Solar-Energy-Absorbing Substances and Oxidative Stress and Inflammatory Diseases

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Cambridge
Scholars
Publishing

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This book first published 2017

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-4438-5062-4
ISBN (13): 978-1-4438-5062-9

Acclinis falsis animus meliora recusat
The mind charmed by false appearances refuses to admit better things
Quintus Horatius Flaccus, 65–8 B.C.

Nullus est liber tam malus ut non aliqua parte prosit
No book is so bad that some parts of it could not be useful
Gaius Plinius Secundus, Pliny the Elder, 23–79 A.D.
Gaius Plinius Caecilus Secundus, Pliny the Younger, 61–114 A.D.

In vitium ducit culpae fuga, si caret arte
When we try to avoid a fault, we are led to the opposite unless we be very careful
Quintus Horatius Flaccus, 65–8 B.C.

Non multa, sed multum
Not multifarious, but many
Gaius Plinius Caecilus Secundus, Pliny the Younger, 61–114 A.D.

Feci quod potui faciant meliora potentes
I have done what I could let those who can do better

TABLE OF CONTENTS

ABSTRACT

Critical evaluations are presented on myths and facts about solar-energy-absorbing substances, including sunscreen agents, their influence on skin cancers and other cancers and diseases, and beliefs that have been promulgated over the years about the prevention of skin cancers by using sunscreen agents, i.e., the use of solar-energy-absorbing substances that actually are known to undergo photophysical and photochemical reactions generating toxic oxygen species and other maladies in biological systems. A general consensus is emerging that the use of sunscreen agents cannot prevent the photoinitiation of malfunctioning of many biological systems, such as immunosuppression, DNA degradations, and malignant melanomas, just to mention a few. On the contrary, sunscreens and their formulation components could be involved in enhancing the negative solar-energy-induced effects by skin penetration and transport of xenobiotics through the skin and by their own adverse properties, such as estrogenic environmental effects. This review encompasses a wide range of topics that are relevant to understanding the complexities of biological effects that are generated by solar radiations. The main areas include the photochemistry of skin components urocanic acid and melanins, allergic reactions caused by sunscreen agents and ingredients in commercial sunscreen products, radiation-induced damages to the human skin including DNA components, glycations, immunosuppression and related systems, cancerous dermatologic changes, human skin cancers induced by solar radiations and mechanisms of anticancer drugs, mechanisms of photoexcitations and energy dissipations, formation and reactions of reactive oxygen species (ROS), photochemistry of organic and inorganic sunscreen agents, exogenous and endogenous antioxidants as possible sunscreen ingredients, and as oral medications either for the prevention or cure of various diseases including cancers. Critical appraisals are presented of clinical studies involving vitamins and nonsteroidal anti-inflammatory agents, including Aspirin™, for either alleviating, mitigating, or even curing of various inflammatory diseases including cancers. Finally, we scrutinize the intertwining of reactive oxygen species with processes of infection, chronic inflammation, chronic pain, pruritus, cancer, and other inflammatory diseases. We have attempted to avoid an

overly specialized presentation of topics throughout this work in order to enable a non-specialist reader to follow the most advanced topics.

ACKNOWLEDGMENTS

The authors are sincerely grateful to Professor Luceido Greci, Dipartimento di Science e Tecnologie Chimiche Universita Politecnicà della Marche, Ancona, Italy Professor Kálmán Hideg, Department of Organic and Medicinal Chemistry, University of Péc, Hungary and Dr. Dominique Moyal, L'Oréal Recherche, France for the impartial and critical evaluations of our manuscript and the constructive suggestions.

We thank Mrs. Thelma Lubkin for expert computer literature retrievals, Piotr Jawdosiuk, Monika Jurzyk, Ondrej Zaborsky and Szymon Kosiński, Panslavia Chemical LLC, Milwaukee, Wendy Grober, Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, for technical assistance, Dr. Richard Markuszewski, formerly Program Director of the Ames Laboratory at Iowa State University, and retired Vice President from the Institute of Gas Technology, for critical proofreading of the manuscript and Mr. J. Michael Clumpner, Nova Molecular Technologies, Janesville, WI, and Gary Klein, International Specialty Chemicals, Tarrytown, NY, for financial donations.

