BLUE LIGHT HAZARD:
New Knowledge, New Approaches to Maintaining Ocular Health

REPORT OF A ROUNDTABLE
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SUMMARY

Short wavelength visible light, the spectrum from 380 to 500 nm that includes violet, indigo, blue, and some blue-green light, plays a paradoxical role in health and vision. Not only is blue light essential for color vision, recent research has found that light in this band triggers critical physiological responses, including pupil constriction and circadian rhythm synchronization. However, blue light may also be damaging to the eye, and the term "blue light hazard" has been coined to describe the danger this light presents to critical structures within the eye.

Blue light can induce formation of toxic reactive oxygen species that cause photochemical damage, leading to the death by apoptosis first of critical retinal pigment epithelial (RPE) cells and then photoreceptors. This slow process, in which damage accumulates over a lifetime, has been implicated in the pathogenesis of retinal degenerative diseases such as age-related macular degeneration (AMD).

The fact that blue light is both beneficial and toxic raises a critical question: Can we protect the eye from harmful blue light without simultaneously denying it the physiologically necessary blue light? One way to accomplish this would be with a lens that selectively filters out the harmful wavelengths while transmitting the beneficial ones. Recent work has enabled this by more fully defining the range of harmful blue light.

To determine whether specific bands within the blue-violet spectrum are responsible for blue light's phototoxic effects on the RPE, researchers from Essilor's Paris research and development laboratories joined forces with scientists from the Paris Vision Institute to develop a unique illumination system that allowed cultured porcine retinal cells to be exposed to narrow (10-nm) bands of light at moderate irradiances normalized to typical retinal sunlight exposure. Using this test system, it was discovered that RPE phototoxicity was concentrated in a relatively narrow band, with little overlap of the wavelengths necessary for the beneficial physiological effects of blue light. This finding paved the way for selective photofiltration: the creation of lenses that reduce the level of exposure to the harmful portion of the blue-violet spectrum while permitting the rest of the visible spectrum to enter the eye at a normal level. Thus, the eye's necessary visual and non-visual functions can be maintained while exposure to hazardous wavelengths is reduced.

With the creation of Crizal® Prevencia™ No-Glare lenses, Essilor has turned this concept into a reality. These lenses reduce exposure to ultraviolet (UV) light — coming from in front or reflecting off the back surface of lenses — and they attenuate the harmful wavelengths of blue light. Because they reduce (but don't fully block) transmission of just a narrow band of blue-violet light, excellent color transmission, as well as transparency, are maintained, providing superior clarity of vision. Because the damaging effects of blue-violet light are cumulative, wearing Crizal® Prevencia™ No-Glare lenses may help protect the eye by reducing lifetime exposure to harmful UV and blue-violet light. With more and more clinicians prescribing spectacle lenses from the chair, Crizal® Prevencia™ No-Glare lenses provide a helpful tool for patients to protect themselves from UV and the harmful wavelengths in the blue-violet spectrum.

INTRODUCTION

The human eye is adapted to life in a world of light. Sunlight not only enables vision, it triggers essential physiologic functions, including circadian entrainment (synchronization of internal circadian rhythms) and the pupillary light reflex.[1] But along with its many beneficial effects, sunlight exposure can also bring harm to both skin and eyes—the spectrum of optical radiation spans a wide range of wavelengths, not all of which are benign.

The eye is subject to injury from both acute and long-term exposure to solar and man-made optical radiation. The serious dangers that UV radiation presents to both eyes and skin are well established. Now, mounting evidence has alerted scientists and clinicians to the damage that long-term exposure to blue light may cause to retinal photoreceptors.

With this in mind, Essilor formed an expert panel that met in March 2013 to evaluate what is known about blue light hazard and the means of ocular protection available. This report, which summarizes the roundtable discussion, will:

- Provide an overview of the interaction between light and the eye;
- Describe the current understanding of the role blue light plays in health and vision;
- Review the present state of knowledge about blue light hazard and the mechanisms by which blue light may damage retinal cells;
- Discuss a recent research study identifying a specific, narrow band of blue light that is phototoxic to the retinal pigment epithelium cells; and
- Introduce a new spectacle lens solution that for the first time offers a way to reduce exposure to both UV and damaging blue light without affecting either color vision or blue light's beneficial effects.

