AIR POLLUTION'S EFFECT ON THE SKIN, PART II

In the April column of The Sunscreen Filter (p. 46) I described the ever-expanding problem of air pollution and its effect on human health in general and the skin in particular. Air pollutants were classified as primary or secondary and methods for quantification and regulation were addressed. In this column, I will review the direct impact of air pollution on the skin. After all, the skin is the human body's largest organ and, as such, any factors affecting the skin's health will impact the body's health as a whole.

Dermal Skin Absorption

Dermal absorption is a complex process whereby substances are transported across the multilayered skin biomembrane and into the body's living tissues.[1] This process is strongly influenced by the skin's particular absorption characteristics, which are susceptible to constant changes. Upon topical contact, substances which do not evaporate or are not mechanically removed, may penetrate into the epidermis and subsequently reach the hypodermal vascular network via the dermis. During this process, an absorbed substance may also undergo biotransformation.[2] The stratum corneum is most impermeable against hydrophilic agents, whereas the subjacent epidermal layers are most impermeable against highly lipophilic agents.[3] Moreover, skin on different areas of the same organism have different absorption patterns; e.g., scrotal skin is 12 times more permeable than forearm skin and forehead skin more than cheek skin.[4] For description of human skin, consult reference.[5]

In addition to the skin's properties, characteristics of the substance being absorbed also influence dermal absorption, including the substance, vehicle (for dissolved substances), occlusion, concentration and exposure pattern. The most important substance properties affecting transdermal absorption are: 1, liposolubility; 2, molecular weight (smaller molecules penetrate more easily); 3, electron configurations and dissociation constants (the greater a molecule's polarity and/or ionization, the less penetration); 4, the properties of carrier substances (polar or non-polar interface with skin components)—this is a key factor; 5, the dilution factor of compound-of-interest/vehicle substance; and 6, the presence/absence of specific radicals favoring/inhibiting penetration.[6]

Pathways of Penetration

Transdermally absorbed substances are usually liquids or in a liquid vehicle, including compounds which first dissolve in moisture on the skin's surface. That said, it should be noted that many substances that normally do not efficiently penetrate the skin through the cellular layers of the epidermis are able to effectively access the deeper layers and blood vessels of the skin via hair follicles and sweat/sebaceous glands. For example, the forearms, especially if hairy, are easily penetrated by chemicals which enter via the hair shaft duct. Additionally, landmark research on the penetration of topically applied antioxidants through the skin barrier established that molecular purity, pH below 3.5 and solute concentration between 10% to 20% are vital in order to deliver vitamin C into cutaneous tissue.[7] These three criteria became known as the Duke Antioxidant Parameters and established the framework for topical antioxidant delivery.

Gross effects of transdermal pollution absorption include UV radiation, soot and smoking, which serve as significant factors in skin deterioration that results in skin hyperpigmentation and sluggish skin cell renewal.[8]

A 2009 study by the French Institute of Public Health Surveillance demonstrated more immediate causal relations between air pollution exposure, viz., PMs_{10} PMs < 10µm in diameter) and ground level ozone exposure and adverse topical consequences, viz., skin rash and conjunctivitis.[9] Evaluation des Risques de la Pollution Urbaine sur la Santé (ERPURS) program data demonstrated that ground level ozone was the major significant factor affecting acute pollution-related eye conditions.[10]

Ocular inflammation and dryness was demonstrably more prevalent in areas with higher concentrations of air pollutants. Moreover, atopic eczema or dermatitis and allergic rhinoconjunctivitis were demonstrably correlated with higher concentrations of air pollution.[11] Furthermore, a Japanese study has demonstrated that air pollutants induce oxidative protein damage in the stratum corneum and immunoglobulin response, thus exacerbating atopic dermatitis and disrupting barrier function.[12] Additionally, an epidemiological time-series analysis correlated emergency room visits for dermatologic conditions in Huashan Hospital to ozone concentrations in Shanghai.[13]

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Take Your Vitamins!