The authors are also grateful to Mrs. Lydia Dyer and to Professor Andrew Kakabadse of the Henley Business School, England, for recommending and advocating the manuscript to Cambridge Scholars Publishing Ltd, England, which has led to its acceptance for publication. We are happy for the assistance of Dr. Sharbil Firsan in editing and proofreading the manuscript for this second printing of the book.

INTRODUCTION

Solar radiation is of paramount importance for the sustenance of all living species on this planet, whereby it provides the energy for the maintenance of health, livable climatic conditions, and illumination for visual perception. It also mediates the photosynthesis of plant materials from carbon dioxide and water in the presence of chlorophyll, at the same time generating the essential molecular oxygen gas.

About 5000 to 2500 years before the present (B.P.), the peoples of ancient civilizations, e.g., the Egyptians, Assyrians, Babylonians, Aztecs, Incas, and ancient Greeks were overwhelmed by the power of sunlight and deified and worshipped the sun as the sun god Ra or Re in Egypt [1–3] and Helios in Greece [2]. However, in Greece about 2400 B.P. [2], the philosopher Anaxagoras dared to declare that the god Helios is simply a big fiery rock, and the famous physician Hippocrates advocated exposure to sunrays for ameliorating physical and even mental health problems. Similarly in the Roman Empire about 1800 B.P. [2], the physician Galen(us) was prescribing heliotherapy, and the practice of "sunbathing" was widely accepted during the Greco-Roman era. Since the decline of the Roman Empire, photo/(helio)-therapy and exposure to solar radiation for health and cosmetic purposes, with some interruptions during the Middle Ages, continued unabated to the present, and, at the beginning of the last century, the general opinion prevailed that solar light has a beneficial effect on health. However, during the past two centuries, publications sporadically appeared [2] on the detrimental effects of solar radiation on humans and various other species in vivo and in vitro, and, in the middle of the last century to the present, it was firmly established [1–9] that there are harmful consequences of either prolonged or frequent exposures to solar and other sources of ultraviolet radiation. The serious effects of the interaction of ultraviolet light with components of the human skin were shown to result in dermatological changes of the skin, leading ultimately to the development of skin cancers [1–9]. As a matter of fact, the ultraviolet part of solar radiation has been considered a "perfect carcinogen" and implicated in the carcinogenesis of human skin [4, 5].

The realization by the 1920s that solar radiation is the cause of erythema, i.e., the reddening, inflammation, and the "sunburn" effect of the human skin, led to the commercial development of the so-called sun-

screens. The first compounds selected for sunscreen applications were benzyl salicylate and benzyl cinnamate. These compounds were readily available at that time because they had been synthesized and patented on several occasions since 1869 for various pharmaceutical applications [10]. The commercial sunscreen products were marketed for the first time in 1928 in the United States [11, 12]. By the way, the word sunscreen is a misnomer, a catchword. The compounds are in reality ultraviolet-light-energy-absorbing substances. Nevertheless, the catchword is still used for simplicity's sake. Over the past eighty years, a large number of various compounds have been synthesized and evaluated for sunscreen use; however, only about fifty compounds are registered internationally [5, 11–13] to be used in lotion, cream, and spray "formulations" for protection against solar radiation. In the United States, these products are sold to the public as "over-the-counter" drugs [13].