LIGHT AND THE EYE

Optical Radiation

The electromagnetic spectrum has three bands of what is termed optical radiation: UV encompasses wavelengths from 100 nm to 380 nm; visible light comprises radiation between 380 nm and 780 nm; and infrared (IR) consists of wavelengths from 780 nm to 10,000 nm (Figure 1). These can all be further divided into sub-bands. Within the UV spectrum there is UVA (315 nm to 380 nm), UVB (280 nm to 315 nm), and UVC (100 nm to 280 nm)*; the IR spectrum contains IRA (780 nm to 1,400 nm), IRB (1,400 nm to 3,000 nm), and IRC (3,000 nm to 10,000 nm); and the visible light spectrum can be generally classified as short- (blue), medium- (green), and long-wavelength (red) light.[2]

Visible light, like all electromagnetic radiation, has energy; the amount of photon energy is a function of wavelength, with shorter wavelengths being most energetic. Thus, blue-violet light is the highest-energy band of the visible spectrum.

*The exact wavelengths of various bands differ slightly in work by different groups.

Light Absorption in the Eye

Visual perception occurs when light strikes the retina, an intricate structure of highly specialized cells that form the innermost layer of the globe. Before reaching the retina, incoming light must penetrate the ocular media, the transparent tissues and fluids that lie between the front of the eye and the retina. The ocular media—consisting of the cornea, aqueous humor, lens, and vitreous humor—either absorb or transmit light, depending on its wavelength.

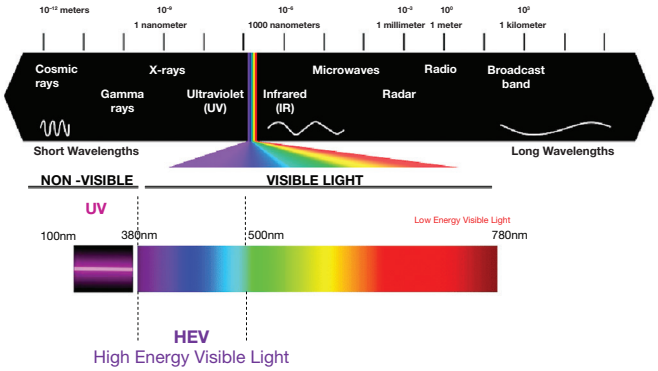

FIGURE 1. The electromagnetic spectrum and optical radiation.

Almost all of the UV that reaches the eye is absorbed by the cornea or the crystalline lens, so that in adult eyes only 1% to 2% of incoming UV is transmitted to the retina.[3] The cornea and crystalline lens also block IR above 980 nm; and the vitreous absorbs the IR above 1400 nm that is not absorbed by the lens. The net result of light filtering by the ocular media is that the retina is exposed almost exclusively to the visible portion of the solar spectrum (Figure 2).

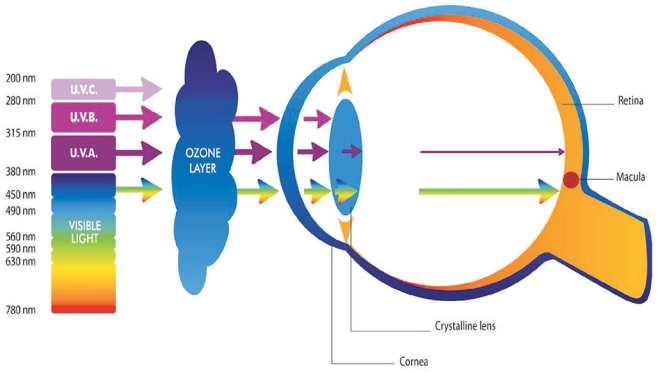

FIGURE 2. Absorption and transmission of solar radiation in the eye. The cornea and crystalline lens filter out UVB and most UVA, so that the most energetic light reaching the retina is short wavelength blue-violet light.

Light Transduction: the Visual Cycle

Visual function depends on two types of photoreceptors within the retina: rods and cones. Required for scotopic vision, rod vision lacks color information and is characterized by high sensitivity but low resolution. Highly concentrated in the center of the macula, cones enable both sharp image resolution and color detection.

Rods and cones in the retina initiate the visual process when

visual pigments absorb photon energy and convert it into neural signals. This biological conversion of light to electrical signals is supported by an enzyme-mediated process called the "visual cycle" that allows efficient reuse of key chemicals in the reaction.

