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THE EFFICACY AND SAFETY OF SUNSCREENS: BALANCING UV PROTECTION WITH HEALTH AND ENVIRONMENTAL CONCERNS OF BENZOPHENONE-3

Manali Sharma [*], Y. S. Sarangdevot and Jaya Agnihotri

B. N. College of Pharmacy, B. N. University, Udaipur - 313002, Rajasthan, India.

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Correspondence to Author:
Manali Sharma

Assistant Professor
B. N. College of Pharmacy,
B. N. University, Udaipur - 313002,
Rajasthan, India.

E-mail: manalipharma13@gmail.com

ABSTRACT: Ultraviolet (UV) radiation from natural sunlight is a well-recognized contributor to skin damage, including sunburn, photoaging, and an increased risk of skin cancer. Photoprotective agents such as sunscreens and sunblocks play a crucial role in reducing these effects by absorbing, reflecting, or scattering UV radiation. Benzophenone-3 (BP-3) is a widely used organic UV filter that effectively absorbs UV radiation and enhances the photostability of personal care products. However, its extensive use has prompted scientific and regulatory interest regarding its safety profile and environmental fate. Regulatory agencies in several regions have established concentration limits for BP-3 based on available toxicological and exposure data, yet human exposure remains common, highlighting the need for continued evaluation. Sunscreens and sunblocks differ in their mechanisms of action, with chemical filters primarily absorbing UV radiation and physical filters providing surface-level reflection and scattering. Both approaches contribute significantly to the prevention of UV-induced skin damage. UVA and UVB radiation, particularly long-wave UVA, are known to penetrate the skin and are associated with cumulative biological effects, including photoaging and DNA damage. The growing global incidence of skin cancer reinforces the importance of effective and broad-spectrum photoprotection. Modern sunscreen formulations combine inorganic filters such as titanium dioxide and zinc oxide with organic UV absorbers to enhance efficacy. While BP-3 has been shown in experimental and observational studies to exhibit biological activity, including skin penetration and systemic absorption, reported associations with cellular, endocrine, or developmental effects are largely based on in vitro, animal, or limited epidemiological evidence and remain an area of ongoing investigation. Consequently, current research efforts focus on improving sunscreen safety through comprehensive risk assessment, development of alternative UV filters, refinement of regulatory guidelines, evaluation of environmental impacts, and increased public awareness. Achieving an optimal balance between effective photoprotection and long-term safety remains a key objective in sunscreen research and public health policy.

INTRODUCTION: Ultraviolet (UV) radiation from natural sunlight is a well-recognized cause of both acute and chronic skin damage, including sunburn, photoaging, and an increased risk of skin cancer [1].

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Photoprotective agents such as sunscreens and sunblocks are widely used to reduce these harmful effects by limiting UV penetration into the skin. Understanding the mechanisms and safety profiles of these agents is essential for optimizing skin protection and minimizing potential health risks **Fig. 1** [2-3].

Benzophenone-3 (BP-3; 2-hydroxy-4-methoxy-benzophenone) is a commonly used organic UV filter in sunscreen formulations due to its ability to absorb UV radiation and enhance product photostability. In addition to sunscreens, BP-3 is incorporated into various personal care products, including cosmetics, fragrances, shampoos, and conditioners. This widespread application, along with its environmental presence, has led to increased human exposure [4-5]. Regulatory agencies have therefore established concentration limits for BP-3 based on available safety data. Nevertheless, biomonitoring studies report detectable levels of BP-3 in human samples, indicating ongoing exposure and underscoring the need for continued evaluation of its toxicological profile and risk–benefit balance **Fig. 2** [6].