Incidentally, during the same period, skin cancer cases, in particular melanomas, have grown at an alarming rate [5, 9]. Thus, in the 1930s, dermatologic cancers were practically unknown, in spite of the fact that large portions of the population were working on farm fields, exposed all day to solar radiation. At present, melanomas are the fastest growing cancers [5, 9]. Concomitant with these developments, the sales of sunscreen products worldwide also progressed at a brisk pace to more than three billion dollars annually [10]. There have been several hypotheses advanced to explain the rapid growth of melanoma cases, such as the depletion of the ozone layer, the enlargement of the "ozone hole," and the substantial increase of xenobiotics in the atmosphere, attributable to industrial pollution and the use of motor vehicles worldwide [14, 15]. In the meantime, it has been shown in a number of investigations that, on irradiation with ultraviolet light, many sunscreen compounds can cause allergic and toxic reactions on the human skin [16, 17], and undergo photochemically induced transformations, such as isomerizations, dimerizations, derivatizations, degradations, and reactions with molecular oxygen to give reactive oxygen species (ROS), which can cause the so-called oxidative stress in biological environments [5, 14, 18, 19].

In the present review, we critically evaluate various deleterious factors evoked by solar ultraviolet radiations in naturally occurring and synthetic ultraviolet-light-energy-absorbing substances, including sunscreens [4–9, 16–20]. The ultimate goal is to be able to assess the possible merits and demerits of currently used radiation "filters" and the reasons for the unprecedented growth of dermatological cancers.

SCOPE AND LIMITATIONS

The aim of this book is to establish a compelling general pattern for photochemical transformations of ultraviolet-light-energy-absorbing substances, in particular, in the presence of molecular oxygen, resulting in harmful reactive oxygen species that can cause mutations, carcinogenesis, and ultimately skin cancers. Comparatively little information is available in the scientific literature on the possible enhancement of the carcinogenic properties of ultraviolet radiations by sunscreen agents.

In the past fifty years, a steep increase has occurred in the number of publications on the harmful effects of ultraviolet radiations and the protective properties of sunscreens and other substances. Hence, it is impossible to make an exhaustive collection of references on the many interrelated and relevant topics for the present review. Instead, a selective search has been conducted with emphasis on data that have been published mainly during the past two decades. Efforts were made to include as much as possible review articles and monographs about the most relevant topics, since these publications contain more exhaustive collections of references. In this process, it was unavoidable that some worthy articles may have been overlooked.

In cases of biological evaluations, credence was placed first on the results of tests obtained on humans, then on in vivo tests obtained with the so-called "animal models", and last on in vitro tests. Furthermore, it was felt that interpretations of test data obtained on animals should be treated with caution when drawing conclusions on analogous conditions in humans. The results obtained using UVC radiation were seldom included since this radiation, to date, is effectively absorbed by the ozone layer, and, hence, is not involved in interactions with the human body. However, this radiation has been used to establish principles and to study biological mechanisms.

The present review uses chemical structures and schemes extensively, in contrast to many other relevant publications that tend to be descriptive. A number of related areas are excluded because they are outside its scope. Nevertheless, a few comments are warranted on some of the excluded topics. Thus, there exist a large number of non-malignant dermatologic diseases, which either are caused by solar ultraviolet radiations or are ameliorated or aggravated by radiations [6, 14, 15]. The photodermatoses

can have various origins, such as genetic, metabolic, degenerative, xenobiotically induced, and idiopathic, i.e., of unknown origin [14].

The skin disease psoriasis is treated with UVA in conjunction with methoxypsoralenes. The naturally occurring psoralenes are fucocoumarins, and are known to have tumorogenic properties [5–9, 15]. Nevertheless, it appears that this PUVA therapy is the best available treatment for the alleviation of this uncomfortable condition, while taking into account the possible risk for developing skin cancers.

Psoralenes have also been extensively employed, unwittingly, in cosmetics and sunscreen formulations for rapid suntanning effects in commercial suntan parlors [5–9, 15–21]. The radiations employed in these cases can be as high as 100% UVA radiation, with a 12 times higher dose than is present in solar radiation [9]. It appears that, under these circumstances, there would be a high risk of developing skin cancers. Nevertheless, about twenty-five million Americans seem to be oblivious to this risk, and are increasingly participating in these practices [9].