The visual pigments that initiate the process are made up of an opsin combined with the chromophore 11-*cis*-retinal. The important photochemical reaction is the conversion of the 11-*cis*-retinal to all-*trans*-retinal, caused by photon energy striking the pigment. This changes the shape of the retinal molecule, breaking its connection with opsin and leaving the opsin free to initiate a series of reactions that leads to a neural signal and ultimately to vision.

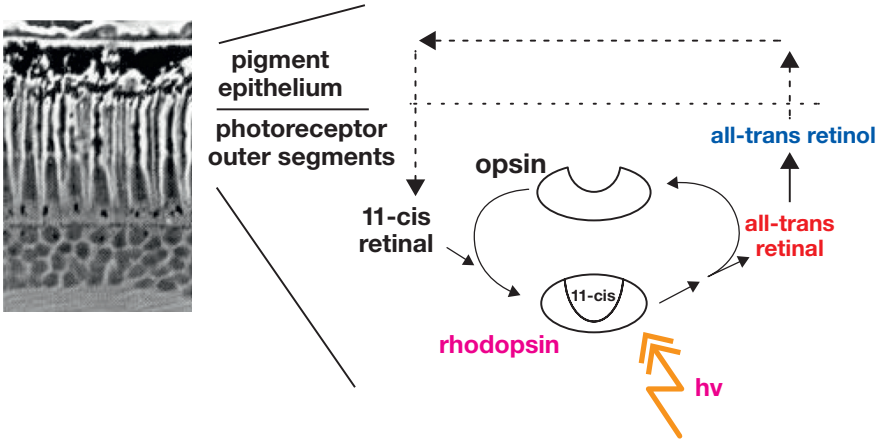

FIGURE 3. The visual cycle.

In the meantime, the all-*trans*-retinal is converted to all-*trans*-retinol and transported to the retinal pigment epithelium (RPE) where it is either stored or reconverted to the 11-*cis*-retinal form for transport back to the photoreceptors. There it can recombine with opsin to complete the visual cycle (Figure 3).

The visual cycle takes place within the outer segment of the rods and cones and in the RPE cells. The RPE cells are not photoreceptive, but they are essential to the regeneration of visual pigments and also play a critical role in the survival and normal function of photoreceptors. With microvilli on their apical surfaces interdigitating with the outer segments of photoreceptors, the RPE cells supply the photoreceptors with nutrients and oxygen. They also help maintain the homeostasis of photoreceptors by phagocytosis and digestion of oxidized photoreceptor outer segments.

Light Damage in the Eye

Although light is essential to vision, light exposure can also cause pathological changes to ocular tissues through absorption of photon energy. When absorbed, photon energy can be dissipated

COMMENTARY: An Insurance Policy for the Eyes

Short wavelength visible light, particularly violet and indigo, reaches the retina in substantially greater doses than does ultraviolet (UV) radiation. Indeed, the conditions associated with UV exposure are generally confined to the anterior segment of the eye, due to nearly complete absorption of UV by the crystalline lens.[1]

When we think about how light interacts with the molecules that compose living cells and tissues, what concerns us is photon energy, which is inversely correlated with wavelength. At a 400-nm wavelength, for example, photons are much more energetic and have a greater potential to alter the molecules they strike than photons at 500 nm. Light at wavelengths in the neighborhood of 400 nm consists of the highest-energy photons to reach the retina, and there is reason for concern about this high-energy light's effects there.

The "Blue-light Hazard"

The most certain impact on retinal health and vision from exposure to higher-energy visible (indigo and blue) light is acute phototoxicity, as seen in humans who stare directly at an arc lamp or the sun. It is established that this damage is photochemical, not thermal, and studies in primates have made it possible to define the action spectrum for this type of damage, which peaks around 440 nm.[2]

It is certainly reasonable to suppose that over the long term, and especially as aging changes erode cellular defense mechanisms, retinal exposure to high-energy light could have a damaging effect. Many in vitro studies, including those detailed in this report, have helped us to understand the photochemical and cellular mechanisms by which this damage occurs.

Visual pigment, retinoids, and bisretinoids (in particular A2E, a major photosensitive component of lipofuscin) have been implicated in photochemical damage to the outer retinal layers, and additional not-yet-identified chromophores may also act in this way. High energy visible light exposure also induces oxidative damage, to which retinal cells are especially vulnerable.[3]

Challenges to Research

Corresponding epidemiological studies examining the link between light exposure and AMD have been less conclusive, in part because of the difficulties of conducting such studies. For example, the dosimetry necessary to conduct a conclusive epidemiological study of light exposure and AMD is extremely challenging. Two otherwise similar people, standing side by side at a beach and facing the same direction may easily have significantly different pupil sizes and lid-openings, and therefore different levels of retinal light exposure. But epidemiological studies tend to assume that two such people's retinas would receive the same light dose.

