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Blue Light and the Skin

Rolf Schütz

DSM Nutritional Products, R&D Personal Care & Aroma, Kaiseraugst, Switzerland

Abstract

In photodermatology, UV radiation is the component of the solar system that has attracted the most interest as it represents the greatest risk of skin damage from solar exposure. Efficient protection strategies have therefore been developed to protect skin against powerful solar radiation. Recently, there has been increasing evidence to suggest that less energetic radiation, such as visible light and infrared radiation, might also influence skin physiology. Yet, it remains unclear, regarding risk assessment, whether visible light irradiation induces positive or negative effects in skin and when appropriate protection is needed. This review focuses primarily on blue light as part of the visible spectrum and sets out current mechanistic understanding of the benefits and risks of blue-light exposure to skin. Furthermore, it discusses phototherapies and potential strategies for protecting against detrimental effects of blue light such as hyperpigmentation and premature skin aging.

Introduction

Life on earth has evolved under the presence of sunlight. Solar energy is harvested in organisms by specific photoacceptors and transformed into essential processes such as photosynthesis and vision. In higher vertebrates, organs exposed to sunlight, such as the eyes and skin, have developed various strategies that enable them to both benefit from radiation and protect against, prevent and repair any harmful effects. In photodermatology, UV radiation is the component of solar irradiance which has attracted the most interest as it represents the greatest risk of skin damage from solar exposure. Thanks to the knowledge gained over recent decades, efficient protection strategies have been put forward. These strategies are based primarily on adapting outdoor behaviors to individual circumstances and applying sunscreens, so as to protect against the harmful

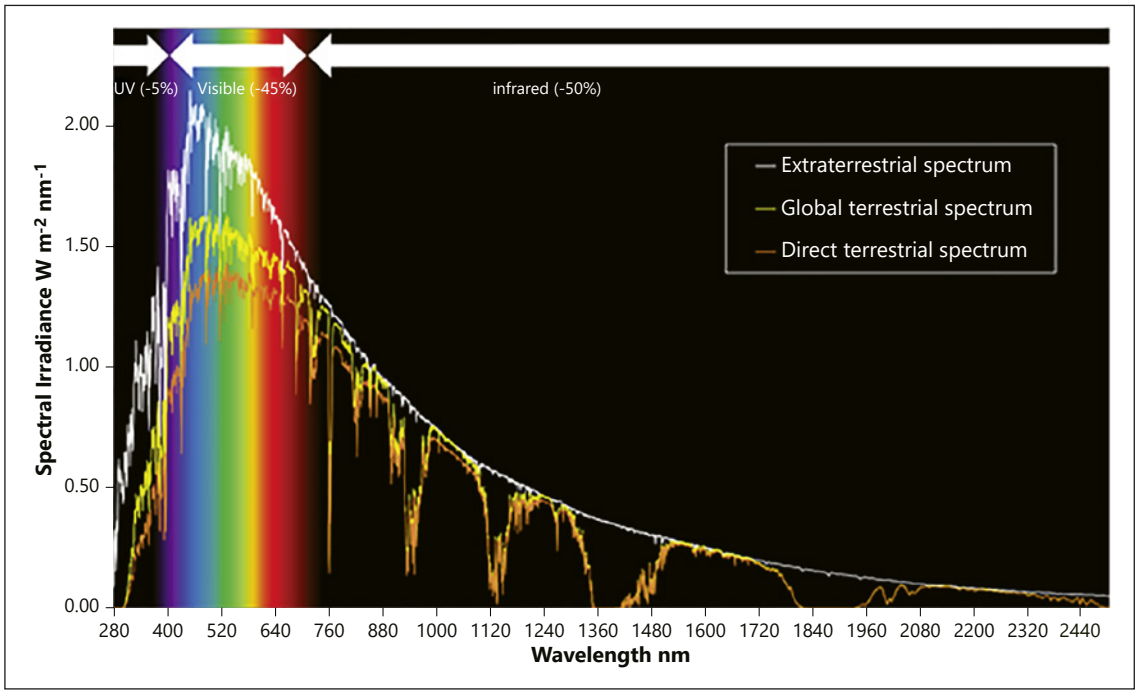

Fig. 1. Solar power distribution (in watts per square meter per nanometer of bandwidth) adapted from American Society for Testing and Materials (ASTM) G173–03 Reference Spectra [2] representing extraterrestrial spectral irradiance, the global total (direct and diffuse) spectral irradiance on the 37° sun-facing tilted surface for the atmospheric conditions, and direct normal spectral irradiance. The total integrated irradiances for the direct and hemispherical tilted spectra are 900.1 W m^{-2} and 1,000.4 W m^{-2}. Sunlight consists of about 5% UV radiation, 50% visible light, and 45% infrared light at sea level.

effects of the sun while benefitting from the positive ones. Recently, there has been increasing evidence that less energetic radiation than UV, such as visible light and infrared radiation, might also influence skin physiology. However, it has not yet been shown in a proper risk assessment, whether the cumulative effects are more harmful or beneficial and whether appropriate protection is needed. This review focuses on blue light as part of the visible spectrum and sets out current understanding of the benefits and risks of blue-light exposure to skin. Additionally, potential strategies are provided for protecting against detrimental effects of blue light as an environmental factor that may contribute, for example, to skin aging and hyperpigmentation.

What Is Blue Light?

The sun emits a tremendous amount of energy in electromagnetic radiation (solar constant 1,361 W/m^2 [1]). Only part of this solar radiation penetrates the atmosphere and reaches the Earth's surface as sunlight in the form of UV radiation (280–400 nm), visible light (400–760 nm), and infrared light (IR, 760 nm–1 mm). Solar spectral distribution on Earth (Fig. 1 [2]) comprises around 5% of irradiance in the UV range, 50% in the visible range, and 45% in the IR range at sea level [3]. Solar UV radiation at the surface of the Earth is composed of ~5% short-wavelength UVB rays (280–315 nm) and ~95% long-wavelength UVA rays (315–400 nm), while UVC