Many of the more readily observable problems resulting from air pollutant-induced skin pathologies are due to vitamin C and E vitamins (tocopherols and tocotrienols) depletion by air pollution-derived free radicals in the skin.[14]

E vitamins (tocopherols and tocotrienols): a family of powerful antioxidant lipid-soluble vitamins with excellent free-radical scavenging ability. E vitamins protect essential fatty acid and vitamin A levels in the body and are immune-supportive. E vitamins in the epidermis are part of the barrier against skin moisture loss, prevent oxidation-based cellular aging, aid in nourishing cells, are anti-inflammatory and strengthen capillary walls. They significantly inhibit scarring from wounds and the appearance of stretch marks. All E vitamins contain a chromanol ring that is responsible for their free radical-scavenging abilities, due to its phenoxy group (see Fig. 1)

E vitamins are the predominant human epidermal lipophilic antioxidant with 90% higher levels in the epidermis than the dermis.[15] Normal dietary (non-supplement) E vitamins are metabolized and are in transit in the circulation for at least seven days before accumulation in the sebaceous glands, and subsequent secretion, in sebum, to the skin's surface. Note that individuals with high sebum production ("oily" skin) demonstrates higher E vitamins' ratio of 20/1 and gradually decreases into the deeper layers.[16]

UV and/or atmospheric pollutant exposures lower the skin's E vitamin concentrations, predominantly in the stratum corneum, and with the level of depletion greater in the more superficial; i.e., external irradiation and pollutant-accessible layers. Two-hour ozone exposure concentrations up to twice the peak levels for heavily air polluted areas, e.g., Mexico City (highest ozone levels in the world) or Los Angeles (highest ozone levels in the US), caused a 25% loss in stratum corneum E vitamins content. Six consecutive days of this two-hour regimen resulted in a 75% loss of original stratum corneum E vitamins concentrations. Although ozone concentrations were higher than real-world levels, the duration of exposure was also much briefer. Further evidence supports these findings and suggests that the combination of ozone and ultraviolet light cause three times greater depletion of E vitamins than ozone alone.[17]

Vitamin C is normally found in substantial levels in both the dermis and epidermis (higher in the epidermis), but vitamin C content in both the epidermis and dermis declines with age.

E vitamins are expended in countering the radical-induced peroxidation of ceramides, cholesterols and unsaturated fatty acids, which are in large part responsible for the barrier function of the stratum corneum. When excess radicals from air pollution, such as ozone and NOx species, are absorbed into the skin, excess barrier lipid oxidation transpires, and vitamin E is depleted, with the consequence that barrier function is reduced and even more pollutants may now permeate the skin. Moreover, stratum corneum barrier lipid oxidation products may potentially induce inflammatory responses in subjacent skin layers. Human epidermal structures change and E vitamins' concentrations decline with age, potentially permitting increased UV penetration.[18]

Topical vitamin E supplementation is present throughout history, from ancient oil massages to modern moisturizers. It has been demonstrated that topical application also significantly increases E vitamins' levels in the dermis with possible accumulation in the sebaceous glands. E vitamins and their derivatives (tocopherol acetate, tocopherol linoleate or tocopheryl nicotinate) are currently included in cosmetics as antioxidants, and they are claimed to expedite skin healing and reduce scarring.[19]

Although E vitamins are considered significant ingredients in topical applications due to their antioxidant activity, some E vitamins also absorb UVB (but not UVA) spectrum radiation. Therefore, some E vitamins also have sunscreen functionality. Unfortunately, a corollary of this property is that some E vitamins are photolabile and are subject to photodegradation. Thus, improving vitamin E

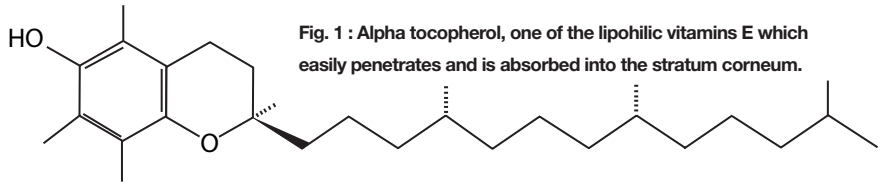


Fig. 1 : Alpha tocopherol, one of the lipohilic vitamins E which easily penetrates and is absorbed into the stratum corneum.