In addition, much of the data on which these epidemiologic studies rely is retrospective, and thus subject to the vagaries of memory. I can't say for certain

as heat and/or trapped via a photochemical reaction. Acute exposure to intense light can cause thermal injury (eg, skiers' photokeratitis), while lower levels of exposure may, over a lifetime, cause the slow accumulation of harmful photochemical waste products that lead ultimately to cell death.

It is well established that solar UV is hazardous to ocular health. Chronic exposure to solar UV has been shown to increase the risk of developing pterygium, cataract, and a variety of other ophthalmic conditions. But because UV is almost fully absorbed by the ocular media before reaching the retina, the harmful effects of UV radiation are concentrated in the cornea and the crystalline lens. However, scientific findings on blue light suggest that fully protecting the eyes from light damage requires more than just blocking UV.

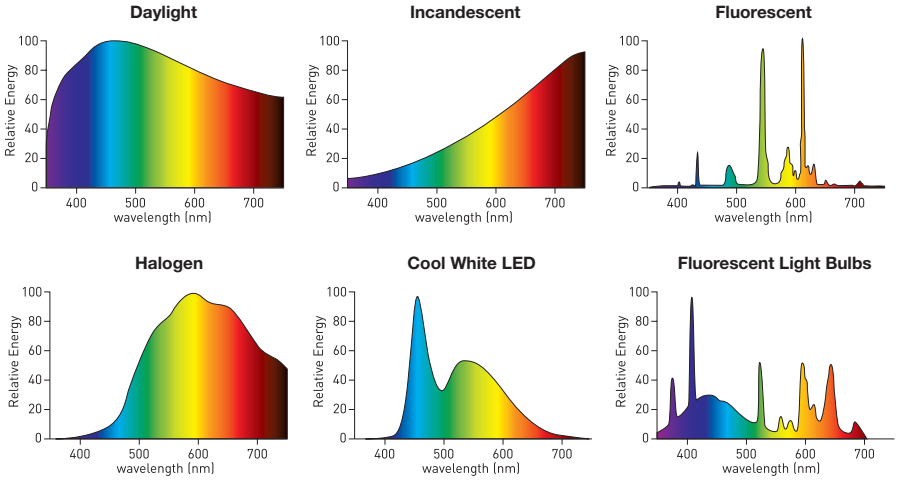

FIGURE 4. Spectral distribution of different light sources.

Blue Light: Concept and Sources

In the visible spectrum, wavelengths between 380 and 500 nm include violet-, blue-, and green-appearing wavelengths. This portion of the spectrum is also known as high-energy visible (HEV) light because of the high photon energy associated with these short wavelengths.

The sun is the primary natural source of blue light, but human beings are also increasingly exposed to blue light from artificial sources, which vary widely in spectral distribution. Solar radiation is 25% to 30% blue light, depending on the reference solar spectrum; and while conventional incandescent lamps emit very little blue light (about 3%), newer artificial light sources produce a considerably higher amount of blue light (Figure 4). Approximately 26% of the light from the energy-efficient and increasingly popular compact fluorescent lamps is in the blue portion of the

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how much I played outdoors as a child; and although I might venture to guess I spent more time outside than the average child of today, the modern child's indoor environment likely contains multiple blue-rich displays and light sources.

Blue Light in Health and Vision

There is no evidence that short wavelength light (below 440 nm) has significant ocular benefit. On the contrary, sharpshooters and others who demand very sharp outdoor vision often rely on blue-light-filtering lenses, both because light of shorter wavelengths is scattered by the atmosphere more greatly than longer-wavelength light and because UV and high-energy visible light cause the crystalline lens to fluoresce very slightly, resulting in a thin haze which may increase with age.[4]

Of course, lenses that block the entire blue spectrum are impractical for everyday use, not only because of their effects on color perception and facial appearance but also because of the physiologically important circadian function, which requires irradiance in the range of 470 nm. So while blocking the entire blue spectrum, as with the yellow-hued blue blockers available in convenience stores, is undesirable, some attenuation of the shortest visible wavelengths would be expected to have minimal impact on vision or health—and may even improve vision very slightly in some environments.