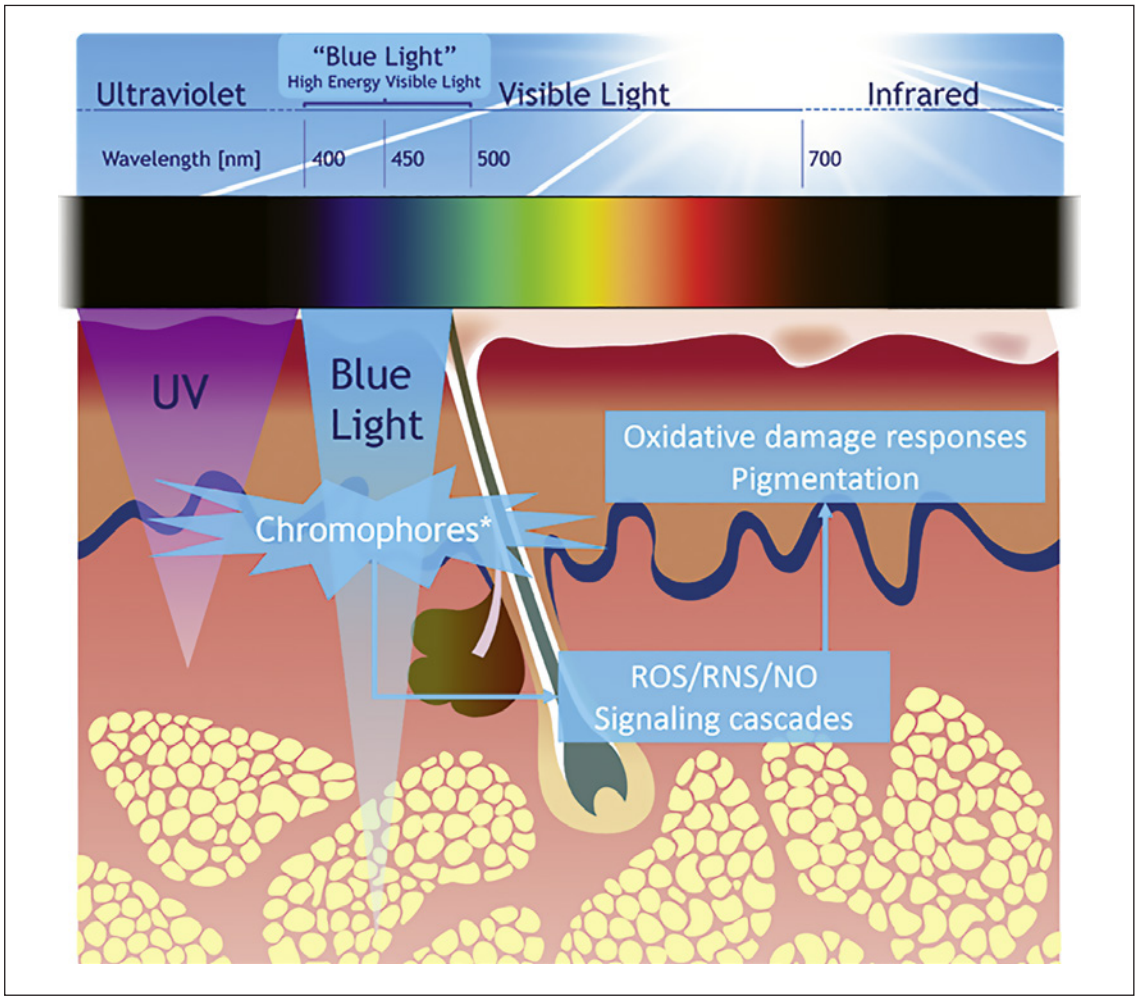

Fig. 2. Solar radiation on the skin. Blue light penetrates deeper than UV radiation, reaching the hypodermis. Penetration depth increases with higher wavelengths and peaks at near-infrared radiation (not depicted). Depth is also affected by the position and absorption spectrum of the chromophore in the skin. At molecular level, blue light is absorbed by specific endogenous chromophores, inducing oxidative stress and activating signaling cascades that lead to the modulation of cellular processes such as oxidative damage responses and pigmentation events.

(100–280 nm) is absorbed by ozone layers. Next to UV radiation, blue light makes up 20–30% of the daylight.

Most solar emission is not visible to human photoreceptors. Only a thin portion of the electromagnetic spectrum – between UV and IR radiation – provides the visible light that interacts with the eye's visual system, enabling the sensation of vision. Generally, visible light is regarded as the wavelength spectrum that is visible to most human eyes. Visible light is usually defined as radiation between 400 and 700 nm [4]; although under ideal conditions, humans can perceive light by exceeding the adjacent boundaries of near-UV and IR radiations, for example, ranging from wavelengths between 380 and 780 nm. Blue light refers to the most energetic light in the visible spectrum (Fig. 2) and is sometimes also called high-energy

visible light. Most commonly, it starts at 400 nm, with violet light after UVA, and ends in turquoise at 500 nm. As the spectral subdivisions of UVA, UVB, and visible light are arbitrary, the wavelength range may vary for different disciplines [4]. For photobiological considerations, the boundary of 400 nm between UVA and visible light is artificial as a photon with a wavelength of 399 nm (UVA) will most probably have the same effect as one with a wavelength of 401 nm (blue light). In this review, visible light refers to the wavelength range of 400–700 nm, commonly used in photodermatology.

Sources of Exposure to Blue Light

Nowadays, blue light can be found both outdoors and indoors, but this was not always the case. A long time ago, the only source of blue light for humankind was the sun. Eventually, after fire was utilized as additional lighting, incandescent lamps – a source of light emission similar in spectrum the sun – provided a reliable artificial form of light for about 100 years. More recently, pressure to use more energy-efficient lighting alternatives has led to the phase-out of incandescent lighting with bans of incandescent light bulbs taking effect from 2005 onward. The introduction of low-energy lighting, such as compact fluorescent lamps and light-emitting diodes (LEDs), and the widespread use of computer and mobile technologies have changed the nature of the light as we perceive it today. Most current white-light LED (i.e., blue LED with yellow phosphor) lighting devices have a spectral power distribution different to other light sources. Generally, LEDs emit blue light, primarily from 450 to 470 nm, combined with green/yellow light without significant UV, red, or any near infrared wavelengths [5].

In radiometry, quantitative power densities of light sources on a receiving surface are expressed as irradiance (W m^{-2}). The global solar irradiance for the hemispherical tilted spectrum reaches around 1,000 W m^{-2} on a horizontal surface at ground level [6]. Visible light (400–700 nm) accounts for about 45% (i.e., 450 W m^{-2}) of solar intensity, that is, ~450 W m^{-2}. The blue-violet portion represents about one fifth of visible irradiance and gives global irradiances of approximately 90 W m^{-2}. Indirect, diffuse solar radiation ranges from 10% to 85% of global radiation, resulting in blue-light irradiances of 9–77 W m^{-2} depending on the solar altitude and the degree of cloudiness. On the other hand, consumer electronics (i.e., smartphones, tablets, and computer monitors) emit bright (LED) light for viewing composed of a higher proportion of blue-violet light than longer wavelengths and low blue-light-integrated irradiances ranging from 0.02 to 0.4 W m^{-2} at the manufacturers' recommended reading distances [7–10]. Irradiance values may vary among studies based on different distances between light source and sensor, as the irradiance from a light source will change proportionally to the inverse of distance squared. In general, irradiances from solar light are more than two orders of magnitude higher than irradiances from electronic devices [10, 11], while irradiances from artificial lighting are found somewhere in between.

General risk assessment takes account of known hazards and extent of exposures according to the simplistic formula: Risk = Hazard × Exposure. Assuming that the blue-light hazard is equal for solar and artificial sources in a first approximation (and independent of the irradiances), the risk would depend solely on the radiant exposure represented by the dose [J m^{-2}]. In other words, due to the very different irradiances of the sources, theoretically, the same risk can be expected from sun exposure as from exposure to electronical devices for a time more than 2 orders of magnitude longer. However, even though, on average, Americans spend 90% of their daylight time indoors and thus, only 10% outdoors [12], the exposure dose and the irradiance obtained outside from the sun will be, by far, more relevant

Table 1. Luminance (cd cm^{-2}) of natural and domestic radiant sources [5]

Natural	Lighting	Screens
Sun: $1{,}600 \times 10^6$	LED white: 50×10^6	LED-TV: 400–2,000
Snow: 50,000	60 W bulb: 0.12×10^6	Smartphone: 400–600
Sky: 2,000–8,000	Fluor tube: 0.01×10^6	LCD-monitor: 300–400

for skin compared to the dose and irradiance received from artificial (indoor) sources.

