

Skin Irritation from Cosmetics & the Environment: A New Understanding

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At the start of the New Millennium, 78 million “baby boomers” in the United States will redouble their efforts to look and feel young through the use of “anti-aging” cosmetics and pharmaceuticals. And for perhaps the first time in history, medical science has provided tools that actually do “turn back the clock” on aging skin. During the last 20 years, skin scientists have provided an unprecedented understanding of how, and more importantly, why, skin looks older as we age. From these studies and the hundreds of millions of dollars of research by pharmaceutical and biotechnology companies, consumers can, for the first time, buy products that not only reduce the appearance of fine lines and wrinkles of aged skin but actually change the skin’s biochemistry to more closely resemble younger skin.

During the 1990s, the first true “anti-aging” cosmetics were introduced into the mass market. These products were backed by dermatologists and well-controlled clinical trials – read that “hard science.” The “alpha-hydroxy acid revolution”, as it was called, provided consumers with cosmetics containing glycolic acid, lactic acid, and other alpha-hydroxy acids (AHAs) and the related beta-hydroxy acids (BHAs) that had been used for years by dermatologists and plastic surgeons to successfully rejuvenate the skin. During this period, the United States FDA also approved the first prescription drug, Renova™, that can reduce fine wrinkles and other signs of aging skin. Since the active ingredient in Renova™ is retinoic acid, a member of the vitamin A or retinoid family, many cosmetic companies jumped on the “retinoid band wagon” with cosmetics containing related ingredients such as retinol (vitamin A alcohol). In the last 10 years, virtually every cosmetic company has introduced “anti-aging” cosmetics that include one or more of these ingredients, all claiming to reduce the visible signs of aging skin.

Cosmetic Irritation: A Barrier to Highly Effective Products

Within months after these products were introduced, many consumers became aware of what physicians had known for many years – effective products could be very irritating to the skin. Unlike the bland and ineffective lotions and creams that had been used for years, AHA, BHA and retinoid-containing products frequently produced sensory irritation (stinging, burning and itching) and redness, sometimes so severe that consumers stopped using the products. Companies quickly responded by reducing the levels of the offending ingredients. While this reduced irritation, it also drastically reduced their “anti-aging” benefits to the skin.

It turns out that skin irritation is frequently the limiting factor, the “barrier,” that prevents products from providing the maximum potency possible. Consumers with “sensitive skin” significantly add to the problem. As many as 50% to 75% of women report that they have “sensitive skin,” having experienced irritation from personal care products and cosmetics. People with respiratory allergies such as hay fever and asthma, for example, tend to be more sensitive to chemical irritants although the irritation is not caused by an allergic reaction. And many other factors can make even “normal” skin sensitive.

Environmental Irritation

The environment not only influences our daily lives, but it is also a major regulator of skin sensitivity that can cause even people with typically normal skin to have sensitive skin. For example, many people notice that a non-irritating product which they have used for a long time may become irritating when applied after a long plane flight. This increased sensitivity occurs due to the low relative humidity in planes, sometimes less than 5%-10%, which causes the skin to dry out. When the skin is dry, it loses some of its “barrier function” - its ability to prevent absorption of topically applied chemicals. As the permeability of the skin increases, more potentially irritating chemicals are absorbed and irritation can occur. Low humidity occurs, of course, as a result of weather conditions and high elevation, for example, particularly during the winter when the air is dry to begin with and heating in the home and offices decreases the relative humidity even further.

On the other end of the humidity spectrum, very high humidity can also cause non-irritating cosmetics to be irritating since wetting the skin can also cause increased absorption of irritating chemicals.

Once irritation occurs, it can start a vicious circle. Irritation itself can reduce the skin’s barrier function, thus increasing absorption of irritating chemicals, which, in turn, increases irritation, etc. Add to these conditions the potentially irritating effect of the sun and the wind on the skin, and it helps to explain why even the toughest skin can become sensitive to irritation in the right conditions.

Can a Product Have Both High Potency AND Low Irritation?