Increased Exposure?

While there is a global trend toward more energy-efficient lighting with LED and compact fluorescent lamps, consumer preference in the US has not favored those blue-rich light sources. Here, the bigger concern may be with modern, higher-luminance displays (computer monitors, smartphones, and tablets) which are blue-rich and virtually ubiquitous.

It is unclear what long term effect this increased exposure to short-wavelength light will have on us; but it is certainly cause for further study and for taking some steps to reduce needlessly high exposures to short wavelength light. Therefore, lenses designed to reduce violet light exposure and accomplish this without interfering with vision and circadian function, seem like a very reasonable insurance policy.

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spectrum; and the 35% of the optical radiation from cool white light-emitting diodes (LEDs) is blue.[4]

BLUE LIGHT IN HEALTH AND VISION

UV and visible light have long been observed to cause photochemical damage to retinal photoreceptors and RPE cells.[5-7] Since the anterior structures of a healthy eye naturally protect the retina from UV, retinal phototoxicity is primarily due to photochemical damage induced by the cumulative effects of long-term exposure to visible light, in particular blue light.

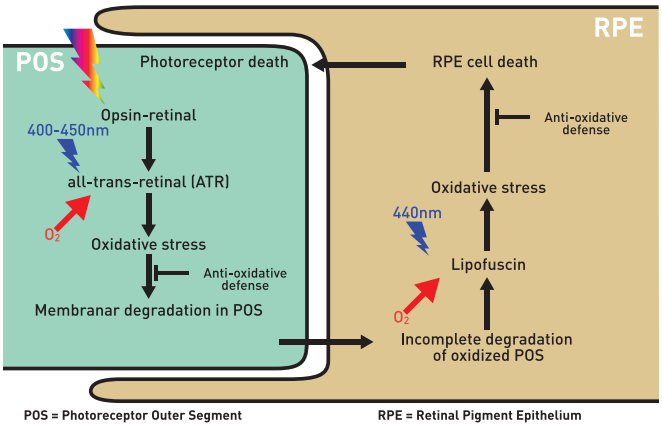

FIGURE 5. Phototoxicity mechanisms in outer retina.

Being in the most energetic portion of the visible spectrum, blue light has the greatest potential to induce the photochemical damage that may ultimately be a factor in retinal disorders such as age-related macular degeneration (AMD).[8-11] On the other hand, blue light is important to visual processes including color perception. More recent research has also demonstrated that blue light plays an essential role in non-visual functions, such as circadian entrainment and the pupillary light reflex.[1,12,13]

Blue Light is Vital for Life

These non-visual functions depend on a newly discovered third photoreceptor type that exists along with the rods and cones. Called intrinsically photosensitive retinal ganglion cells (ipRGCs), these cells contain melanopsin, a photopigment, and, unlike cone cells, they are not concentrated in the fovea. Instead ipRGCs form a photoreceptive network broadly across the inner retina.[12] Because melanopsin is so important to the daily resetting of our biological clocks, the absorption spectrum of melanopsin is sometimes called the chronobiological spectral band. This band peaks at about 480 nm, within the blue range.[13]

The ipRGC response to light in the chronobiological band regulates many non-visual physiologic functions in the human body, including circadian entrainment, melatonin regulation, pupillary light reflex, cognitive performance, mood, locomotor activity, memory, and body temperature.[1,13-16] Studies have shown that pupil constriction, the eye's natural defense against exposure to strong light, is wavelength-dependent and peaks at 480 nm.[14-16] The exact physiology by which ipRGCs control these functions have not been fully elucidated.

What is clear, however, is the essential role that blue light plays in daily life. Thus, simply filtering out the entire blue spectrum in order to reduce the "blue light hazard" may interfere with the physiological functions driven by the reaction between ipRGCs and light in the chronobiological band. Indeed, one recent study has shown that blocking light at 470 nm could disrupt the sustained phase of the pupil constriction reflex.[17]

Blue Light Phototoxicity

Blue light damage occurs when a photosensitizer absorbs photon energy of a specific wavelength, setting in motion a series of intracellular chemical reactions. Rods, cones, and RPE cells of the outer retina—the cells responsible for photon absorption and visual transduction—are rich in photopigments and therefore susceptible to photochemical damage.