Radiometric measures provide information about the absolute brightness of a radiation source, whereas photometric terms consider the sensitivity of the eyes, spectrally weighed by the standard photometric visibility curve, thereby providing information about the perceived brightness of a source by a human observer. Luminance (cd m^{-2}) is the photometric measure of the luminous intensity emitted from a surface per unit area of light in a given direction. The luminance of the sun is the most powerful source for visible light (Table 1 [5]), whereas luminous intensity from the sky is much less intense. Snow can significantly boost the perceived brightness by reflecting up to 90% of the global solar radiation. Again, the sun emits luminance in greater orders of magnitude than artificial lighting and electronic devices, thus representing the most powerful singular source of blue light.

The Biological Effects of Blue Light on Skin

Blue Light Affects Skin and Eyes

In humans, the eyes and skin are the primary organs that sense light. Obviously, exposure to visible light is experienced by the eyes first, stimulating specific photoreceptors and enabling us to see our environment. In healthy adults, UV transmittance is blocked primarily by the cornea and eye lens. Visible light, however, passes through the eye structure, reaching the retina. There, the photons will be absorbed by the photoreceptor cells that contain light-sensitive retinal proteins called opsins (OPN). The cones with blue, green, and red opsin 1 (OPN1s) and the rods with rhodopsin (OPN2) mediate photopic and scotopic vision, respectively. In addition, the retina contains a third class of photoreceptor neurons: the intrinsically photosensitive retinal ganglions cells (ipRGCs) that express the short-wavelength, blue-light sensitive melanopsin (OPN4, $\lambda_{max} \approx 479$ nm) [13]. The ipRGCs are crucial for relaying nonimage-forming light information from the retina to the brain, primarily to control the pupillary light reflex and circadian rhythm. Ultimately, blue light suppresses the production of pineal hormone melatonin, influencing sleep-wake cycles through increased alertness. While blue light can enhance performance and mood during the daytime, evening exposure to blue light – for example, through widespread use of electronic devices and LED lighting – may therefore delay sleep onset [5, 9, 14]. It is also well known that the shortest wavelengths in the visible spectrum are the most dangerous in terms of photochemical damage to the retina. "Blue-light hazard" may cause photokeratitis and retinal injury, for example, by looking directly at the sun or a solar eclipse for just a few minutes.

Blue Light Penetrates Deeply into the Skin

In contrast to the eyes, the effects of visible light on the skin are less well studied. How much solar radiation penetrates the skin, depends on wavelength and the properties of each skin layer. At first approximation, the penetration depth correlates with the energy distribution of the solar radiation spectrum. When sunlight meets the human skin, 4–7% is reflected on the stratum corneum [4]. The transmitted light will be scattered by cell organelles and collagen fibers or absorbed by chromophores in the deeper skin layers. While most UVB energy is absorbed by the epidermis, around 80% of UVA radiation can penetrate the dermal-epidermal junction and around 10% reaches the hypodermis (Fig. 2) [3]. Even though visible light photons are less

energetic than UV photons, visible light may still have a substantial effect on skin, due to its deeper dermal penetration and 12–15 times higher abundance. Visible light efficiently penetrates skin tissues – about 20% finishes in the hypodermis [3]. Although red light penetrates deeper, blue light may still affect skin layers up to a 1 mm penetration depth, corresponding to an intensity decrease of 1/e in transmittance [15]. Penetration depth peaks at near-infrared radiation and gradually decreases with longer wavelengths: IR-A (700–1,400 nm) penetrates the epidermis, dermis, and subcutaneous tissue up to a penetration depth of 5 mm, whereas IR-C (3,000 nm–1 mm) is almost completely absorbed by the epidermis due to the presence of water. Exposure to infrared radiation is perceived as heat. The depth to which radiation penetrates also depends on the position and absorption spectrum of chromophores in the skin.

At Molecular Level UV Radiation and Blue Light Are Absorbed by Skin Chromophores

According to "the First Law of Photochemistry," known as Grotthuss-Draper law, light must be absorbed by a chemical substance for a photochemical reaction to take place. Solar radiation interacts as it passes through the skin layers by essentially transferring energy to different cellular photoacceptors (chromophores), stimulating the excitation of atoms or molecules by moving the outermost (valence) electrons to higher orbital energy levels (Fig. 2). The absorbed energy is then released from the chromophores in this excited state through different mechanisms: by emitting photons (luminescence), transferring their vibrational energy to the environment (thermal decay), or undergoing photochemical reactions to form new molecules. For example, vitamin D synthesis is initiated when epidermal 7-dehydrocholesterol is photolyzed to the previtamin D_3 through absorption of UVB radiation [16]. Chromophores, which undergo intersystem crossing and produce free radicals and singlet oxygen upon photoexcitation, are known as photosensitizers. During photosensitized oxidation reactions, oxygen radicals (type I, e.g., superoxide anion) and singlet oxygen $^1O_2$ (type II reaction) are generated, ultimately resulting in oxidized or oxygenated products of key biomolecules such as unsaturated lipids, proteins, and nucleic acids [17]. Eventually, lipid peroxidation may lead to cellular membrane disruption; oxidized proteins and enzymes may lead to modified structure and functionality; and oxidation of nucleic acids may lead to mutations and altered protein synthesis.

Following the UV radiation in the spectral distribution, (violet-) blue light may theoretically induce photobiological effects similar to UV radiation [18]. While the effects of UVA radiation are mainly due to indirect oxidative damage caused by reactive oxygen species (ROS), the photobiologic effects of UVB are initiated predominantly by direct DNA damage. High-energy photons from UVB radiation can be directly absorbed by DNA through aromatic heterocyclic nucleobases, leading to mutagenic bipyrimidine DNA photoproducts, mainly the cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts. The carcinogenic effects of sunlight are dominated by UVB, yet UVA is estimated to account for 10–20% of carcinogenicity [19]. The main mechanism of melanogenesis is mediated by UVB-induced DNA damage via activation of the p53 protein [20]. Obviously, the melanin pigment is the critical endogenous protective factor against ultraviolet radiation (UVR). Interestingly, CPDs are also produced in human skin exposed to UVA radiation via a different mechanism to UVB, and in even larger amounts than the most common oxidatively generated lesion in human skin – 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) [21]. Oxidative stress is often recognized as the major genotoxic pathway in the UVA range. UVA induces the formation of ROS and reactive nitrogen species (RNS) by absorbing energy with photosensitizers such as nucleic acid bases, aromatic

Table 2. Harmful and beneficial effects of blue light on the skin; the excited chromophores can generate ROS/RNS and NO, activate signaling pathways (e.g., G-protein-coupled signaling), and downstream processes, resulting in mediated cellular responses that may lead, ultimately, to altered skin condition