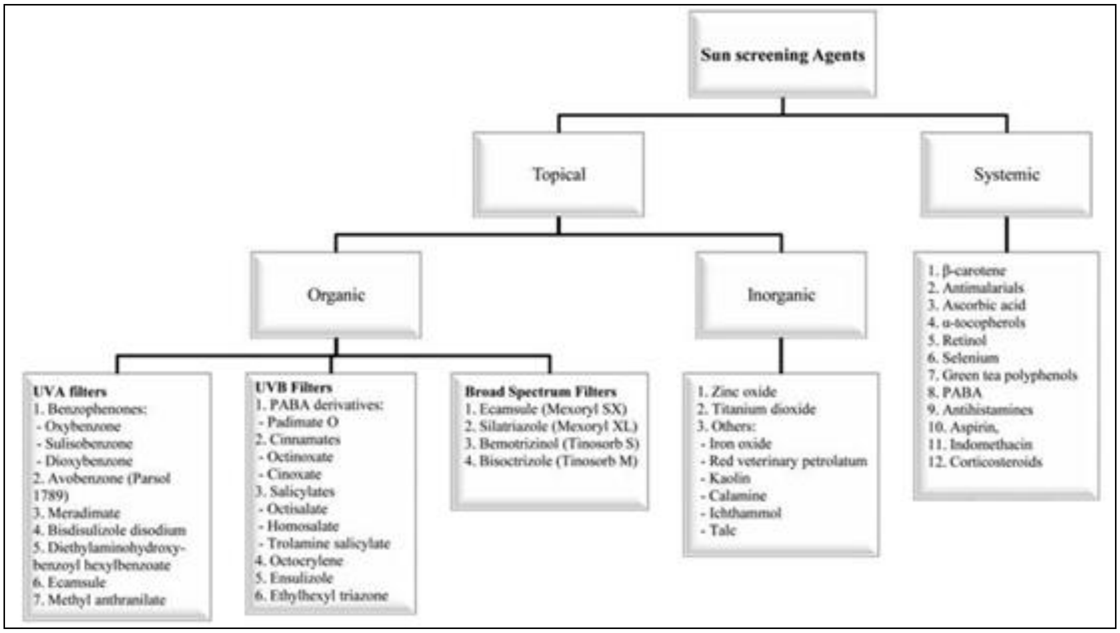

FIG. 1: CLASSIFICATION OF SUNSCREENING AGENTS

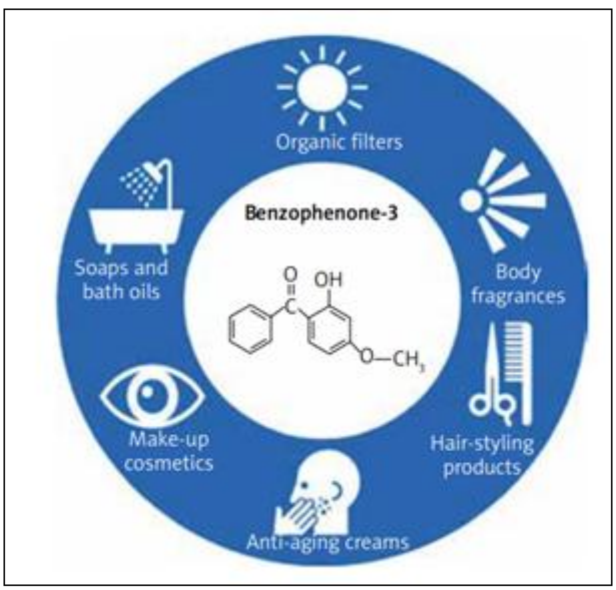

FIG. 2: BENZOPHENONE-3 SOURCES IN PERSONAL CARE PRODUCTS [7]

Photoprotective Agents:

Sunscreens vs. Sunblocks: Photoprotective agents can be categorized into two primary types: sunscreens and sunblocks. Sunblocks are generally opaque when applied to the skin, providing a physical barrier that blocks a higher percentage of UV light compared to sunscreens. Sunscreens, on the other hand, are typically translucent and require frequent reapplication to maintain their efficacy.

Both types of agents are essential in protecting the skin from the harmful effects of UV radiation, although their mechanisms and applications differ significantly [8-9].