The “battle lines are drawn.” In one corner are the highly effective “anti-aging” ingredients used for years by dermatologists that have been proven effective to reduce the appearance of aging skin. Unfortunately, they can all be highly irritating.

In the other corner are the vast majority of cosmetics that are not irritating, but have little “anti-aging” benefits since their levels of irritating “anti-aging” ingredients have been diluted so much that they barely work at all.

Would it be possible to combine these two ends of the spectrum to provide products that are highly effective AND don't irritate the skin??

The Medical Basis for Skin Irritation

To answer this question, we must first examine what skin irritation is, why it occurs, and how it might be reduced.

The most common complaint from consumers is that products cause stinging, burning and/or itching, usually shortly after the product is applied. These symptoms, called collectively "sensory irritation," usually occur without visible signs of irritation, for example, redness or swelling. Even though no visible signs of irritation occur, "invisible" skin damage may be occurring. How do ingredients in cosmetics cause sensory irritation?

The skin, it turns out, has many ways by which it senses its environment. All of these sensing elements use specialized nerves that connect to the brain where they reach consciousness. For example, when the skin is heated, specialized heat sensors are activated and send a signal to the brain that says "it's getting hot." Conversely, if the skin is cooled, different sensors are activated that transmit a cold sensation. Other skin sensors that act independently of the others include the ability to detect fine textures, for example the perception of the softness of velvet, or the roughness of sandpaper. Still other nerves conduct vibration and position sense – the ability to accurately detect the position of a finger held in space.

A-Delta Nerves Transmit Sharp, Localized Pain

Of importance to irritation are two additional sensing systems that transmit annoying or painful stimuli, called nociceptors (from the Latin nocere, to injure). These nociceptive systems use two distinct nerves, called A-delta and type C, that are present throughout all skin. You can activate A-delta nerves by taking a sharp pointed object, a pencil tip or a pin, and gently pushing it into the skin without breaking the skin. When you push hard enough, not surprisingly, it will hurt. If you close your eyes, you will be able to detect the exact point at which the skin is hurting with great accuracy. This sensation is called "highly localized pain" and acts as a warning signal to allow you to rapidly and accurately detect the potentially harmful stimuli and to protect yourself accordingly. Highly localized pain is transmitted by a nerve subset called A-delta. When stimulated, A-delta nerves are activated and transmit a signal to the spinal cord, which in turn, relays the signal to the brain where it is interpreted as pain (**Figure 1**).

Type C Nerves Transmit Stinging, Burning & Itching

The skin also has a completely distinct nociceptor system that does not transmit pain but instead transmits the sensations of stinging, burning and itching. If you think back to a time when you had a mosquito or insect bite or were exposed to something that caused itching, you will realize that these

sensations are quite different from the pinprick. In particular, unlike the pinprick which is highly localized, sensations of stinging, burning and itching are poorly localized and may extend over several inches of skin or more. This occurs because the nerve subset that conducts these sensations, called type C nociceptors, covers broad areas of skin with one nerve root. Type C nociceptors are unique in other ways as well. They become activated when they are exposed to a broad range of chemically and biologically unrelated substances, for example, acidic chemicals (e.g. AHAs & BHAs) neutral chemicals (e.g. preservatives), or basic chemicals (e.g. hair dyes). Additionally, type C nociceptors have receptors for the chemical histamine that is released during allergic reactions and is a potent stimulator of itching, redness and swelling. This system seems to have evolved to detect even the most minor chemical imbalances in the outermost layers of the skin. By rapidly attracting attention, this system allow us to identify the cause of the irritation and protect the skin.

