EDITORIAL

Systemic Absorption of Sunscreen
Balancing Benefits With Unknown Harms

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UV radiation is the most important known modifiable risk factor for the development of skin cancer including melanoma. Behavioral measures to reduce this risk factor include seeking shade, wearing hats and protective clothing, avoiding outdoor activities during peak sunlight hours, and regularly using sunscreen.[1]

Related article page 256

Sunscreen ingredients fall into 2 distinct categories: mineral or chemical. Mineral sunscreens contain physical UV filters, such as zinc oxide and titanium dioxide, that offer broad-spectrum UV coverage by reflecting or refracting UV radiation from skin. Chemical sunscreens contain UV filters that absorb UV radiation and, when used in combination, can provide equal if not superior broad-spectrum UV filtration compared with mineral sunscreens. Chemical sunscreens are less likely to leave chalky or tinted white residue on the skin, which is more cosmetically acceptable especially on darker skin types. Given these relative advantages, chemical sunscreens are found in the majority of commonly available sunscreen formulations within the $1.95 billion sun care industry in the United States.[2]

Sunscreen is regulated as an over-the-counter medication by the US Food and Drug Administration (FDA) and is indicated for the prevention of sunburn and skin cancer. Although the safety of mineral sunscreen filters has been established, the safety of chemical sunscreen filters has come under increased scrutiny in light of recent data from investigators at the FDA.[3] An open-label, randomized clinical trial by Matta et al[4] published in *JAMA* in 2019 demonstrated that, under maximal use conditions, 4 chemical UV filters (avobenzone, oxybenzone, octocrylene, and ecamsule) were absorbed through the skin and achieved systemic levels exceeding the FDA threshold for safety testing (plasma concentration >0.05 ng/mL). These were notable findings because systemic safety testing has not been previously documented for these common sunscreen ingredients.

The study did not address key questions about sunscreen safety. First, what is the amount of systemic absorption after a single application of sunscreen? Second, following the application of sunscreen, how long does it take for plasma concentrations of sunscreen ingredients to fall below the FDA threshold for safety testing? This study also did not provide evidence of health risks associated with sunscreen absorption. However, data from animal studies and preliminary human data have previously indicated possible health risks associated with some of the sunscreen ingredients evaluated in this study, including endocrine disruption and reproductive harm.[5]

In this issue of *JAMA*, Matta and the same group of FDA investigators conducted a second open-label, randomized clinical trial to determine the systemic absorption and pharmacokinetics of 6 common chemical sunscreen ingredients contained in 4 commercially available formulations (3 sprays and 1 lotion).[6] The current study included 3 of the 4 sunscreen filters from the previous study (avobenzone, oxybenzone, and octocrylene) and 3 additional UV filters (homosalate, octisalate, and octinoxate). The study followed a similar protocol requiring participants to apply sunscreen to 75% body surface area once on day 1, followed by maximal use (application 4 times a day) on days 2 through 4. Plasma levels of sunscreen ingredients were serially measured over a 21-day period to assess pharmacokinetics. The investigators also performed skin tape stripping on days 7 and 14 to assess levels of sunscreen filters remaining in the skin after sunscreen application was discontinued. The study was conducted in a clinical research setting, and study participants were not exposed to direct sunlight for up to 7 days they remained in the clinic.

All 6 sunscreen filters achieved plasma concentrations significantly above the FDA threshold after a single application. As in the previous study, concentrations of sunscreen filters increased after each day of application, suggesting accumulation within the blood. The terminal half-life of these filters after maximal use ranged between 27 hours (octisalate in spray formulation) and 157 hours (octinoxate in spray formulation) and differed for each ingredient between sunscreen formulations. Notably, all products tested remained above the FDA threshold at day 7, and plasma levels of homosalate and oxybenzone continued to remain above threshold on day 21. Tape stripping evaluation on days 7 and 14 revealed persistence of sunscreen filters, raising the possibility that the skin could serve as a depot for ongoing absorption after daily sunscreen application is stopped.