UV Radiation:

Spectrum and Impact: UV radiation encompasses a broad spectrum ranging from 40 to 400nm (30–3eV), divided into various categories: Vacuum UV (40–190nm), Far UV (190–220nm), UVC (220–290nm), UVB (290–320nm), and UVA (320–400nm). Of these, UVA and UVB are the most medically significant, with distinct subtypes within UVA—short-wave UVA (320–340nm) and long-wave UVA (340–400nm) the latter constituting the majority of UVA radiation [10-11-13].

The Prevalence and Impact of Sunburn: Sunburn remains the most commonly encountered form of skin damage resulting from UV exposure. Despite the widespread use of sunscreens, improper usage and inadequate application contribute to the high prevalence of sunburn, particularly among individuals with fair skin and young people with sensitive skin. In the United States, sunburn affects approximately 34.4% of adults annually, while in Sweden, children are frequently affected, highlighting the importance of effective sunscreen use in preventing sunburn and its associated risks [14-17].

Rising Incidence of Skin Cancer: The incidence of skin cancer, including squamous and basal cell carcinomas, has been increasing worldwide. This trend has led to a greater emphasis on the use of photoprotective agents, both therapeutically and prophylactically. Evidence suggests that consistent use of these agents can significantly reduce the risk of skin cancer and other UV-induced skin damage, reinforcing the need for widespread awareness and education regarding their proper use [18-19].

Composition and Mechanism of Action of Sun-screening Agents: Modern sunscreens are formulated with combinations of inorganic and organic UV filters to achieve broad-spectrum protection. Common inorganic filters, such as titanium dioxide (TiO_2) and zinc oxide (ZnO), primarily act by reflecting and scattering UV radiation, while organic filters including avobenzone, octocrylene, and bemotrizinol absorb high-energy UV photons and dissipate the energy as heat. The strategic combination of these agents enhances coverage across both UVA and UVB regions of the UV spectrum [20-22]. Inorganic particulates deposited in the superficial layers of the skin increase the optical path length of incident UV photons, thereby improving the sun protection factor (SPF) through enhanced photon scattering and absorption. Additionally, the inclusion of antioxidant components in some formulations helps mitigate UV-induced oxidative stress by reducing the formation of reactive oxygen species, contributing to improved photoprotection beyond direct UV filtering [20-22].

Ideal Characteristics of Sun-screening Agents: An ideal sunscreen should be safe, chemically inert, nonirritating, nontoxic, and photostable. It should provide complete protection against both UVA and UVB rays, with an SPF of 30 or greater, and remain effective even after sweating and swimming. The formulation should be cosmetically acceptable, ensuring that it remains on the upper layers of the skin. Sunscreens should also effectively scavenge reactive oxygen species, preventing oxidative damage and minimizing the cumulative health hazards associated with sun exposure [23-24].

The Role of Insect Repellents in Sunscreen Formulations: To address the risk of insect-borne infections, some sunscreen formulations include insect repellents such as picaridin and N,N-diethyl-3-methylbenzamide (DEET). Picaridin is often preferred over DEET due to its lower potential for chemical penetration when used alongside sunscreen agents like benzophenone-3 (BZ-3) [25-26].

Metabolism and Mode of Action: BP-3 is designed to act on the skin surface; however, its small molecular size allows it to penetrate the skin, entering the bloodstream and potentially affecting various organs. BP-3 has been detected in serum at significantly higher concentrations than other chemical filters. It can bind to carrier proteins in plasma, potentially interfering with the function of sex and thyroid hormones. Animal studies have shown BP-3's presence in vital organs and even human breast milk and amniotic fluid. Its lipophilic nature suggests it could cross the blood-brain barrier, posing risks to the central nervous system. BP-3 is primarily excreted in urine after conjugation with glucuronic acid, but its long terminal half-life suggests potential accumulation in the body. BP-3 absorbs UVA, UVB, and UVC radiation effectively, reducing UV-induced radical formation and possessing antioxidative properties. However, UV irradiation can degrade BP-3, generating free radicals and other reactive intermediates that might harm skin molecules.