Blue light can cause damage to both photoreceptor and RPE cells in primates.[9,18] Cumulative exposure to light in the 380 nm to 500 nm range can activate all-*trans*-retinal accumulated in the photoreceptor outer segments (Figure 5).[19] This blue light photoactivation of all-*trans*-retinal can induce production of reactive oxygen species (ROS), such as singlet oxygen, hydrogen peroxide, and other free radicals, in the photoreceptor outer segments.

The ROS attack many molecules, including polyunsaturated fatty acids, a major component of cell membranes. The large concentration of cell membranes in the retina makes it highly sensitive to oxidative stress. In particular, this stress may disrupt the membranous structures of the photoreceptor outer segments, causing incomplete phagocytosis and digestion of oxidized outer segments in the RPE. The consequence is an accumulation of the waste product lipofuscin in RPE cell granules.

In the eye, lipofuscin, also known as "the age pigment,"

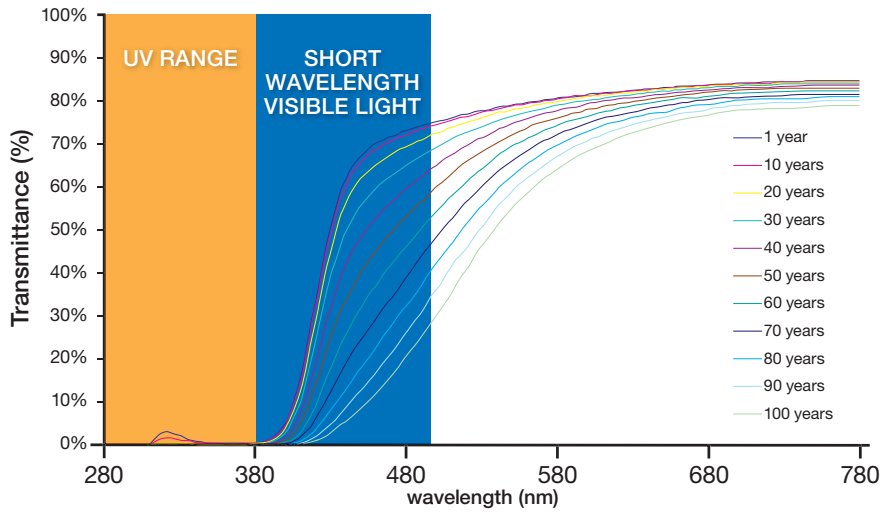

FIGURE 6. Light transmittance of clear ocular media in aging human phakic eye.

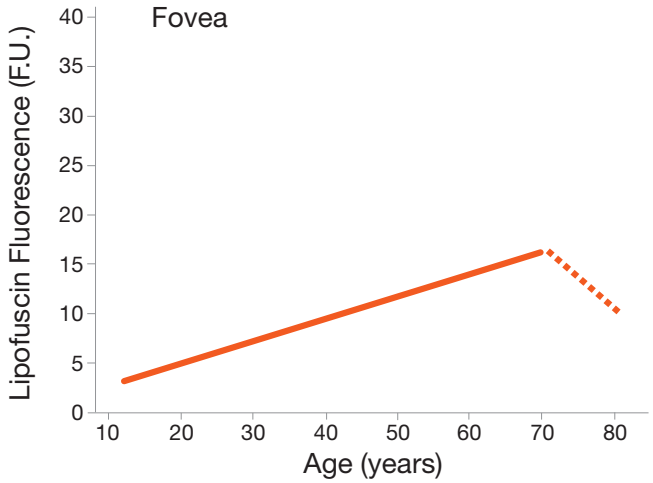

FIGURE 7. Lipofuscin levels in the human fovea increase with age. ***(Figure adapted from Delori FC, Goger DG, Dorey CK. Age-related accumulation and spatial distribution of lipofuscin in RPE of normal subjects.*** **Invest Ophthalmol Vis Sci.** ***2001;42[8]:1855-66.)***

accumulates over the years and builds up at a faster rate in some retinal diseases.[20] Composed of lipids, proteins, and a number of chromophores, lipofuscin is highly susceptible to photochemical changes that can produce permanent cellular damage.[21] Lipofuscin accumulation has been implicated in the pathogenesis of AMD, and intense lipofuscin autofluorescence is frequently observed in regions surrounding the leading edges of geographic atrophy lesions in the retina.[22]