COSMEDERM-7™ Mechanism of Action

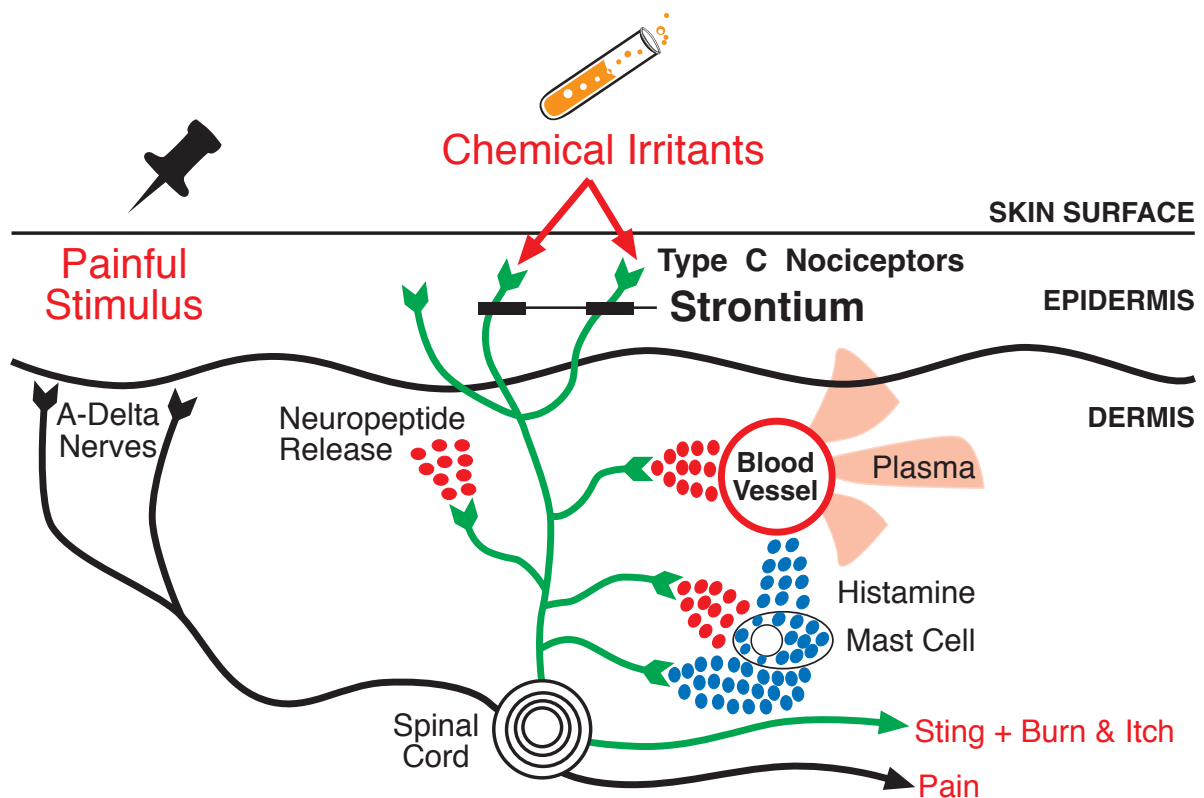


FIGURE 1. Strontium (COSMEDERM-7™) reduces the sensitivity of type C nociceptors to chemical irritants and histamine while not affecting the A-delta nerves that transmit the ability to detect pain or other nerves that contribute to normal tactile sensations.

Type C Nerves Also Cause Redness & Swelling

In addition to stinging, burning and itching, type C nociceptors also serve another function. If a strong enough irritant stimulates them, type C nerves release powerful inflammatory chemicals at the site of the irritant exposure. These chemicals are called neuropeptides (small nerve-derived proteins) and include substance P, neurokinin A and calcitonin gene-related peptide (CGRP). They all act to trigger blood vessel dilation which causes redness and blood vessel leakiness which causes swelling. They also trigger white blood cells to release still more inflammatory chemicals, including histamine, which itself triggers itching and causes further redness and swelling (**Figure 1**). One gets the sense of a vicious circle of irritation that causes further irritation and spirals out of control. This process is called neurogenic inflammation and is a process unique to the type C nociceptive system.

Can the Type C Nociceptive System be Tamed?

It stands to reason that if one could reduce the sensitivity of the type C nerve system, one could not only reduce the tendency of chemicals to cause irritation, but one could also reduce the redness, swelling and tissue damage caused by the neurogenic inflammatory process itself. Consider the following example. A cosmetic ingredient may not cause irritation or any skin problem in people with normal skin. Extensive safety testing further proves that this ingredient is safe to the skin. But in a person with sensitive skin, this ingredient may activate the type C system that will not only cause stinging, burning and itching, but redness and swelling as well. It is therefore the type C nerves themselves that are causing the problem in this example, not toxicity of the ingredient itself!