Chromophores	Mediators	Cellular responses	Clinical effect on skin condition	Ref.
Flavins; e.g., cytochrome *c* oxidase, cryptochromes, NOS	ROS	Oxidative stress Modulates mitochondrial activity, proliferation/ differentiation, cytokine release, MMPs induction, circadian rhythm, apoptosis	Premature skin aging Mediates inflammation responses Photodermatoses Phototherapy in inflammatory skin disorders, bacterial infections, wound healing	[22–24, 31, 36–38, 40, 70, 71]
Porphyrins; e.g., mitochondrial enzymes, cytochrome P450	ROS			
Heme; e.g., Bilirubin, hemoglobin, protoporphyrin IX	Photooxidation, isomerization products	Reduced plasma levels	Hyperbilirubinemia therapy PDT with ALA	[22, 72]
Nitrite/S-nitrosothiols/ Nitrosated proteins	NO	RNS/ROS formation S-nitrosylation Modulates proliferation/ differentiation, inflammatory mediators	Anti-inflammatory effects Vasorelaxation/cutaneous blood flow Hemodynamic disorders therapy	[23, 33]
Opsins/Retinal	G-protein-coupled signaling	Downstream targets, e.g., transient receptor potential channels, kinases Melanogenesis	Pigmentation Pigmentary disorders, e.g., melasma, post-inflammatory hyperpigmentation Barrier homeostasis Vasorelaxation Photobiomodulation	[23, 24, 54, 59, 64]
Carotenoids	Photolysis products	Reduced antioxidant defense	Premature skin aging Photoprotection	[22, 28, 39]
Melanin	ROS	Oxidative stress	Photothermolysis, e.g., hair epilation Pigment darkening	[22]

amino acids, nicotinamide adenine dinucleotide (phosphate), quinones, flavins, porphyrins, carotenoids, 7-dehydrocholesterol, eumelanin, and urocanic acid [3].

In the past, visible light and IR radiation, following tissue absorption, have been thought solely to produce heat with no relevant biological effects on skin. Due to the arbitrary division between UVA and visible light, a continuum of photobiological effects can be expected in the vicinal ranges between UVA and visible light. Like UVA, visible light contributes to free radical generation after excitation of sensitive skin chromophores. A number of skin chromophores, including melanin, carotenoids, porphyrins, and carbonylated or nitrosated proteins, play a role in absorption throughout the UV and visible wavebands (Table 2) [22]. Other potential chromophores that absorb visible light are bilirubin and riboflavin. Riboflavin is the main component of flavin mononucleotide and flavin adenine dinucleotide in flavoproteins. Cryptochromes are a family of flavoproteins that generate ROS upon blue-light-induced flavin photoreduction and are believed to modulate the circadian rhythm in mammals [23]. Favin mononucleotide is also found in nitric oxide synthases (NOS) and mitochondrial enzymes in the electron transport chain [24]. Furthermore, blue-light-sensitive porphyrins are incorporated in proteins of the

respiratory chain (e.g., cytochrome *c* oxidase), in hemoglobin, and in cytochrome p450 enzymes. Most of these primary mechanisms converge in their ability to modulate ROS production.

Free Radical Formation Is the Predominant Process Over the Entire Solar Spectrum

Zastrow et al. showed that free radical formation in irradiated human skin (280–700 nm), particularly ROS, is distributed over 4% for UVB, 46% for UVA, and 50% for visible light [25]. The free radical effectiveness spectrum for summer daylight illumination was calculated from an action spectrum based on electron spin resonance spectroscopy applied to ex vivo skin. As expected, the most intensive peak was observed in relation to UVA light. However, 50% of the total oxidative burden was generated by visible light. Wavelengths in the blue-light range (400–500 nm) contributed significantly to the generation of free radicals, with multiple radical peaks indicating that various chromophores are involved in radical formation. Free radicals initiate a cascade of biomolecular effects of signal and defense mechanisms or destructive events. Other adverse effects of blue light can be considered, most likely, to be a consequence of ROS activity. The contribution of the UV component to skin damage is well understood and leads ultimately to the process of photoaged skin phenotype. Upon UV radiation, ROS produced in skin are the key mediators of oxidative damage. Consequently, UV induces the expression of proinflammatory cytokines and matrix metalloproteinases (MMPs), leading, respectively, to overall skin inflammation and a breakdown of extracellular matrix components.

Blue Light Induces Oxidative Stress and Downstream Processes

Fewer studies have examined the effects of visible light and infrared radiation on skin physiology. Kielbassa et al. proposed an action spectrum in oxidative DNA damage formation which extended from UVA1 (340–400 nm) into the visible range, having a second maximum between 400 and 450 nm [26]. Besides DNA damage, lipid peroxide generation in membrane lipids is a major factor in UV-induced cell damage, resulting in a rapid depletion of endogenous antioxidant enzymes and antioxidants. Skin has developed defense systems against oxidative stress, including the anti-oxidative enzymes catalase, superoxide dismutase, and glutathione peroxidase, which reduce the oxidative effects of UV and visible light irradiation in skin [27]. In addition, cutaneous, nonenzymatic antioxidants such as vitamins C and E, and carotenoids (e.g., β-carotene and lycopene) [28] degrade rapidly upon oxidative stress. Both UVA and blue light can be absorbed by carbonylated proteins (CPs) in the stratum corneum. They act as photosensitizers to generate ROS through a type I reaction [29]. On the other hand, UVA and blue light can initiate CP formation via ROS generation [29, 30]. Carbonyl groups are introduced to proteins by direct metal-catalyzed oxidation of amino acid residues (i.e., from proline, arginine, lysine, or threonine) or when basic residues in proteins react with radical carbonyl species generated during lipid peroxidation. Carbonylated proteins are involved in aging processes. They may contribute to dry skin and yellowing skin.

As the division between UVA and visible light is arbitrary, photobiological effects such as ROS formation after photo-induced activation of photosensitizers, may be similar for UVA and its oxidative stress consequences. Liebel et al. showed that visible light at relatively high doses (66–180 J cm^{-2}) induced ROS formation, the release of interleukin 1 alpha (IL-1α), and MMP-1 in human reconstructed skin in a similar way to UVA/B (6 J cm^{-2}) [31]. Importantly, visible light did not result in thymine CPD formation even at high enough doses to induce significant ROS formation. Energy from visible light may not be enough to stimulate a dimerization reaction in pyrimidines directly. However, it has been reported that visible light initiates type I photosensitized oxidation to produce 8-oxodG in CHO cells and

human skin fibroblasts [32]. The relative harmlessness of blue light in human skin tissue was also supported by Opländer et al., as blue light (453 nm), even at therapeutically nonrelevant high doses of 200 J cm^{-2}, did not induce DNA strand breaks [33].

In addition, blue light has been attributed with anti-inflammatory properties. In contrast to Liebel et al., a decreased release of pro-inflammatory cytokines, such as IL-1α [34], IL-8 [35], IL-1β, IL-2, interferon gamma, and tumor necrosis factor alpha [36], was observed by others following blue-light exposure to cell cultures. In dendritic cells, blue-light irradiation did not affect cell survival but suppressed cell activation and their allogeneic stimulatory potential. [36].