A2E (N-retinylidene-N-retinylethanolamine) is a key photosensitive fluorophore that mediates lipofuscin phototoxicity.[23,24] (A fluorophore is a chromophore that can re-emit light after excitation.) With maximum absorption at around 440 nm, A2E is excited by blue light.[19] The photosensitization of A2E leads to the formation of ROS and to an inhibition of lysozyme's ability to break down cellular structures for recycling.[25,26]

Excessive oxidative stress can cause dysfunction in the RPE cells and, eventually, cell death by apoptosis. Without the supportive functions of the RPE, photoreceptors cannot function properly and will degenerate as well. Lipofuscin accumulation and A2E photosensitization are involved in this cascade of phototoxic effects, which has been implicated in the pathogenesis of AMD.[20]

Aging and Susceptibility to Phototoxicity

Retinal changes associated with age have significant influence over the potential for photodamage. As the eye ages, light transmission and absorption change, primarily owing to the gradual yellowing of the crystalline lens. As a result, the aging lens transmits less visible light overall, with a disproportionate drop in transmission of blue light due to yellow discoloration of the lens (Figure 6).[27-28] But even though it decreases with age, the level of blue light transmitted to the retina remains significant throughout life. Early in life, blue represents about 20% of the visible light received by the retina, dropping to about 14% at 50 years of age and to 10% at 70 years.[29]

Lipofuscin starts to build up in the early years of life, becoming apparent in the RPE cells of healthy human retinas by the age of 10 (Figure 7).[30,31] Accumulating in the lysosomes of RPE cells, lipofuscin increases the potential for photochemical damage in the retina. In the visual cycle, RPE cells actively engulf and digest oxidized photoreceptor outer segments and help to regenerate visual pigments; but debris and waste products accumulated in the lysosomes negatively affect this process.

Weakened Defense Mechanisms

Although the gradual decrease of retinal exposure to blue light with age is protective, other, less helpful effects of aging are also at play.

Macular pigment—which is made up of carotenoids such as lutein and zeaxanthin—efficiently filters out short-wavelength radiation before it reaches the photoreceptors and RPE, providing a natural protection against blue-light damage.[32,33] Macular pigment molecules serve another beneficial role as free-radical scavengers. But, unfortunately, studies suggest that levels of macular pigment decrease with advancing age (Figure 8).[34,35]

The result is that, while less blue light reaches the retina in elderly eyes, the natural defenses and repair mechanisms simultaneously become less effective. The aging retina therefore remains susceptible to photochemical damage from blue light, even as its level of exposure drops.

Link with AMD

AMD, a degenerative retinal disease that affects the photoreceptors, the RPE, Bruch's membrane, and the choroid, is a leading cause of legal blindness among people over age 65.[36,37] AMD is responsible for about half of severe visual loss (defined as visual acuity of 20/200 or worse) in Caucasian Americans over age 40.[37]

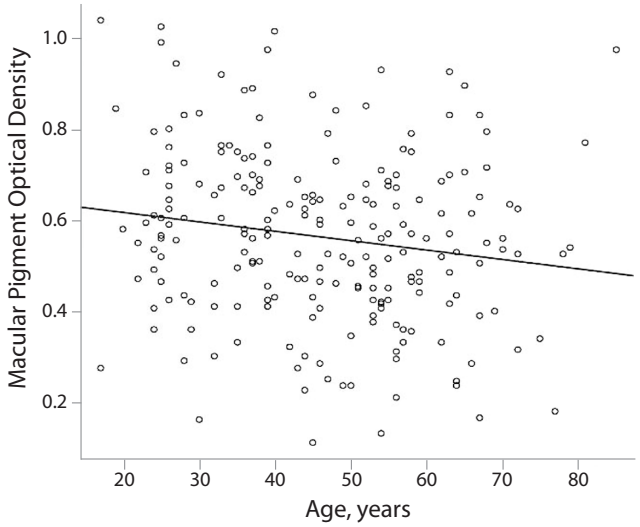

FIGURE 8. Age-dependent macular pigment optical density. ***(Figure adapted from Yu J, Johnson EJ, Shang F, et al. Measurement of macular pigment optical density in a healthy Chinese population sample.*** **Invest Ophthalmol Vis Sci.** ***2012;53(4):2106-11.)***

With the elderly population growing, AMD is rapidly becoming a major public health concern. By 2050, the number of Americans with early-stage AMD is expected to double from 9.1 million to 17.8 million.[38] Extrapolations from current trends indicate that the AMD population worldwide will grow to between 100 and 200 million people over the next 30 years.