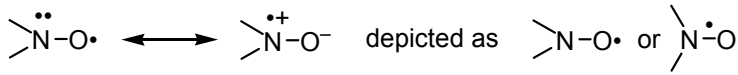
One of the beneficial attributes of solar radiation is the generation and regulation of vitamin D_2 and D_3 levels in humans [22–29]. The exposure of the skin to solar radiation results in the conversion of 7-dehydrocholesterol to vitamin D, which, in conjunction with the parathyroid hormone, regulates the homeostasis of calcium cations. It was found that an application of sunscreen agents to the skin causes a reduction of the formation of vitamin D. However, this reduction was believed to have no serious consequences since, although the levels of vitamin D were lowered, there was no noticeable effect on the serum parathyroid function and the calcium concentration, and it was assumed that the small amount of vitamin D required daily by the human body is provided by diets containing milk, egg yolk, butter fat, and fish. This simple assumption turns out to be only partially correct, since many persons cannot attain the required levels of about 1000 IU per day of vitamin D_3 by diet and occasional exposure to sunlight [30].

As a consequence, many health-related problems, including various cancers and other diseases, have been attributed to the vitamin D deficiencies. These problems are reflected in the following surprising and alarming statistics. Thus, for example, in the USA, the economic burden that is attributable to vitamin D insufficiencies, caused by inadequate UV radiation exposures was estimated at $40–50 billion in 2004, whereas the economic burden for the excess of UV irradiation exposures was estimated at $6–7 billion [26–28]. An extensive literature exists on all these topics, which are beyond the scope of our review [27].

Photodynamic therapy is well established in clinical oncology for the treatment of various cancers, including dermatologic cancers [30]. In this therapy, photosensitizers are used for absorption by cancer cells. On irradiation with a suitable light, the sensitizer molecules are promoted to excited singlet and triplet states, which readily interact with molecular oxygen to give toxic reactive oxygen species, causing the destruction of cancerous cells. This radiation method is closely related to the present review topic; however, the details of photodynamic therapy will not be discussed further.

Excluded from this review are at-length discussions of regulatory procedures for sunscreen products in various countries, formulations of sunscreen products, analytical quality controls, and marketing [31].

In the cited references, the authors use three nomenclatures—nitroxides, nitroxyls, and aminoxyls—for spin-labeled compounds containing the following free radical functional group:



The nomenclature of this functional group in compounds is always –oxyl, e.g., the compound TEMPOL is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl. The International Union of Pure and Applied Chemistry (IUPAC) has recommended the name aminoxyls.

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CHAPTER ONE

PHOTOCHEMISTRY OF THE HUMAN SKIN

A. Human Behavioral Practices with Sunscreen Applications. Predictive Significance of the Sun Protection Factor (SPF) in the Onset of Erythema and Other Biological Entities

It has been estimated that less than five percent of the total solar radiation energy is received by the earth's surface as ultraviolet radiation. This radiation has a pronounced and often long-lasting effect on mammals and plant species. The degree of the effectiveness of solar radiation on the earth inhabitants will depend on some of the conditions under which the sun rays impinge on the "human target", such as the intensity and the wavelength of the radiation, the duration of the exposure, the time of day the exposure occurs, the season, the geographic location, the atmospheric conditions such as clouds and fog, the pollution caused by xenobiotics, the prevailing extent of the ozone layer, the altitude above sea level, the vicinity of reflecting surfaces, e.g., water, snow, and sand, and a number of behavioral practices of the "human target", i.e., duration and type of outdoor activities, the type of clothing worn, the use of medication, which may migrate to the skin surfaces, and the use of UV light absorbing materials, e.g., sunscreens.

Furthermore, the intensity of the UVA and UVB radiations can be differently affected by some of the listed factors in wintertime as compared to summertime, whereby the intensity of UVB radiation will be diminished to a greater degree in wintertime than that of UVA radiation [1, 2]

Ideally, sunscreen application should occur before the first prolonged full body exposure to the sun is contemplated, initially for only short periods, and, preferably, not during the highest intensity of solar radiation. Clearly, this type of practice is a utopian ideal, since, in most cases, the use of ultraviolet filters follows after some degree of discomfort has been experienced, and in the worst cases, the photodamage is clinically detectable. At this stage, severe damage to the skin tissue may have already occurred. The damage can be either of a reversible or irreversible nature,

depending on the prevailing conditions during the sustained solar exposure. The damage can remain latent for long periods of time before a skin disease can be diagnosed.