Opländer et al. found that blue light at wavelengths of 410 and 420 nm led to cytotoxicity in human dermal fibroblasts but did not at 453 and 480 nm [37]. Additionally, at low doses (410, 420, and 453 nm), blue light reduced the antioxidative capacity and proliferation of fibroblasts but did not at 480 nm. It has been suggested that singlet oxygen formation is involved in oxidative stress, mainly at lower wavelengths of blue light. Liebmann et al. showed that blue light at 453 nm was nontoxic up to a fluence of 500 J cm^{-2} and reduced proliferation dose-dependently [38]. Light at wavelengths of 632–940 nm had no proliferative effect, whereas irradiation with blue light at 412–426 nm exerted toxic effects at high fluences. Using Raman spectroscopy, Vandersee et al. showed a significant decrease in cutaneous carotenoids (21%) directly after blue-light irradiation of 100 J cm^{-2} [39]. In parallel to a blue-light-induced increase in ROS and cytokine production, Dong et al. showed that blue light at 410 nm impacted the core clock system in keratinocytes by decreasing period circadian regulator 1 (per1) transcription [40]. To summarize, the above findings support the hypothesis that exposure to visible light can induce ROS in skin, in a similar way to UV, which may lead to oxidative stress-related effects such as the release of proinflammatory cytokines and MMPs. Visible light, IR, and heat from natural sunlight, in addition to UV, have been reported to induce metalloproteinases, to reduce type I procollagen expression and to contribute to inflammatory cell infiltration in human skin [41]. Near-infrared radiation has also been shown to cause oxidative stress through increased ROS formation and MMP expression [25, 42, 43]. A more detailed overview on infrared radiation is provided by Barolet in the following book chapter (Near-Infrared Light and Skin: Why Intensity Matters). Consequently, visible light may be regarded as an additional factor contributing to the signs of premature skin aging, although robust evidence of the clinical impact is still lacking.

Blue Light Induces the Formation of Nitric Oxide and RNS

ROS may also react with nitric oxide (NO) to form RNS, which may directly damage cellular components or reversibly bind to various biological components, for example, proteins containing reduced cysteine moieties yielding S-nitrosothiols (RS-NO). Human skin contains significant quantities of stored, photosensitive NO compounds, especially S-nitrosothiols and nitrite, which conversely decompose upon UVA radiation under NO formation [44]. NO plays a pivotal role as a multifunctional signaling molecule in cutaneous physiology and pathology. Many local UV-induced responses, including erythema and edema formation, inflammation, premature aging, melanogenesis, and immunosuppression, can be influenced by NOS-produced NO in skin [44]. In addition to this effective enzymatic NO production, immediate high-output NO formation due to the photodecomposition of NO derivatives may also trigger localized, NO-specific biological responses such as increased local blood flow or reduced blood pressure.

Moreover, Opländer et al. showed that blue light (420 and 453 nm) is able to induce nonenzymatic NO generation from cutaneous photolabile NO derivates in vitro and in human skin [33].

Irradiation of human skin with moderate doses of blue light (453 nm) resulted in a significant increase in enzyme-independent cutaneous NO formation and localized NO-dependent biological responses such as a rise in cutaneous blood flow. Light exposure at higher wavelengths, including blue (453 nm), green (524 nm), red (689 nm), and infrared (834 nm), was not effective. Conclusively, the hemodynamic vascular parameters of healthy subjects were affected by blue-light irradiation. In contrast to UVA radiation with its concurrent harmful effects, blue-light-induced NO generation may provide an alternative therapy for systemic and local hemodynamic disorders.

Blue Light Induces Skin Pigmentation

One of the skin's first responses to UV radiation, besides skin thickening and erythema, is skin pigmentation, which is characterized by two distinct mechanisms: pigment darkening and delayed tanning (DT). Immediate pigment darkening (IPD) and persistent pigment darkening (PPD) are caused by the oxidation of melanin precursors and the redistribution of melanosomes without the involvement of melanogenesis. IPD is characterized by a grayish darkening which is observed immediately after irradiation and fades shortly afterward (20 min–2 h). PPD occurs at higher UVA doses (>10 J cm^{-2}). It is characterized by brown color formation over a period of hours to days, depending on skin complexion, and can persist for several weeks [22]. In contrast to pigment darkening processes, DT is associated with melanogenesis. Tanning occurs 3–5 days after UV exposure and can persist for several weeks. UVB is more efficient than UVA at inducing DT and erythema via DNA dimers [20].

It is also known that exposure to visible light and near-IR wavelengths induces human skin pigmentation, especially in darker skin [22]. Pathak et al. showed that an action spectrum of IPD, extended to 640 nm, had the highest IPD response between 380 and 500 nm at a fixed exposure of 45 J cm^{-2} [45]. Kollias and Baqer detected skin pigmentation, spectroscopically different to UVA-induced IPD, by using a polychromatic light (390–1,700 nm) at doses greater than 720 J cm^{-2}. The pigmentation was observed for up to 10 weeks on inner arms [46]. Porges et al. observed the induction of IPD, immediate erythema and DT on 20 subjects with skin types II–IV following exposure to visible light (385–690 nm). The threshold dose for IPD was between 40 and 80 J cm^{-2}, while for PPD it was greater than 80 J cm^{-2}. Rosen et al. confirmed, by skin reflectance spectroscopy, that visible light up to 470 nm was able to induce IPD responses [47]. In a more recent study by Mahmoud et al., pigmentation was induced by visible light (400–700 nm, containing 0.19% UVA1 and 1.5% IR) in subjects with skin types V–VI during a 2-week period and was found to be darker and more sustained than the pigmentation induced by UVA1 [48]. Evident pigmentation was observed in skin types IV–VI with visible light and UVA1 at threshold doses of 40 and 5 J cm^{-2}, respectively, whereas using the same light sources and doses, no pigmentation and erythema were induced in subjects with skin type II. In 2013, Ramasubramaniam et al. used filtered natural sunlight to compare pigmentation induced by UV (<400 nm) and visible ranges (>420 nm) on the volar forearms of 18 subjects with skin types IV–V [49]. The IPD from visible light fraction did not differ significantly from that induced by the UV fraction. However, the PPD induced by the UV fraction of sunlight was significantly higher. The reflectance curves indicated that the same type of pigment was formed during both processes, although UVR was 25 times more efficient in inducing pigmentation than visible radiation. More recently, Randhawa et al. reported that visible light was also able to activate melanogenesis processes under ex vivo and in vivo conditions in Caucasian skin [50]. Skin explants from Caucasian subjects were exposed to 150 J cm^{-2} of visible light daily for 5 days and showed increased melanin content, tyrosinase

expression and activity at day 7. Single exposure to visible light (including 0.19% UVA) showed no, or very little, persistent pigmentation (320 and 300 J cm^{-2}), whereas multiple exposures to visible light (2 × 150 J cm^{-2}) resulted in darker and sustained pigmentation. However, not all wavelengths in the visible domain, and especially at the extremities, triggered the same photobiological effects on pigmentation.

As the light sources used in all the reported studies are not standardized and involve different qualities (e.g., partial inclusion of UVA1), irradiances, and doses, they may lead to contractionary results that are difficult to compare [22, 51].

