ABSORBTION OF SUNSCREEN COMPONENTS IN BIOLOGICAL FLUIDS: EVALUATING INGREDIENT CONCENTRATIONS

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REVIEW

Abstract

The widespread use of sunscreen in daily life has prompted concerns regarding the safety of its ingredients. Despite FDA approval of 16 sunscreen components, recent studies urge a reevaluation due to potential adverse effects. This systematic review examines the absorption of sunscreens, their toxicity, and the concentrations of ingredients found in urine and plasma. Conducted searches in Medline (PubMed), Scopus, Embase, and Cochrane until 05/08/2021 yielded data from 21 studies meeting the inclusion criteria. Among these studies, 18 reported complications associated with sunscreen use, such as rash, irritation, immune system disorders, DNA damage to the stratum corneum, and hormonal disruption. Additionally, 4 articles detailed the maximum concentrations of sunscreen ingredients in plasma, while another 4 reported urinary concentrations of these ingredients.

In 2016, the FDA suggested a concern level of 0.5 ng/mL for sunscreen ingredients in plasma. Notably, ingredients like avobenzone, octocrylene, ecamsule, homosalate, octisalate, enzacamene, octinoxate, and oxybenzone were detected at levels exceeding 0.5 ng/mL in the blood after 1-4 daily applications of sunscreen.

While sunscreen application effectively reduces the risks associated with sunlight exposure, concerns arise due to the potential adverse effects related to their penetration through the skin. These findings highlight the need for a comprehensive analysis of sunscreen toxicology. Moreover, highly absorbed ingredients should be replaced with less absorbed compounds to minimize bodily accumulation and associated risks. Additionally, investigating the lifelong exposure of infants and children to sunscreen further emphasizes the necessity for in-depth toxicological investigations.

Keywords: Sunscreens adverse effect; Sunscreens ingredient; Plasma concentration; Percutaneous penetration; Urine concentration.

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INTRODUCTION

Sunscreen products, specifically designed for human sun protection, come in various forms like creams, gels, lotions, oils, sticks, and sprays (Saraswat A , 2012) In the USA, these products are classified as over-the-counter drugs. The initial use of primary synthetic sunscreens dates back to 1928, with the first major commercial product hitting the market in 1936 (Shaath N, 2005). Around one-third of adults typically or consistently use sunscreens when exposed to the sun, with 14% of males and 29% of females in the US regularly applying sunscreen to their faces and other body parts

Sunscreens fall into two main categories: physical and chemical. Physical sunscreens, like titanium dioxide and zinc oxide, work by scattering, reflecting, or blocking UVA, UVB, and UVC radiations (Sayre RM, 1990). Most sunscreens contain organic compounds, such as aminobenzoic acid, avobenzone, cinoxate, dioxybenzone, ensulizole, homosalate, menthyl anthranilate, mexoryl S.X., octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, padimate O, phenyl benzimidazole, sulisobenzone, and trolamine salicylate, which absorb UV radiation and scatter solar energy (Benson HA, 2000). Notably, sunscreen consumption has been on the rise, with usage starting as early as 6 months of age (Shaw T., 2010).

Prolonged exposure to UV radiation over time accelerates skin aging and heightens the risk of skin cancer (Seite S. 2010). UVB rays specifically contribute to DNA damage, epidermal hyperplasia, and skin inflammation (Berton TR., 2001). Skin cancer stands as one of the most prevalent cancer types (Food & Administration D. Sunscreen drug products for over- the counter human use; , 1993), with nearly 5 million new cases reported annually in the US, including around 90,000 melanomas, known as the deadliest form of skin cancer.

Active ingredients in sunscreens, utilized in personal care and cosmetics, function by absorbing photon energies from UVA (320–400 nm) and UVB (290–320 nm) rays (Burnett ME., 2015).

MATERIAL AND METHOD

In recent times, there has been a surge in reports highlighting the adverse effects of sunscreens, with approximately 12% of users reporting irritation (Bryden A., 2006). Moreover, concerns have escalated regarding potential internal organ effects. Both in-vitro and in-vivo studies have observed systemic exposure (Bronaugh RL, 1999). To address safety concerns, the FDA has suggested a steady-state concentration of 0.5 ng/ml in the bloodstream as a threshold for the active ingredients found in sunscreens (Wang J., 2019).

The FDA allows a bloodstream concentration of up to 6% for Benzophenone-3 (BP-3) (Hexsel CL , 2008). A study involving 25 volunteers who applied a sunscreen containing 4% BP-3, twice daily for 5 days, revealed an increase in accumulation with repeated use. The findings indicated that 1.2-8.7% (with a mean of 3.7%) of the total applied amount of BP-3 was excreted in urine (Gonzalez H , 2006).

Studies conducted in vivo investigating the impact of BP-3 on children's birth weight and gestational age raised concerns about the hormonal effects of sunscreen (Ghazipura M , 2017). Additionally, BP-3 has shown proliferative effects on MCF-7 breast cancer cells [28]. The cytotoxicity associated with BP-3 might be attributed to oxidative stress, potentially linked to elevated intracellular levels of Zn2+ (Utsunomiya H , 2019).

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Shamseer L , 2015) throughout this study. Our inclusion criteria encompassed English studies involving sunscreen use in the human population, focusing on the examination of sunscreen ingredient concentrations in blood or urine, as well as side effects following sunscreen application. We excluded review articles, case reports, in-vitro studies, and any studies that did not meet our specified inclusion criteria.