And this is frequently the case for many chemicals found in cosmetics or in other topical products that are inherently safe but may activate the type C system in sensitive skin. If only the type C system could be tamed, if its sensitivity could be reduced to the level found in non-sensitive people, a lot of the irritation problem could be eliminated.

A similar situation occurs in allergic people. Grass or tree pollen, cat or dog dander, or other substances that trigger allergies are not inherently unsafe chemicals. Witness the fact that non-allergic people can walk through a freshly cut rye grass field while inhaling millions of grains of pollen and not even be aware of it. In contrast, if you have hay fever or asthma, the hypersensitivity of the immune system reacts to the pollen with a vengeance causing itching, sneezing, watery eyes and nose, swelling, nasal congestion, and potentially a life-threatening asthmatic attack. In this case, as it is with the skin's type C nerve system, it is the body's exaggerated response to otherwise safe substances that causes the problem, not the substance itself. Allergy therapy seeks to reduce this exaggerated response down to a more normal response. Similarly, a substance that could reduce the sensitivity of the type C nerve system of the skin would also actually protect the skin from itself, and greatly increase the comfort of the person!

The First Protector of the Type C Nociceptors Has Been Found: COSMEDERM-7™

After over 10 million dollars of research and development, a substance has been found that can safely protect the skin against stinging, burning, itching and redness caused by otherwise safe chemicals. It is naturally occurring, found in the food we eat every day, in the ocean, and is naturally present in our bodies. It is the element strontium, which is a chemical relative of calcium. Strontium, also called COSMEDERM-7™, has proved to be remarkable in its ability to protect the skin from irritation while being “invisible” when no irritating stimulus is present.

A particularly unique property of COSMEDERM-7™ is its extraordinary selectivity for the type C nociceptive system. As **Figure 1** indicates, COSMEDERM-7™ only reduces the sensitivity of the type C system and does not affect the sensitivity of the pain-sensing A-delta system. This is important since the warning signal of pain needs to be preserved to allow a person to protect the skin from harm. A local anesthetic like Novocain™, by contrast, would not only block the type C system, but it would also block the A-delta system and other skin sensors, resulting in numbness and lack of other tactile sensations.

To illustrate the potency of the anti-irritant activity of COSMEDERM-7™, the following study was performed using the most powerful AHA chemical peel available, 70% glycolic acid (pH 0.6). This peel formulation is used by dermatologists and plastic surgeons to reduce the visible signs of aged skin and to treat acne. In this study, the glycolic acid with or without COSMEDERM-7™, was applied to the forearms of 11 women with sensitive skin 9 times, twice per week for 4.5 weeks in a double-blind, placebo-controlled, random-treatment assignment study. Subjects rated the degree of sting, burn and itch according to the scale below:

SENSORY IRRITATION SCORES: Sting, Burn, Itch

Commercially Acceptable

0 = none

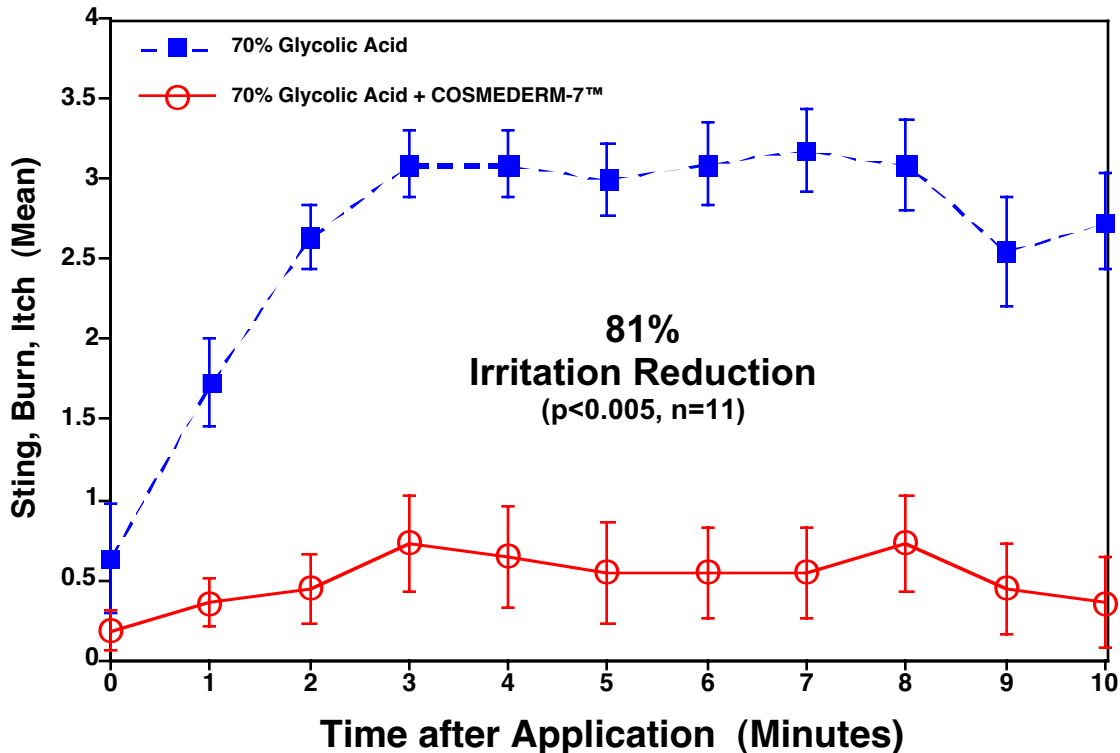
1 = slight-----transient irritation, noticeable but “doesn’t bother” them

Commercially Unacceptable

2 = mild-----continuous irritation, “bothers them”

3 = moderate-----“bothers them”, interferes with concentration

4 = severe -----intolerable irritation, redness and swelling possible

GRAPH 1: Time Course of 70% Glycolic Acid (pH 0.6) Sensory Irritation

Graph 1 presents the sensory irritation scores reported each minute over a 10 minute period for one of the nine 70% glycolic acid applications. The mean (\pm SEM) irritation for the 70% glycolic acid (pH=0.6) treatment alone is indicated by the filled squares and demonstrates the rapid development of intense irritation (mean score of ≈ 3). In contrast, the 70% glycolic acid which contains COSMEDERM-7™, represented by the open circles, demonstrates very low irritation (mean score of ≈ 0.5) over the entire 10 minute period.

Potential For Use in Cosmetics & Personal Care Products

Given the broad and potent anti-irritant activity of COSMEDERM-7™, and its extraordinary safety, it may be used in virtually every category of cosmetic and pharmaceutical products in which irritation is a problem. By allowing products to contain much higher levels of active ingredients, COSMEDERM-7™ allows consumers to experience ultra-high potency products without fear of irritation.

About the Author

Gary S. Hahn, M.D., is a graduate of Stanford University (BS, Biology) and the University of California, San Diego School of Medicine. Dr. Hahn is a licensed physician in California and serves as an Assistant Clinical Professor, Immunology and Allergy Division, Department of Pediatrics at UCSD. Dr. Hahn previously founded Immunetech Pharmaceuticals (now Dura Pharmaceuticals) where he served as Senior Vice President for Research and

Scientific Director and Cosmederm Technologies. He is a member of the American Academy of Dermatology, Society of Investigative Dermatology and is an author of numerous publications, medical book chapters and pharmaceutical patents. He holds the patent on a product called COSMEDERM-7, made from strontium, which his research has found to reduce the sensitivity of type C nociceptors to chemical irritants and histamine while not affecting the A-delta nerves that transmit the ability to detect pain or other nerves that contribute to normal tactile sensations. To reach him, please call (858) 550-7070 or fax (858) 642-0322.*