Melanogenesis Is Regulated by Opsin-3 in Melanocytes

Using colorimetric and clinical assessment, Duteil et al. [52] demonstrated that violet/blue LED irradiation (λ = 415 nm, 10–150 J cm^{-2}) induced dose-dependent hyperpigmentation in subjects with skin types III and IV. Hyperpigmentation was still highly pronounced 2 weeks after irradiation at 415 nm and lasted up to 3 months. Red light (λ = 630 nm) did not induce hyperpigmentation, although a low-energy red laser has been reported previously to enhance immature melanoblast mobility and promoted melanogenesis in vitro [53]. Combinations of blue and red light did not have a synergistic effect on pigmentation. In contrast to the 1.5-fold Minimal Erythema Dose (MED) of UVB irradiation, violet-blue light did not result in significant p53 expression [20], suggesting that other mechanisms were involved at the higher wavelength. The clinically relevant doses of blue light for inducing minimal pigmentation (MPD) were between 55 and 60 J cm^{-2} on skin types III and IV. This corresponds to less than 2 hours of sun exposure during summer (i.e., at a violet-blue solar irradiance of 8.8 mW cm^{-2}) compared with the applied 1.5 MED of UVB, which is equivalent to about 35 min at peak solar UVB emission. More recently, Regazzetti et al. provided mechanistic evidence that blue light (415 nm, ≥50 J cm^{-2}) activated the OPN3 receptor (formerly known as panopsin or encephalopsin) in normal human melanocytes from skin type IV [54]. After stimulation of OPN3, a calcium flux was induced and activated signal transduction, leading to the phosphorylation of melanocytic microphthalmia-associated transcription factor (MITF). The activated MITF – the master transcription factor in melanocytes – upregulated the melanogenic enzymes, tyrosinase and dopachrome tautomerase, which ultimately increased the melanin in cells. Primarily in skin type III and higher, blue light was found to induce higher tyrosinase activity and the formation of multimeric tyrosinase/tyrosinase-related protein complex (TYR/P proteins), which was thought to be a potential cause of blue-light-induced, long-lasting pigmentation in melano-competent skin only. The absence of p53 activation upon blue-light irradiation [20, 52], and the ineffectiveness of antioxidants in protecting against blue-light-induced melanogenesis [54] or in reducing melasma, implies alternative pathways from those known to induce pigmentation by UV, which are also not related to radical formation. The extraocular sensor OPN3, its downstream pathway, and TYR/P proteins may yield a novel therapeutic target for regulating melanogenesis and skin pigmentation disorders, especially in dark-skinned individuals.

On the other hand, Ozdeslik et al. discovered recently that opsin-3 light in human epidermal melanocytes does not mediate Ca^{2+}-dependent phototransduction of UVR, blue, or green light [55]. Moreover, OPN3 acts as a *negative* nonvisual regulator of melanogenesis by modulating the signal transduction of the melanocortin 1 receptor (MC1R) via cyclic adenosine monophosphate (cAMP). Despite being able to bind retinal, the human OPN3 showed no light absorption in the 300–700 nm range and no light-dependent changes in cAMP and Ca^{2+} [55, 56]. The light-independent regulation of melanocyte pigmentation via MC1R points to a novel function for

OPN3. The two studies above provided conflicting data on whether OPN3 signals through Ca^{2+} [54] or cAMP [55] in melanocytes dependently or independently of light as well as on the opposing levels of MITF, TYR, and melanin when OPN3 was knocked down. Olinski et al. suggested that although both studies used primary human epidermal melanocytes, these contradictory results might be explained by differences in temperature-dependent light doses or in growth conditions, which may impact expression and functionality of OPN3 [57]. It is evident, that further studies are needed to understand the signaling and function of OPN3 in melanocytes completely.

Opsins Are Also Expressed in Keratinocytes, Hair Follicles, and Dermal Fibroblasts

Human skin expresses a wide range of opsins, although OPN3 is the most highly expressed in melanocytes and keratinocytes [58]. Its high expression in epidermal skin suggests that OPN3 may have various relevant functions in different skin cell types. Castellano-Pellicena et al. shed further light on the OPN3 function in keratinocytes by demonstrating OPN3-dependent differentiation in response to blue light (453 nm, 2 J cm^{-2}) [59]. OPN3 was overexpressed in the newly regenerating epidermis after wounding, suggesting that OPN3 is required for restoration of the barrier function. Another blue-light-sensing opsin OPN1-SW was found in stratum granulosum which might interact with OPN3 to regulate keratinocyte differentiation.

All human opsins have been found in dermal fibroblasts [60]. Recently, Lan et al. showed an increase in OPN3, OPN1, and OPN5 expressions in dermal fibroblasts following UVA exposure (10 J cm^{-2}) [61]. OPN3 knockdown mitigated the increase of UVA-induced Ca^{2+} flux and MMPs. They concluded that OPN3 is a key sensor for initiating UVA phototransduction, upregulating MMP expression via the calcium-dependent G-protein-coupled signaling pathway, thereby impacting skin photoaging.

Buscone et al. reported that OPN3 and OPN2 (rhodopsin) were also expressed in human hair follicles and that 453 nm blue-light exposure (3.2 J cm^{-2}) significantly prolonged the anagen phase in hair follicles ex vivo. In contrast, 689 nm red light had no effect on hair growth [60].

OPN4 (melanopsin) has even been found in human subcutaneous white adipocytes, which can be activated via a novel melanopsin/TRPC/Ca^{2+} signaling pathway [62]. Repeated moderate exposure to blue light (460 nm, 2.9 J cm^{-2}) promoted increased adipocyte lipolytic rates and adipokine secretion, which may be beneficial for metabolic health. Finally, the presence of OPN-4 in blood vessels was shown to mediate blue-light-specific vascular relaxation without involving NO signaling [63].

Taken together, conflicting data have been published about the effect of blue light on proliferation, differentiation, growth, cytotoxicity, and pigmentation in different biological models. It is of utmost importance to record and report treatment parameters that affect reliability, repeatability, and comparison between different studies correctly. Discrepancies are often related to different experimental conditions that vary mainly in terms of light source, wavelength, irradiance and exposure dose (fluence), and cell or tissue type. Despite all the recent progress in providing evidence for novel mechanisms in skin photodetection and phototransduction in the last decade, much remains to be clarified about how skin cells sense light [64].

Clinical Relevance of Blue Light and Cosmetic Applications

Clinical Effects of Blue Light

Skin chromophores absorbing sunlight is the main event that triggers biological effects in skin. The acute effects of high UVR exposure include erythema (sunburn), pigmentation (tanning), suppression of acquired immunity, enhancement of innate immunity, and vitamin D synthesis.