A further problem is the mode of application of sunscreens to the skin [3–11]. Thus, even in cases where the sunscreen lotion or cream is applied to the skin prior to a full exposure to solar radiation, it is very difficult, if not impossible, to assure an application resulting in a film of perfect evenness and required thickness to achieve the desired protection, since there are no practical means to measure such a requirement. Although there exist photographic methods [8] that can be used [12] in clinical tests to insure a uniformity of sunscreen application to the skin, these methods would be impractical for use by the public "in the field". Thus, in practice, the casual applications of either a spray, which primarily dissipates into the surroundings, or a lotion or cream, will result in a film of uneven thickness, leaving either uncovered or thinly covered areas on the skin, which permit an effective penetration into the skin tissue by ultraviolet rays. Furthermore, the present system of labeling commercial products by manufacturers conveys, unsurprisingly, overly optimistic messages about the safety and effectiveness of their products. These messages include nonirritating, nonallergenic, premature aging prevention, sunburns and irritation, and even cancer prevention properties, which is clearly unsubstantiated in cases of basal cell carcinoma (BCC) and melanoma [3]. In addition, the present system of rating sunscreen preparations for effectiveness by assigning sun protection factors (SPFs), ranging from about 2 to 30 and higher, are primarily a guide for the prevention of a sunburn effect caused by UVB radiation [3, 11], while neglecting the more serious effects of solar radiation caused by the deeper penetrating UVA rays [3]. Thus, the public inadvertently develops a sense of full reliance on the safety and protecting properties of commercial sunscreen preparations [3]. Nevertheless, in order to have some idea about adequate protection against solar radiation by sunscreen products, the FDA in the U.S.A. has issued a recommendation to apply 2 mg/cm^2 of sunscreen agents to the skin [4, 10]. This guideline could be useful provided the public intuitively knows how much of a given sunscreen agent to apply to the skin in order to achieve the desired effect. In actual practice, however, it has been found that the quantities of sunscreen agents on the skin amounted to only 0.5 mg/cm^2 or less, i.e., a much lower dose than that recommended by the FDA [5–9]. Since the relationship between the percentage of absorbed UV radiation by the sunscreen at the skin and the SPF is not linear but logarithmic, the following result can be derived for the effective SPF [5, 6]. Thus, if the listed SPF for a sunscreen agent is 15, the effective SPF at a 0.5 mg/cm^2

coverage of the skin would be 5–6 times less, i.e., about 2.5–3 [4, 5]. Therefore, even in the unlikely event the whole skin was uniformly covered by the sunscreen product, the protection would be rated as poor and no better than the hereditary protection rendered by urocanic acid and melanins at no cost.

Under these conditions, it was estimated by the Environmental Working Group in the U.S.A. that the SPF of 15 actually results in a SPF value of about 2 with a UV transmission, i.e., the amount of radiation that reaches the skin, of about 50%. The same considerations in the case of SPF 30 result in an actual SPF value of 2.3 with a UV transmission of 43%. For an SPF 50, the actual SPF value would be 2.6 with a UV transmission of 38%, and an SPF 100 would be reduced to an actual SPF value of 3.2 with a UV transmission of 21%.

Concerning the SPF ratings of commercial sunscreen products by the manufacturers, it has become general practice in recent years to rate the sunscreen products with SPF values higher than 30, implying a superior product quality with higher SPF values. As a matter of fact, SPF values above 30 have only a psychological effect on the customer without a gain in quality, since it was shown by a plot [**Fig. 1A-1**] of the reduction of the erythemogenic radiation against SPF values to flatten at SPF 30, where 97% of the erythemogenic UV radiation has been absorbed, and the change from 97% to 99% was shown clinically to be irrelevant [13]. Therefore, in some countries, the labeling of commercial sunscreen products is restricted by authorities to SPF 30 and 30+. In 2011, the FDA allowed the use of SPF 50+ in spite of insufficient evidence that sunscreens with values above SPF 50 are of benefit [13]. The use of SPF 50+ is practiced in many other countries.