Studies on aquatic organisms indicate that BP-3 can induce oxidative stress, affecting antioxidant enzyme activity and glutathione levels, leading to potential adverse effects on metabolism and energy production. Similar oxidative stress-related effects have been observed in higher organisms, suggesting BP-3's potential to bioaccumulate and exert harmful effects through oxidative stress generation [27-28].

Potential Toxic Effects on Human Health:

Skin and Cellular Effects: Benzophenone-3 (BP-3) has long been recognized as a cause of photoallergic contact dermatitis and is among the more frequently reported sensitizers in sunscreen formulations. Cross-reactivity with structurally related compounds such as octocrylene and ketoprofen has been documented, and rare cases of severe hypersensitivity reactions have been reported.

Experimental studies indicate that BP-3 and its metabolites can penetrate skin cells and, under UV exposure, induce oxidative stress, mitochondrial dysfunction, and apoptosis in human keratinocytes. These effects are largely attributed to increased reactive oxygen species (ROS) generation and lipid peroxidation, though their clinical relevance at typical exposure levels remains under investigation.

Genotoxicity and Developmental Effects: BP-3 has been shown to cross biological barriers, including the placenta, raising interest in its potential developmental effects. Evidence from in vitro systems and aquatic and insect models suggests that BP-3 may exert genotoxic or mutagenic effects, including DNA damage and altered gene expression.

However, human data remain limited and inconsistent. Epidemiological studies evaluating prenatal exposure to BP-3 have reported mixed findings, with some suggesting associations with developmental outcomes and others reporting no significant effects. Consequently, current evidence does not allow definitive conclusions regarding BP-3-related developmental toxicity in humans [29-31].

Reproductive and Endocrine Effects: BP-3 is classified as a potential endocrine-active compound due to its ability to interact with estrogen, androgen, and progesterone receptors. Animal and *in-vitro* studies indicate that BP-3 exposure may influence gametogenesis and reproductive hormone signaling. In humans, BP-3 has been detected in biological fluids, including seminal plasma, and has been explored for possible associations with reproductive disorders such as endometriosis. However, epidemiological findings regarding fertility outcomes are inconsistent, and causal relationships have not been firmly established.

Neurotoxicity: Experimental evidence suggests that BP-3 can cross the blood–brain barrier and affect neuronal cells. *In-vitro* and animal studies indicate that BP-3 exposure may impair neuronal viability, induce apoptosis, and alter neurodevelopmental processes, particularly during early life stages. While some studies have proposed potential links between early BP-3 exposure and long-term neurological outcomes, evidence from human studies remains limited. As such, the relevance of these findings to neurodegenerative disease risk in humans remains speculative and warrants further investigation [31-35].

Conclusion and Future Direction: Photoprotective agents, particularly sunscreens, play a critical role in preventing UV-induced skin damage and reducing the long-term risk of skin cancer. Their effectiveness in providing protection against both UVA and UVB radiation highlights their importance as a cornerstone of comprehensive photoprotection strategies. Advances in sunscreen formulation have significantly improved efficacy and user compliance, reinforcing their public health value.

Despite these benefits, increasing attention has been directed toward the safety of certain sunscreen ingredients, including benzophenone-3 (BP-3). While BP-3 is an effective UV absorber and photostabilizer, its widespread use, systemic absorption, and environmental persistence have raised questions regarding potential long-term effects. Experimental and epidemiological studies suggest possible associations with endocrine activity and other biological effects; however, the available human data remain limited and, in some cases, inconsistent. These uncertainties underscore the need for cautious interpretation and highlight existing knowledge gaps. Future research should prioritize well-designed longitudinal and mechanistic studies to better characterize real-world exposure levels, bioaccumulation potential, and long-term health and environmental outcomes associated with BP-3 and similar UV filters. Continued development of safer, broad-spectrum alternatives and refinement of regulatory frameworks based on evolving scientific evidence are essential. Additionally, improved public education on appropriate sunscreen use and formulation selection will help maximize protective benefits while minimizing potential risks. Overall, achieving a balanced approach that maintains effective photoprotection while ensuring human and environmental safety remains a key objective for future sunscreen research and development.

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