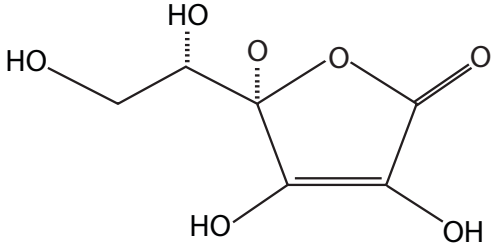
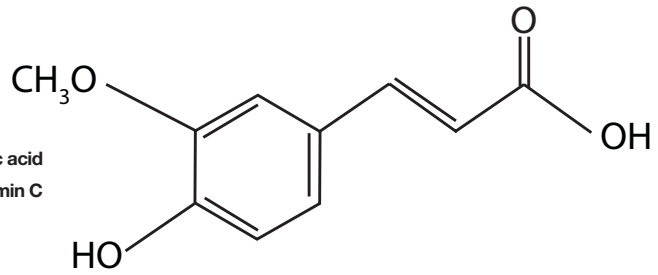


Fig. 2: Ascorbic acid, the protonated form of vitamin C, which does not penetrate the stratum corneum but may penetrate the epidermis via hair follicle shaft and/or sweat/sebaceous ducts.



[Fig. 3 : Ferulic acid improves vitamin C stability]

photostability in topical applications is paramount for improving the effectiveness of such applications.[20]

Vitamin C (ascorbic acid) is a weak sugar acid structurally similar to glucose. Vitamin C is found as the L-ascorbate enantiomer (the deprotonated form) in biological systems, as a pH5, or less, is necessary for protonation to form the acid. Vitamin C is a vital cofactor in several enzyme reactions, especially those involving collagen synthesis, which is paramount in wound healing and strengthening capillary walls, which prevents easy bruising, in animals. Vitamin C deficiency results in collagen synthesis dysfunction thus causing scurvy.

Ascorbate acts as an antioxidant by, initially, donating a single electron to neutralize a free radical stopping its progression capable of causing further cellular damage.

Vitamin C is normally found in substantial levels in both the dermis and epidermis (higher in the epidermis). Vitamin C content in both the epidermis and dermis declines with age. Vitamin C is normally supplied to the skin by the bloodstream. In the 1980s L-ascorbic acid was determined to be an essential cofactor for collagen biosynthesis.[21] Additional support for the protective effects of antioxidants against environmental insults was determined in the early 21st century with the findings that the combination of vitamin C, ferulic acid (Fig.3) and phloretin substantially decrease ultraviolet-induced photodamage.[22]

Airborne pollutants, including both ozone and second-hand smoke, have been demonstrated to induce free radical damage and decrease vitamin C levels in the skin, leading to decreased collagen synthesis, which results in increased wrinkling, connective tissue disruption, microvascular fragility, and impaired wound healing.[23]

The deleterious effect of transdermal absorption of airborne pollutants may be ameliorated by topical vitamin C application. A 12-week vitamin C topical application regimen (3-10%) resulted in reduced wrinkling, protein fiber damage and skin roughness; and increased collagen production. Moreover, topical vitamin C application has been demonstrated to partially reverse structural deterioration in the dermal/epidermal interface. Furthermore, topical vitamin

A RAY OF SUNSHINE ON CAPITOL HILL

• Who says government is broken? On April 8 and 9 members of the PASS Coalition (Public Access to Sunscreens) went to Washington DC to meet with staffers of 18 senators and congressmen on Capitol Hill. Walking through the halls of this great institution is always an inspiration. Democracy at its best—in action! Our meetings were fascinating and productive. We were divided into two teams. Team UVA met with staffers for Representatives Capps (D-CA-24), Maloney (D-NY-12), Matheson (D-UT-4), Castor (D-FL-14), Cooper (D-TN-5), Gingrey (R-GA-11), Blackburn (R-TN-7), Griffin (R-AR-2), Bilirakis (R-FL-12) and Senators Sanders (I-VT) and Hagan (D-NC). Team UVB met with staffers for Representatives Dent (R-PA-15) and Senators Whitehouse (D-RI), Roberts (R-KS), Burr (R-NC), Warren (D-MA), Baldwin (D-WI) and McConnell (R-KY). Without exception, our message to Congress was well received and promises to co-sponsor and support for the current bipartisan and bicameral bills were heard.

On April 7, the House had a hearing on HR 4250 (Sunscreen Innovation Act) that was attended by Dr. Janet Woodcock, the director of the FDA. She faced tough and direct questioning by many members of the House, especially by the bills sponsor, Congressman John Dingell (D-MI). The process is moving ahead and we hope and believe that the bill will pass in the near future paving the way for much needed reforms in the regulations of the US sunscreen industry. See: https://www.youtube.com/watch?v=LLNEtD_sldA Bills S.2141/HR4250 as it stands has four primary components:

• Eligibility. Under the Act, existing FDA eligibility requirements will be maintained; aningredient must be used safely for at least five years in at least one country.

