparations and develop food allergies afterwards, or vice versa.

Other natural ingredients identified as allergens in moisturizers are placenta,[70] chitin (a cellulose-like biopolymer and important structural element of the integuments of arthropods, particularly crustaceans, mollusks, unicellular micro-organisms, seaweed, and fungi), and chitosan (deacetylated chitin).[78,79]

40.2.6 Sunscreens

Because of the media attention being given to the carcinogenic and accelerated skin-aging effects of sunlight, sunscreens are being used increasingly not only in sunscreen products but also in other cosmetics including moisturizers, in which they may be responsible for photocontact and contact allergic reactions.[80] Some sunscreen agents such as benzophenone-3, which may also cause contact urticaria[81] and even anaphylaxis,[82,83] and dibenzoylmethane derivatives have been recognized in the past as being important allergens.[1,2,84] The 4-methylbenzylidene camphor, cinnamates, and phenylbenzimidazole sulfonic acid are only occasional, sometimes even rare, causes of cosmetic reactions. The first cases of reactions to the newer sunscreens have recently appeared: photoallergic contact dermatitis from octyl triazone[85] and octocrylene.[86] In our experience,[2,4,5] the contribution of sunscreens to cosmetic allergy is relatively small despite the increase in their use. The low rate of reported allergic reactions observed, however, may well be because a contact allergy or a photoallergy to sunscreen products is often not recognized, since a differential diagnosis with a primary sun intolerance is not always obvious. Furthermore, the patch-test concentrations generally used might be too low, in part because of the risk of irritancy.

40.3 IDENTIFYING SENSITIZING SUBSTANCES IN MOISTURIZERS

Taking the history of the patient and noting the clinical symptoms and localization of the lesions are critical. Allergen identification for a patient with a possible contact allergy to cosmetics is performed by means of patch testing with the standard series, specific cosmetic-test series, the product itself, and all of its ingredients. We can only find the allergens we look for. For skin tests with cosmetic products

the patients supply themselves, there are several guidelines.[87] Not only patch and photo-patch tests but also semi-open tests (in case of possible irritants), usage tests, or repeated open application tests (ROAT) may need to be performed to obtain a correct diagnosis. Once an allergen has been identified, it is the dermatologist's task to provide specific advice about the products that can be used safely since subjects sensitive to specific ingredients must avoid those products that contain them. Although cosmetics are labeled, providing the allergic patient with a list of cosmetics that can be used is, in our experience, the most practical and effective tactic.[88]

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41 Regulatory Aspects on Safety

Monica Tammela

CONTENTS

41.1 INTRODUCTION

Skin moisturizers are used by a majority of the population in different degrees. Skin moisturizers, in addition to their beneficial effect on the skin, must be devoid of any deleterious effect on human health. They must not cause damage to human health under normal or reasonably foreseeable conditions of use.

In most cases, skin moisturizers are intended to keep the skin in a good condition, and are therefore considered as cosmetic/hygienic products and must comply with the legislation for these products. The manufacturer is in principle responsible for the safety of each product. However, in addition, the legislation in many countries may restrict the use of certain ingredients, and demand specific documentation of ingredients and the final product.

Certain skin moisturizers, however, may be considered as medicinal products and are then covered by special documentation and registration requirements not discussed in this chapter.

The main part of the safety assessment of finished products could be based, in principle, on data from the different ingredients used. The many thousands of different products on the market are all derived from a smaller number of ingredients. The toxicological profiles are also adequately studied

on separate substances. To avoid costly duplication of studies and unjustifiable use of animals, toxicity testing on the different ingredients and particularly those of most concern is preferable. For example, the documentation, evaluation, and listing of coloring agents, preservatives and UV-filters within the European Union (EU) and the Cosmetic Ingredient Review within the United States are important.

41.2 DIFFERENT TYPES OF INGREDIENTS

As reviewed in this book, skin moisturizers contain a wide variety of ingredients. A typical basic formula for a moisturizer includes water, polyol, lipid, surfactant, special moisturizer, preservative, and perfume.[1] Some of the ingredients are included to have beneficial effects on the skin, others are needed to get a suitable composition. So far, some types of ingredients have been of most toxicological concern. Preservatives and perfumes are two types of ingredients, which need special toxicological attention. Colors and UV-filters are two other types of ingredients for which special requirements have been made. Within the EU compounds used as preservatives, UV-filter and colors require an evaluation by authorities prior to their use in cosmetic products. The documentation and safety are evaluated by a scientific committee before they are permitted and placed on the lists of the Cosmetics Directive.[2] General and specific requirements that the manufacturer should provide are specified in the "*Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation*" 5th revision.[3]

Within EU the use of a large number of different substances are prohibited or restricted, annex II and III in the Cosmetics Directive. The list of prohibited substances includes for example, some pharmacological active substances (e.g., glucocorticoids, oestrogens), and other substances known to be harmful to the consumers (e.g., certain salicydanilides). Prohibition of substances classified as carcinogenic, mutagenic, or reprotoxic category 1 and 2 have been introduced recently. Substances for which the use are resticted includes for example, boric compounds, fatty acid, dialkanolmides, monoalkanolamines, trialkanolamines, polyacrylamides. An increasing number of substances are covered by the prohibition or restrictions due to evaluations of the responsible scientific committee within the European Commission. The former Scientific Committee on Cosmetics, and Cosmetics and Non-Food Products has recently been replaced by the new Scientific Committee on Consumer Products. The work done by the committee can be followed via the website,[4] where their opinions are made publicly available.