Our search spanned PubMed (http:/ncbi.nlm.nih.gov/pubmed), Scopus (http:/WWW.scopus.com), Embase (http:/WWW.embase.com), and Cochrane (https:/www.cochranelibrary.com/) up to 05/08/2021, encompassing all articles relating to sunscreen use in humans for comprehensive analysis.

Out of 3148 studies initially considered, 869 duplicate articles were removed, leaving 2279 articles for screening by reviewers. This screening process involved two independent reviewers assessing the articles. After a thorough title-abstract screening, 358 articles were evaluated in full text. Ultimately, 21 articles aligned with the inclusion criteria and were thoroughly examined by the reviewers. These selected studies documented complications arising from sunscreen usage, along with the concentrations of sunscreen ingredients found in human plasma and urine over durations ranging from a single day to several years, encompassing either partial or whole-body applications.

RESULTS AND DISCUSSIONS

Out of the 21 articles selected for data extraction, 4 detailed the maximum plasma concentrations of sunscreen ingredients, 4 articles outlined the concentration of ingredients in urine, and 18 articles documented complications associated with sunscreen use.

Active ingredients in sunscreens, including avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate, enzacamene, and octinoxate, exhibit systemic absorption upon application to human skin. In a study by Janjua et al. in 2008, sunscreens containing 10% each of benzophenone-3, octinoxate, and enzacamene showed maximum plasma concentrations of 187 ng/mL for females and 300 ng/mL for males for benzophenone-3, indicating higher plasma concentrations than the other ingredients (Janjua N , 2008).

Another study by Matta et al. found that using 2 mg/cm^2 of various sunscreen formulations (lotions and sprays) covering 75% of the body resulted in plasma concentrations of oxybenzone ranging from 169 to 209 ng/mL, avobenzone at 1.8 ng/mL, octocrylene at 5.7 ng/mL, homosalate at 23 ng/mL, octisalate at 5.8 ng/mL, octinoxate at 7.9 ng/mL, and ecamsule at 1.5 ng/mL (Matta MK , 2019). Comparison between lotion and spray forms revealed higher concentrations of active ingredients in the plasma with lotions. Notably, systemic exposure remained above 0.5 ng/mL for over 50% of participants up to 7 days for avobenzone, octisalate, and octinoxate; 10 days for octocrylene; and 21 days for homosalate and oxybenzone (Matta MK , 2019).

Systemic exposure to all sunscreen components across various products exceeded 0.5 ng/mL

after a single application and sustained levels above this threshold for up to 23 hours post-application. The systemic exposure for all examined active ingredients remained above 0.5 ng/mL for more than 50% of participants: up to 7 days for avobenzone, octisalate, and octinoxate; 10 days for octocrylene; and 21 days for homosalate and oxybenzone (Matta MK, 2020).

In a study by Hiller et al., plasma and urine samples were collected from 20 healthy volunteers before, during, and after a real-life exposure scenario involving the use of a commercial sunscreen formulation for one day. They found avobenzone concentrations reaching 11.7 ng/mL and octocrylene at 25.0 ng/mL in human plasma (Hiller J , 2019).

Repeated exposure to sunscreens and their metabolites leads to accumulation within the human body, particularly evident when exposures are repeated over consecutive days. For instance, the application of sunscreen formulations containing 10% of each BP-3, octinoxate, and enzacamene (at 2 mg/cm2) on the entire body daily for a week resulted in average urine concentrations of 60 ng/mL for BP-3, 5 ng/mL for octinoxate, and 5 ng/mL for enzacamene in females, and 140 ng/mL for BP-3, 7 ng/mL for octinoxate, and 8 ng/mL for enzacamene in males (Janjua N , 2008). Notably, repeated whole-body application of benzophenone-3 (BP-3) increased BP-3 excretion after 2 days, reaching a steady-state after 3 to 5 days before subsequently declining (Janjua N , 2008).

Furthermore, after six days of applying sunscreen four times daily, the average urinary levels of octocrylene and avobenzone were 7.9 ng/mL and 1.7 ng/mL, respectively (Hiller J , 2019).

Following the application of sunscreen onto the skin, organic sunscreens like avobenzone, benzophenone-3, octocrylene, enzacamene, and octinoxate were detected in urine (Kunisue T, 2012). Notably, benzophenone-3 exhibited the highest urine concentration among the various UV filters (KunisueT, 2012) of sunscreen remains elusive.

CONCLUSIONS

Sunscreens play a crucial role in mitigating the risks associated with sunlight exposure on the skin. However, conclusive documentation of the long-term adverse effects To mitigate potential risks, ingredients with high systemic absorption could be replaced by less penetrating substances that can be fully excreted.

It's advisable for consumers to apply these substances solely to sun-exposed areas of the body to minimize potential accumulation. Prescribers of sunscreen should be particularly vigilant regarding sunscreen ingredients, especially when recommending them to children, pregnant women, individuals with a history of skin conditions, hormonal disorders, or vitamin D deficiency. Additionally, exploring the incorporation of nanotechnology could limit their penetration beyond the epidermis, potentially preventing entry into the bloodstream and reducing the risk of accumulation in body tissues and subsequent side effects.

Considering the lifelong use of sunscreens and the significant percutaneous penetration of organic compounds, it's prudent to undertake comprehensive acute and long-term toxicological assessments to ensure safety.

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