• Transparent Review. Eligible ingredients will be submitted to an Advisory Committee for review and FDA will make a final safety and effectiveness determination.

• Predictable Timeframe. The Act requires that the current sunscreen backlog be reviewed within 8 months and new submissions be reviewed within 11 months.

• Accountability. FDA is required to submit reports to Congress regarding the progress of theprogram 12 months following enactment and every two years thereafter.

The Sunscreen Innovation Act of 2014 adds language to Subchapter A of Chapter 5 (Drugs) of the Federal Food Drug and Cosmetic Act(FFDCA) that modifies the existing Time and Extent Application (TEA) process for review and approval of sunscreen ingredients. Interestingly, in Sec. 3 of the Act entitled "Sunscreen Testing and Labeling" the FDA is required to issue a determination within 180 days(!!) with respect to appropriate testing andlabeling requirements for sunscreens sold as an aerosol and whether a sunscreen may contain a label indicating an SPF greater than 50. We trust that this bill, once approved by both chambers of Congress, will finally reform the process of regulating sunscreens in the US. We urge you to contact your senators and congressmen to voice your support for those bills.

C application may be effective in treating acne and reducing melanin production and oxidation.[24] Moreover, topically applied vitamin C stability has been demonstrably increased by addition of other antioxidants to the solution, including vitamins E and ferulic acid.[25]

A chronic effect of the depletion of the primary antioxidants, viz., the E vitamins and vitamin C, in surface epidermal layers is the reduction of overall antioxidant capacity within the skin and consequent depletion of other vital antioxidant molecules in the epidermis, leading to intrinsic antioxidant defense system failure.26 Because the skin constitutes the primary barrier against pollution, topical application of properly formulated antioxidants for optimal penetration is a very effective strategy to overcome the pollution and age related depletion of cutaneous antioxidants. Ongoing industry research suggests topical antioxidant formulations show potential to both prevent and repair the pollution-induced oxidative stress in the skin. However, far more research is needed to define the precise molecular mechanisms behind the damaging effects of pollution and ways to quantify the protective benefits offered by topical products.

In conclusion, the skin is the human body's largest organ, comprising some 16 ft^2 to 22 ft^2 of epidermis, dermis, and hypodermis and up to 50% of the body's fat and, as such, any factors affecting the skin's health will impact the body's health as a whole. This two-part review has illustrated that air pollution is ubiquitous and exercises a surprisingly extensive effect on human skin health, in particular:

1. The transdermal absorption of alarmingly large quantities of pre-radicals, sometimes accounting for 50%, or more, of bloodstream content of these substances, as compared to the amount(s) derived from inhalation;

2. Ozone-based depletion of endogenous antioxidants; viz., vitamins E, and consequent depletion of vitamin C,

3. In synergy with UV photo-oxidative mechanisms to deplete epidermal surface vitamin C and vitamins E levels; as well as

4. Interacting with UV radiation to photoconvert air pollutant-derived dermally absorbed pre-radicals into active radicals.

These air pollution insults on human skin, with or without UV-complicit exacerbation, which, if not treated, will not only result in serious chronic skin pathologies, such as cancer or loss of epidermal barrier function, but will ultimately result in organismal antioxidant defense system failure. Therefore, antioxidant countermeasures are necessary to ameliorate these insults to skin health.

The most effective countermeasures are topical applications of antioxidants to the skin at the point of insult. Vitamin C and E vitamins are the most prominent candidates as ingredients in such applications because they are:

- Two of the primary antioxidants in the skin;
- Easily obtainable from several sources; and
- Effectively absorbed into the skin, under appropriate conditions.

Thus effective topical antioxidant formulations designed for dermally absorbed air-pollutant skin protection should include both vitamin C and E vitamins, both stabilized with additional antioxidants and photoprotective sunscreens, with vitamin C being the more effective photoprotectant in the UVA range, and E vitamins being more effective in the UVB range, are absorbed into different areas of the skin, with the E vitamins absorbing into the lipid-phase compartments and vitamin C into the aqueous-phase compartments and mutually stabilize each other.

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