Within the fragrance industry a self-regulatory work is increasing the safety of the substances used if the IFRA Code of Practice is followed.[5] Recently, most of the IFRA guidelines on fragrance ingredients have been included in the legislation within EU.

For other ingredients, for which no regulation is specified from the authorities, the manufacturer has the full responsibility. The manufacturer is responsible to use ingredients and a final composition of the skin moisturizer so that there is no risk of harmful effects for the consumer.

41.3 TOXICOLOGICAL REQUIREMENTS ON INGREDIENTS

To assure that an ingredient does not pose a risk for the human health, all possible toxicological endpoints must be considered. That includes possible acute and chronic effects both locally and systemically. The exact information and studies needed depends on the compound and its properties. As a guidance to the toxicological properties to be considered, *The SCCNFPs Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation* could be used.[3] The general toxicological endpoints are listed in Table 41.1. The first part of the list (points 1 to 6) constitutes items necessary for all compounds. Depending on the properties and outcome of this first part, additional points (points 7 to 9) might be necessary. Considerable skin absorption is an example of

TABLE 41.1
General Toxicological Requirements

1. Acute toxicity
2. Irritation and corrositivity
3. Skin sensitization
4. Dermal/percutaneous absorption
5. Repeated dose toxicity
6. Mutagenicity/genotoxicity
7. Carcinogenicity
8. Reproductive toxicity
9. Toxicokinetic studies
10. Photo-induced toxicity
11. Human data

circumstances where these additional points are necessary. The last two points, 10 and 11, may also be necessary or helpful in certain cases.

It is important to remember that as our knowledge about the effects of different substances on the human body increases, ingredients already in use might need further testing and re-evaluation.

41.3.1 Acute Toxicity

Acute toxicity is necessary to evaluate the amounts that do or, in many cases, do not affect the living organism at a single exposure. It can be necessary for assessment of accidental exposure. However, mostly it is helpful to choose the levels in subsequent toxicological examinations. For new substances it should be performed only for the need in other legal requirements, for example, due to chemical legislation and worker protection. No exact figures are required, ranges or intervals might be enough. Both oral and dermal route might be adequate, but in most cases oral route is used. Acute toxicity is of minor importance for most ingredients in skin moisturizers, but can be important for additives with special effects.

41.3.2 Irritation and Corrositivity

Possible irritative effects of the substance on the skin must be assessed. Preliminary knowledge can in this case be derived from experiences of other substances with similar structure. If any hesitation exists, studies must be performed.

41.3.3 Skin Sensitization

Predictive tests on the potential of the compound to cause skin sensitization are essential. The introduction of new potent sensitizers must be avoided. So far only animal tests are sufficiently reliable to predict a low sensitizing potential, although alternatives can exclude potent sensitizers.

41.3.4 Dermal/Percutaneous Absorption

As skin moisturizers are applied to the minor or major outer part of the human body the skin absorption of ingredients is important to know to make it possible to estimate the systemic exposure. If skin absorption studies are lacking, 100% absorption could be assumed in the safety evaluation.

41.3.5 Repeated Dose Toxicity

To substantiate the safety of the substance for the population exposed, a subchronic study must be performed. The study should be designed to obtain a no-adverse-effect level. A 90- or 28-day study in rats is usually used.

41.3.6 Mutagenicity/Genotoxicity

To exclude substances with mutagenic/genotoxic potential, as a minimum, a combination of two suitable *in vitro* tests is necessary.

41.3.7 Carcinogenicity

Depending on the outcome of previous testing on mutagenicity/genotoxicity and systemic exposure, complete carcinogenicity testing might be necessary to exclude these risks.

41.3.8 Reproductive Toxicity

The risk of different reproduction disorders must be evaluated if there is a considerable systemic exposure, as moisturizers are extensively used within the population.

41.3.9 Toxicokinetic Studies

If there is a systemic exposure of the substance it is important to examine the disposition, metabolism, and excretion of the substance to make it possible to extrapolate *in vitro* and *in vivo* data to man.

41.3.10 Photo-Induced Toxicity

Most of the toxicological studies mentioned previously are needed also for other uses of the substance. However, different types of investigations involving light sources also are, in many cases, a special requirement for use in cosmetic products. This is specifically required when the cosmetic product is expected or intended to be used on sunlight-exposed skin.

41.3.11 Human Data

For many substances used in cosmetics, humans might have been exposed earlier intentionally or unintentionally. All data from these experiences are useful in the safety evaluation both for substances and later for the products.