It is critical to recognize that these 2 studies conducted by the FDA do not provide any evidence that chemical sunscreens cause harm. However, the current study does provide important additional information documenting systemic absorption of commonly available chemical sunscreen filters and strengthens the need for current FDA efforts recommending safety testing for certain chemical sunscreen ingredients to confirm they are generally recognized as safe and effective.[7] Safety data requested for sunscreen products include clinical studies to examine skin irritation and allergic sensitization, photosafety, absorption studies, and specific testing in children. The requested data also include nonclinical studies to determine long-term carcinogenicity risks,

developmental and reproductive risks, and toxicokinetic data. The Sunscreen Innovation Act[7] required the FDA to publish the rule finalizing the over-the-counter sunscreen monograph by November 26, 2019. This proposed date has now passed; thoughtful discussion will be needed to establish a reasonable compliance date to allow all stakeholders—including the FDA, sunscreen industry, scientists, the public, and most importantly, individuals who need access to sunscreen—to take necessary steps.

Until these safety data are available, should clinicians continue to recommend the use of chemical sunscreen? This is a pragmatic question that affects the daily regimen of many individuals and is a critical clinical question. In making an informed decision, clinicians must determine whether the magnitude of the benefit exceeds the risk of potential harm for a specific individual. Importantly, this balance may be different, depending on characteristics of the sunscreen user (eg, for individuals with darker skin types and for children) and may depend on the frequency and duration of application (eg, daily vs intermittent use; starting in infancy or later in life).

The most important purported health benefit of sunscreen is the reduction of skin cancer risk. Evidence for this benefit is strongest for individuals with light skin. Those with darker skin types have a much lower risk of skin cancer, and whether certain skin cancers, such as melanoma, are associated with UV exposure in this population is not fully understood.[8] It is notable that almost half of the study participants self-identified as black or African American. More evidence will be needed to determine the benefit of sunscreen in individuals with darker skin, especially if health harms are discovered. The possibility of harms from systemic absorption of chemical sunscreens may change the risk-benefit balance in children as well. UV exposure, particularly sunburns in lighter-skinned individuals early in life, has the strongest association with keratinocyte carcinoma as well as melanoma risk.[9] The exclusion of the pediatric population from these clinical studies leaves an important gap in the current understanding of the systemic absorption of sunscreen. Children likely have different transdermal absorption rates and may be at increased risk of sequelae from elevated plasma levels of UV filters. If the overall long-term benefit of diligent photoprotection with sunscreen may be greatest in early life, is the uncertain harm from absorption of chemical sunscreen acceptable? Subsequent studies must carefully evaluate the potential risks and benefits of chemical sunscreens in different groups to determine whether its use has net health benefits.

Sun and sunscreen are almost ubiquitous exposures, therefore, improved understanding of the harms or potential harms of each to human health is of paramount importance. The reports published by Matta et al provide important information on the systemic absorption of chemical sunscreen filters that deserve attention, discussion, and additional study to understand their clinical relevance. Because good evidence indicates that UV exposure is a key modifiable cause of skin cancer and melanoma, sunscreen should continue to be an essential part of UV safety, which includes photoprotective clothing, eyewear, and avoidance of intense sun exposure. In the absence of clear data demonstrating harm, the use of chemical sunscreen may still be considered appropriate; the use of mineral-based sunscreen is a well-established safe alternative. Elevating the science of the benefits and harms of sunscreen should be a priority. The sunscreen industry must begin conducting these safety studies as recommended by the FDA. Until then, the harms of absorption of sunscreen filters will remain uncertain.

ARTICLE INFORMATION

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Additional Information: Dr Shinkai is a voting member of the American Academy of Dermatology (AAD) regulatory policy committee. Dr Adamson is a member of the AAD Skin Cancer and Skin of Color Work Group.

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