SPF values are obtained on the basis of the so-called minimal erythema dose (MED), i.e., the smallest dose of radiation that, at 24 hours, causes a minimally perceptible, but well defined, erythema after one single irradiation of the skins of volunteers. Since volunteers are used, one could expect that the MED would depend on the type of skin, pigmentation, and other factors, such as food intake by the volunteer, medications, and other conditions. Hence, various individual persons could have somewhat different MEDs. Therefore, for SPF calculations, an average MED value is used [13]. The sun protection factor (SPF) values are obtained by the following equation [13]:

$$\text{SPF} = \frac{\text{MED obtained in the absence of suscreen}}{\text{MED obtained with the tested suscreen}}$$

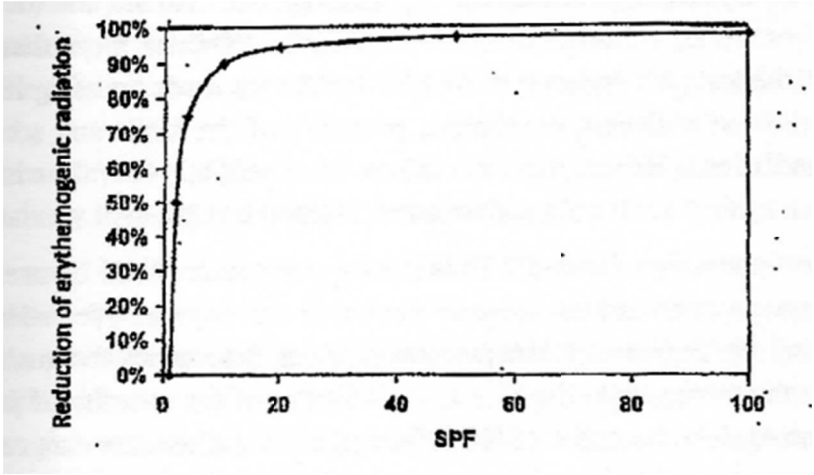

Fig. 1A-1. The logarithmic relationship between the percentage of filtered UV radiations and sun protection factor (SPF).

The values of the sun protection factor that are found on commercial products are indicative of the capacity of a given sunscreen product to provide protection against the sunburn effect (erythema) that is caused by irradiation of the skin with sunlight. Thus, e.g., an SPF of 20 as shown on the commercial product label would imply to the user that one could stay in the sun 20 times longer using the sunscreen than without the product application, provided, however, that the sunscreen is uniformly applied to the skin at 2 mg/cm^2. Since the UVB radiation, covering the 280–315 nm range of the UV spectrum, is about 1000 times more erythemogenic than the UVA2 (range 315–340 nm) and the UVA1 (range 340–400 nm), and, although the UVA radiations comprise more than 95% of the sunlight, the tests used for arriving at the SPF factors are conducted by using lamps emitting simulated solar radiation composed primarily of the UVB and some UVA, i.e., UVA2 radiations. Hence, SPF values are essentially useful as indicators of protection against sunburn, i.e., dermatitis, erythema [13].

The sun protection factor is inadequately understood by users and in scientific aspects, such as limitations of the implied protection, overestimation of protection, and the degree of UVA protection that determines the quality of protection. Furthermore, while the SPF is an indicator of the quantity of protection, the protection against the onset of reactive oxygen species (ROS) formation, that always occurs upon UV irradiation of sun-

screens and excipients on the human skin, and the degree of immunoprotection and warning of the onset of other maladies are uncertain [14–16].