Chronic exposure of the skin to UVR leads to the well-known consequences of pigmentary disorders, photoaging, photoimmunosuppression, photocarcinogenesis, and photodermatoses [65, 66]. Visible light has been shown to induce a tanning response in melano-competent skin and to contribute to oxidative stress and erythema in all skin types [51, 67]. Based on in vitro or ex vivo data, it has been suggested that visible light and infrared light may also induce skin damage throughout the dermis due to generation of free radicals, which could contribute to premature skin photoaging [31]. In dermatology, photodermatoses are a broad group of skin disorders primarily caused or exacerbated by exposure to UV and/or visible radiation. Photodermatoses with an action spectrum in the visible light range include solar urticaria, chronic actinic dermatitis and cutaneous porphyrias [22]. Nevertheless, visible light is used frequently to treat dermatoses and for cosmetic applications [68]. Traditionally, phototherapy with blue-light sources (460–490 nm) has been used to treat hyperbilirubinemia in neonatal jaundice [22]. Accumulated serum levels of bilirubin – a metabolic product of heme degradation – are cleared by blue-light-induced photooxidation to produce water-soluble photoisomers. Nowadays, visible light is widely used in phototherapy and photodynamic therapy (PDT) through exposure to daylight, LEDs, fluorescent lamps, intensive pulsed light, and low-level lasers [22, 23]. An administered or endogenous photosensitizer, along with visible (or UVR), produces cytotoxic singlet oxygen and free radicals to destroy (mainly) abnormal cells or microorganisms. Clinical improvements in acne vulgaris have been reported by blue-light therapy [69, 70]. Photoexcitation of the bacterial porphyrins of *Cutibacterium acnes* generates singlet oxygen, eventually destroying bacteria and having an anti-inflammatory effect. In wound healing, as an alternative to conventional antibiotic therapy, blue light has an antimicrobial effect that combats bacterial infection, while red light is thought to stimulate proliferation and re-epithelialization of injured tissue [71]. The antiproliferative and anti-inflammatory properties of blue light have been used as local phototherapy (photobiomodulation therapy) to treat inflammatory skin disorders such as atopic dermatitis, psoriasis, and eczema which are characterized by sustained inflammation and hyperproliferation of skin cells [24]. However, the clinical use of blue light for inflammatory skin conditions is generally still at an early stage of development.

PDT is a well-established, noninvasive treatment for a range of dermatologic disorders and signs of skin aging [72]. To destroy various cells and tissues, the simultaneous presence of three components is required: a photosensitizer, a light source, and oxygen. Blue light, in conjunction with the topical photosensitizer 5-aminolevulinic acid (ALA), is the standard treatment for actinic keratosis.

There is increasing evidence that photosensitive opsins are involved in various functions in the skin, including melanogenesis, wound healing, photoaging, and hair growth. In the near future, the therapeutic benefits of photobiomodulation for various skin disorders could therefore be expanded by targeting opsins [64]. The ability of visible light to induce pigmentation, especially in darker skin types, is also of clinical relevance, possibly contributing to the pathogenesis or relapse of photo-induced pigmentary disorders. Melasma, cutaneous hyperchromias (sun spots), and post-inflammatory hyperpigmentation in particular worsen after sun exposure, especially in the summer period, despite the use of sunscreens for UV (but not visible light) protection [51, 65]. Tinted sunscreens containing iron oxide have been shown to be more effective against melasma relapses compared with the same sunscreen without protection in shorter wavelengths of visible light [73].

Blue Light – Friend or Foe?

In view of what has been reported about visible light, should blue light be considered a friend or a

foe? As described, blue light encompasses both sides of the coin. Evidently, any physiological effects largely depend on the individuals' health and skin condition and on the extent of exposure. A systematic review of the literature on the potential therapeutic effects of photobiomodulation showed that the majority of publications (72%) reported *beneficial* effects of blue light, including the modulation of inflammation, the promotion of wound healing, and the reduction of bacterial growth [24]. Interestingly, most of the beneficial studies (63%) employed radiant exposures of less than 10 J cm^{-2}, for example, by reducing inflammation and promoting gene expression, whereas higher doses (>55 J cm^{-2}) were typically used for their antibacterial effects [24]. The therapeutic window may significantly vary in different applications and skin conditions. Few studies reported a biphasic dose response: beyond a maximal effective dose the response diminished or was even inhibited at very high fluences. Small increases in ROS production might stimulate cell proliferation and mitochondrial activity, while larger increases can induce apoptosis. Photobiomodulation at higher wavelengths (810 nm laser, 3 J cm^{-2}) has been shown to produce ROS in normal cells, but when used in oxidative stressed cells, ROS levels are lowered [74].

Nevertheless, blue light also provokes measurable photoreactions in healthy skin under realistic exposure, which when taken to an excessive level, for example, during a sunny summer day at the beach, might contribute to the onset of skin pigmentation changes or even to premature skin aging. Such biological effects have been observed using irradiances and doses that correspond to those received under natural sun exposure [23]. Depending on the endpoints investigated in photobiological studies, light doses employed to achieve biological effects can span from as little as 1–5 J cm^{-2} to potentially higher than 200 J cm^{-2}, which can be easily achieved within a day of sun exposure. The pro-pigmenting dose of visible light of 40–80 J cm^{-2} is equivalent to 1 h 30 min–2 h 30 min direct sun exposure in the summer period [48, 52].

Recent studies investigated the impact of light-emitting electronic devices on skin [7, 8]. However, when extrapolating in vitro results to clinical signs of skin aging, the clinical relevance under realistic in vivo conditions remains unclear. In this context it is important to consider the wavelengths and doses applied in studies, but also the irradiances of light sources [11]. Not only is the duration for achieving an effective dose significantly longer with devices than with sun exposure, but also the different irradiances can influence the biological effects. Erythema and pigment responses to UVA have been reported to be dependent on irradiances [75] as have the photobleaching and pain sensation in PDT with aminolevulinic acid [76]. Likewise, 30 min of exposure to solar-simulated blue light (420–490 nm, 0.864 J cm^{-2}), equivalent to an 8-h exposure to a powerful screen (30 μW cm^{-2}), on the half-faces of 12 melasma patients, for 5 consecutive days, did *not* worsen melasma lesions [10]. Acute irradiance and doses from electronic screens are probably too low to induce significant changes in skin appearance. However, for the time being, the potential impact of the cumulative effects of chronic exposure to artificial sources on skin conditions cannot be ruled out. The bottom line is that more attention should be placed on indoor exposure to blue light from sunlight passing unfiltered through windows than from electronic screens.

Cosmetic Concepts for Blue Light Protection

In view of the photobiological effects of visible light, particularly blue light, to achieve full protection against sun-induced skin disorders and aging, it is proposed that photoprotection be extended beyond the current UVB and UVA range into the visible spectrum [77, 78]. Diffey et al. have suggested that modern sunscreens should provide a balanced spectral absorption similar to the protection given by shade and clothing fabrics [79].