41.4 SOURCES OF TOXICOLOGICAL INFORMATION

First, a request about all available toxicological information should be made to the raw material supplier. In addition, data from usual toxicological sources, databases, and literature is supplementary. As toxicological studies substitianting safety of a substance are prepared within companies and not usually published, different attempts have been made to make them more available. In the United States the Cosmetic Ingredient Review reports on the safety on different ingredients.[6] Within EU, reports from the Scientific Committee on Consumer Products (former Scientific Committee Cosmetics and Scientific Committee on Cosmetics and Non-Food Products) are available for some ingredients.[4] If suffient toxicological information is not to be found, studies must be conducted.

41.5 METHODS

For the toxicity studies needed, internationally accepted methods as those reported within EU[7] or in accordance with the OECD Guidelines for testing of chemicals are recommended. Tests for assessing photomutagenicity, photoirritationcy, photosensitization, and skin absorption have not been included so far in abovementioned guidelines. Guidance to the types of tests could also be found in the document from SCCNFP.[3]

New studies have to be conducted according to Good Laboratory Practice (GLP). However, old studies should not automatically be invalidated if they do not comply with guidelines or GLP requirements. Due to ethical reasons other testing procedures based on scientifically justified models and procedures can be accepted.

Alternative to methods using animals has developed during the past years and can be followed through the European Commission, which report on the progress of this development in Reference 8.

Recently the testing of final products on animals has been prohibited within the EU,[9] and will cover also ingredients as alternative methods will be developed and accepted.

41.6 SAFETY EVALUATION OF PRODUCTS

In general the safety evaluation of the finished product can be obtained by ascertaining the toxicity profile of the different ingredients. But it is important to evaluate each different toxicological end point and if the documentation is adequate for the assessment.

Important factors to consider in calculating the exposure are, for example, concentration of ingredients in the product, quantity, frequency and area of skin contact, and nature of consumers.

For some of the effects the concentration in the products is most important, for example, the local tolerance on the skin and eye. For some of the other effects it is necessary to estimate the presumed use by a normal or perhaps an eager user and the total amounts are more adequate. Guidance to relevant exposure estimation can be found in part 6 of SCCNFP. "Safety evaluation of finished products" in the notes of guidance.[3] The European cosmetics industry has, for example, estimated the exposure levels to be 0.8 g/day of face cream, 1–2 g/day of general cream and 8–16 g/day of body lotion for a female user.[10] It is also important to predict the use of the special product and the expectations from the single user. Groups of users with especially sensitive skin are important to take into account.

It is also necessary to look at the product as a composition. Possible interactions and potentiations of effects between the different ingredients locally or systemically must be considered. The possibility of different penetration due to the composition and the possible effect on toxicity must be evaluated. For skin moisturizers a lot of experience is gathered for previous compositions and products on the market. For local effects such experience may be reliable, but one has to pay special attention to systemic toxicity, which is very difficult to discover during use by consumers.

Within EU, documentation for each specific product should be readily available at the manufacturer or importer within the community.[2] This so called Product information shall include:

a. The qualitative and quantitative composition of the product.
b. The physico-chemical and microbiological specifications of the raw materials and the finished product and the purity and microbiological control criteria of the cosmetic product.
c. The method of manufacture.
d. Assessment of the safety for human health of the finished product.
e. Name and address of the qualified person responsible for the safety assessment.
f. Existing data on undesirable effects on the human health resulting from use of the cosmetic product.
g. Proof of the effect claimed for the product, where justified be the nature of the effect or product.
h. Data on any animal testing performed by the manufacturer.

Recently, information on ingredients and undesirable effects, points a and f, should be made available by the manufacturer/importer within the EU after request from the public.

41.7 ADDITIONAL TOXICOLOGICAL ASPECTS

Apart from the strictly regulated types of ingredients, colors, preservatives, and UV-filters, the main part can be used under the manufacturer responsibility. From the past we can get important toxicological aspects that ought to be noticed. In some cases toxicological problems have been discovered among constituents such as emulsifiers and emollients.

41.7.1 Contaminants

In the manufacturing process of ingredients a lot of different chemicals are used. The residue levels of these starting materials must be controlled, not only to have a high quality raw material, but also in relation to their toxicological profile. In the past, the residue level of dioxane used in the manufacturing process for ethoxylated substances was considered as a health hazard, as dioxane was shown to be carcinogenic in mice. Recently, maximal allowed residual concentrations of acrylamide, used in the manufacturing of polyacrylamides, have been established within the EU. It is important also to state that the specification of the ingredient during the toxicological testing and evaluation to make the results relevant for the ingredient when used in a cosmetic product.

41.7.2 Formation of New Substances

Under certain circumstances, formation of new substances can be seen during manufacturing, storage or use. Formation of different nitrosamines was found in products with dialkanolamines together with some nitrosating agents. 2-Bromo-2-nitropropane-1,3-diol and 5-bromo-5-nitro-1,3-dioxane are two, but not the only, examples of such substances. This formation of nitrosamines is important to avoid or minimize, as many different nitrosamines are shown to be carcinogenic is animals.

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