In numerous publications over the years, the use of sunscreen preparations has been described for the prevention of the onset of damages to biological entities induced by solar radiations, such as immunosuppression, DNA damages resulting in thymine dimer formations, oxidative damages to the DNA caused by reactive oxygen species (ROS), and skin cancers, just to mention a few [17–19]. As will be seen in subsequent sections of this review, highly divergent results have been frequently reported by various authors on the same topic. Thus, e.g., in the case of some skin cancers, the applications of sunscreens have been found to be either (a) effective (b) ineffective or (c) contributing to the initiation of cancers. These divergencies can be explained on the basis of recent scientific recognitions. Thus, the question is whether the onset of the erythema, its prevention by application of sunscreens, and the use of the SPF as a predictive device for the estimation of the preventative qualities of sunscreens, could also be applied to the estimation of the onset of damages to other biological systems. In such cases, it would mean that persons with different MEDs would experience the onset of erythema to coincide with the onsets of damages to various biological systems, and the SPFs of sunscreens could be used as indicators for possible durations of exposure by the skin to UV radiations of sunlight [17–19]. However, in recent years, it was shown that the onset of erythema is not an indicator for the onset of damages to other biological systems. Furthermore, it was found that the onset of damages to biological systems other than erythema, such as damages to the DNA, immunosuppression, and oxidative damages by ROS often occur before the onset of the erythema. Hence, the SPFs of sunscreens are of no value for estimating the possible duration of protection by sunscreen against the UV radiation induced damages to those biological systems [17–19]. This whole area is exceedingly complex in detail, and has been extensively investigated [19–21]. (See **Section 2F**.)

UVA and UVB radiations can cause immunosuppression even at suberythemal doses. The photoinduced immunosuppression is of concern since it is believed that, as a consequence of immunosuppression, mutation of the p53 gene can occur resulting in loss of apoptosis control by the gene. Furthermore, the Langerhans cells contact hypersensitivity (CHS) and other biologically important entities are affected [22, 23]. Furthermore, there are great concerns about the endocrine disruptive properties of UV energy absorbing substances present in sunscreens and cosmetic products. These adverse effects have been studied in vitro and in vivo with

mice, rats, rainbow trouts, minnows, and human volunteers [24]. (For further biological properties of sunscreens, see **Section 2F**.)

It appears that the sun protection factor has no relevance to these events, since, on the basis of SPF values, it might be possible to estimate the period of exposure to the sun without a visible erythema, while no information can be obtained about the possible onset of the immunosuppression and other biological events that may occur prior to the erythema [17–23]. Hence, it seems to be unlikely that the exceedingly complex initiation pathways leading to cancers, in particular skin melanoma, could be prevented by using sunscreen agents. Nevertheless, a successful in vivo study with human volunteers was reported [25] using 0.5 and 1.0 mg/cm^2 of sunscreens with SPF 70–100 for protection against photodamage and skin cancers, whereas no protection was obtained by using sunscreens with SPF 30 and 50 [25].

UVA and UVB radiations induce structural and cellular changes in the tissues of the human skin by forming radicals and reactive oxygen species (ROS), whereby UVA radiations at 320–400 nm induce the formation of radicals and ROS in the lower parts of the dermis [26, 27].

The UV radiation induced harmful oxidative reactions are not unique to sunscreen products, since compounds of various classes with similar conjugated chromophores can undergo such reactions. Of particular importance is being aware that a large number of orally administered drugs and their metabolites readily migrate to the human skin and are exposed to UV radiations.

The extent of radical and ROS formation and the protection of the human skin by sunscreen agents can be quantitatively measured in vivo at the human skin by electron paramagnetic resonance spectrometry (ESR) and expressed as the radical sun protection factor (RSP).

The RSP can be similarly used as the SPF for the determination of increases in time for sun exposure of the skin with sunscreen to generate the same number of radicals and ROS as compared to unprotected skin [26, 27].

Another sun protection factor, the p53 labeling index, is obtained in vivo by an assessment of the sunscreen effectiveness in preventing the UV radiation induced DNA damage [28].

The use of SPF numbers on commercial sunscreen products should be abandoned. Instead, a device should be developed similar to the UV Color Index of the World Health Organization (WHO) that would enable the sunscreen user to assess by color changes the degree of solar radiation at prevailing exposure conditions.

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