Current UV filter systems provide efficient photoprotection in the UVB and UVA range. However, organic UV filters show absorption properties in the UV range only, usually dropping to zero between 380 and 400 nm to retain their colorless aspect. Only optically opaque, particulate UV filters can give protection by scattering and reflecting light. Two inorganic UV filters, titanium dioxide (TiO_2) and zinc oxide (ZnO), and the particulate organic filter methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT), have been proven to reduce transmission in the blue-light range [22, 80, 81]. To achieve cosmetic acceptance, inorganic filters are often micronized to a particle size less than 50 nm in diameter which lowers the refractive index, resulting in a less whitish appearance on skin. Micronized TiO_2 protects efficiently against UVB (280–215 nm) and UVA2 (315–340 nm), but micronized ZnO has better UVA1 (340–400 nm) protection and a lower refractive index compared to TiO_2. Theoretically, transmissions of 10–20% can be achieved with the regulated maximum amount of inorganic UV filters. The calculated transmission for a combination of 3% TiO_2 and 4% MBBT is around 44%, and the average protection factor (PF = 1/Transmittance) in the blue-light range (400–500 nm) was PF = 2.3. Topical application of these light-scattering UV filters in a sun protection factor (SPF) 30 sunscreen formulation has been shown to significantly reduce pigment darkening in 14 subjects with skin types III and IV after a repetitive dose of LED blue light (430–450 nm, 45 J cm^{-2}) on 5 consecutive days [81]. In addition, Regazzetti et al. proposed iron oxides in tinted sunscreens to protect against shorter wavelengths of visible light, while antioxidants did not prevent blue-light-induced tanning [54].

However, a complete blockage of blue-light radiation is probably not desirable as the active ingredients should not counteract the beneficial aspects of blue light. Combinations with antioxidants might be complementary as they would scavenge blue-light-induced ROS but with little impact on phototransduction pathways. Antioxidant Licochalcone A reduced blue-light-induced ROS in fibroblasts and prevented depletion of cutaneous carotenoids when topically applied in a SPF50+ sunscreen, while UV filters alone were ineffective [82]. On the other hand, the use of the antioxidant N-acetylcysteine did not prevent blue-light-induced melanogenesis [54].

Table 3. Strategies for product development with blue-light protection claims

Rationale	Ingredients
Block by physical shield	Particles, absorbers
Prevent oxidative Damage	Antioxidants
Reduce (hyper-) pigmentation ◄⟶	Whitening agents
Stimulate cell metabolism	Extracts
Protect outdoor or indoor	Dependent on formulation

Although still at a generally moderate level, cosmetic products claiming blue-light protection – especially for skin care applications and, to a lesser extent, color cosmetics and sun care – have been on the rise in the last years. There are different rational strategies for constituting ingredients in products with a blue-light claim (Table 3): The most effective strategy is to block blue light before it reaches the living skin. The very well-known approach from UV filter photoprotection involves using a physical shield by extending UV protection with the light-scattering particulate filters TiO_2, ZnO, and MBBT, or with absorbing pigments such as iron oxides for tinted formulations. Once light has reached the skin, the next step is to prevent dominant oxidative damage to biomolecules with antioxidants such as Vitamin C/E, niacinamide, polyphenols, or cell extracts. Furthermore, hyperpigmentation can be targeted in darker-skin phototypes. Strategies to reduce blue-light-induced pigmentation events include common concepts such as inhibition of tyrosinase, interference of subsequent signaling pathways, or melanosome transfer. Another option is to generally stimulate

cell metabolism and strengthen cellular defense and resilience against oxidative stress in mitochondria by providing energy, cofactors, and building blocks with cellular extracts [83]. It might be important to preserve mitochondria which seem to be more susceptible to blue light due to their blue-light-sensitive chromophores in mitochondrial enzymes of the electron transport chain, for example, cytochrome *c* oxidase. Lastly, personalized formulations could be developed to target specific applications, such as indoor and outdoor formulas, and encourage consumer compliance. Future sunscreens should meet the individual needs of consumers based on their sun exposure behavior, skin type, age, and disease risk [78]. Individuals with higher skin types are more susceptible to pigmentary disorders such as melasma and post-inflammatory hyperpigmentation and, so, should be protected against visible light. On the other hand, fair-skinned individuals are more sensitive to oxidative stress and UV radiation [67].

Conclusions

In the last two decades, scientific evidence has substantiated that high-energy light adjacent to the UV spectrum also affects skin physiology. Even though blue-light photons are less powerful than UV photons, they may still have relevant positive and negative effects on skin due to their higher abundance and deeper dermal penetration. Although the UV fraction of the solar spectrum is most harmful in terms of skin damage, excessive visible light portions, especially blue light, also induce skin changes such as photo-transduction and oxidative stress, which contribute to hyperpigmentation and photoaging in the long term. While protecting skin against UVR is still of utmost importance, it should not stop at the virtual wavelength limit of 400 nm, as the physiological effects also continue at longer wavelengths. Indeed, certain skin chromophores appear to be specifically activated by blue light. Discrepancies in the mechanistical effects of blue light and its benefits or damages are often linked to the lack of data comparability between in vitro methods and the clinical relevance of data under realistic in vivo conditions. Further long-term clinical trials and relevant empirical data are needed to make a proper risk assessment. At present, neither visible light nor IRA radiation seems to be directly associated with skin cancer.

Photo(dynamic) therapies with blue light are commonly used and is expanding for treating skin disorders, including acne, inflammatory dermatoses, cutaneous infections, actinic keratosis, and sun-damaged skin. In healthy skin, blue-light irradiation from sun exposure is cosmetically relevant as a factor in skin aging and uneven skin tone, potentially inducing erythema, melasma, sun spots, or post-inflammatory hyperpigmentation. It may also support cutaneous blood flow via enzyme-independent NO formation. Thus, photoprotection is about to be redefined beyond UV. Today's UV protection is extending to include holistic sunlight protection systems. An ideal sunscreen provides balanced, personalized protection against all relevant wavelengths of natural sunlight. Modern products should include photostable, broad spectrum UVA/B filters, to protect against sunburn, photocarcinogenesis, photodermatoses, and photoaging, combined with substantiated active ingredients that protect against hyperpigmentation and premature skin aging beyond the UV range. The cosmetics industry has already begun to introduce the concept of a "blue-light protection factor," similar to the UVA protection factor methods [80]. Still, the top priority is on perfecting an accurate and precise method for SPF and UVA protection factor that is also unambiguous, safe, and fully comprehensible for sunscreen consumers. Alternative methods for in vivo SPF testing (ISO 24444:2019) are currently being evaluated by the ISO working group 7 "Sun Protection Test Methods" [84]. In the near future, we will gain more robust knowledge of the relevant effects of

the solar spectrum beyond UV on human physiology and psychology, especially in terms of understanding the long-term impact of blue light in vivo, the role of skin chromophores, and the selection of target-specific active ingredients. Until then, it is essential that people continue to apply adequate and balanced photoprotection against the harmful effects of sunlight.

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Conflict of Interest Statement

The author is an employee of DSM Nutritional Products. Some of active ingredients mentioned in this manuscript, that is, the UV filters, extract of the microalga *Scenedesmus rubescens*, and niacinamide, are marketed by DSM Nutritional Products under the trade names PARSOL® TX, PARSOL® ZX, PARSOL® Max, PEPHA®-AGE, and Niacinamide PC. The author reports no other conflicts of interest to declare.

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Author Contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, manuscript preparation, final approval of the version to publish, and accuracy or integrity of any part of the work.

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Rolf Schütz
DSM Nutritional Products
R&D Personal Care & Aroma
Wurmisweg 576
CH–4303 Kaiseraugst (Switzerland)
rolf.schuetz@dsm.com