Multiple factors increase a person's risk of developing AMD,

including age, tobacco use, genetic factors, and an antioxidant-deficient diet.[39,40] Blue light exposure, owing to its impact on lipofuscin accumulation and A2E-mediated phototoxic effects, has come to be considered another potential risk factor.

Several epidemiological studies have found evidence of a relationship between chronic sunlight exposure and AMD. The Beaver Dam eye study found that levels of sun exposure in the teen and early adult years were strongly associated with a higher risk of developing retinal pigment abnormalities and early AMD.[41,42] In the Chesapeake Bay Waterman Study, a group of subjects with advanced AMD had had high levels of blue light exposure over the preceding 20 years.[43,44] Recently, the European Eye (EUREYE) Study reported a significant association between lifetime blue light exposure and AMD in individuals with low dietary levels of antioxidants (including vitamins C and E, zeaxanthin, and dietary zinc).[45]

Breakthrough Science

The potential connection between blue-light phototoxicity and retinal diseases such as AMD suggests that reducing blue-light exposure would be beneficial to long-term ocular health. Although research in animal models and in-vitro experimental settings has generated substantial evidence that blue light can cause cellular damage to photoreceptors and RPE cells, the wavelengths within the blue-violet spectrum responsible for this damage have not been as precisely identified until now.

Eyes could be protected by simply blocking all blue light (as yellow "blue blocking" glasses aim to do), but this solution distorts color, has unwanted cosmetic effects, and eliminates the physiologically critical light in the chronobiological band. But selective blocking of the hazardous wavelengths (and just those wavelengths) required investigation to determine just what those wavelengths are.

To delineate the damaging bands within the blue-light spectrum, research scientists from Essilor partnered with the Paris Vision Institute (Paris, France) to create an in vitro model for the study of retinal phototoxicity.*

* Based in Paris and linked to Pierre & Marie Curie University, the Vision Institute (IDV) is considered as one of Europe's foremost integrated eye condition research centers. It is here that 200 researchers and doctors and 15 manufacturers work together on discovering and approving new therapies and new preventive solutions, as well as compensatory technologies for sight impairment.

COMMENTARY: Preventive Eyecare — Lens Technology Gets Specific

DIANA L. SHECHTMAN, OD, FAAO

The role of ultraviolet (UV) radiation in the pathogenesis of ocular conditions like cataract, pterygium, and UV keratopathy is well known. Most of the UV incident upon the eye is absorbed by the cornea and crystalline lens, and is thus associated primarily with conditions of the anterior segment.[1] On the other hand, high energy blue-violet visible light, lying just outside the UV band, typically passes through the cornea and lens.[1] Thus, this light is the highest energy visible light to reach and affect the posterior segment.

While it has been challenging to accurately measure and prove a causal link between age related macular degeneration (AMD) and long term retinal light exposure, there is evidence that long term sunlight exposure is one of the risk factors contributing to AMD.[2]

AMD can have a devastating effect on a patient's vision and quality of life. Anti-VEGF therapy and AREDS-type supplements have been used to manage patients with AMD, but these options do not provide a cure or restore vision to its pre-morbid state. It would be far better to find effective ways to reduce the risk of developing AMD in the first place.

The need for good preventive measures is given urgency by the rapid growth of the elderly population and the prevalence of AMD within that population. In addition, exposure to high energy blue light is likely to increase significantly as people convert from incandescent and halogen lighting to compact fluorescent lights and LEDs, which produce a far higher proportion of blue light. In addition, the proliferation of digital screens in use today has caused an increase in our exposure to blue wavelengths. The impact of this increase is potentially concerning, though further studies are warranted.

Recently, research by Essilor in collaboration with the Paris Vision Institute has contributed to the growing body of evidence surrounding the mechanism of blue-light mediated retinal damage.[3] Their study isolated the specific narrow band of blue-violet light (435 nm ± 20 nm) that contributes to retinal pigment epithelium (RPE) cell apoptosis in an in vitro AMD model. Given the fact that blue light is still a necessity for color perception and physiological functions like the regulation of circadian rhythms, selectively blocking only the dangerous band(s) of blue light is critical. This discovery, and the lens technology that enables it, may prove to be a public health breakthrough.

We already counsel patients about UV exposure and offer specific lenses and filters to help protect their eyes. Further research is necessary; but lenses designed to provide optimum vision, protect against UV, *and* selectively block the narrow band of blue-violet light implicated in RPE apoptosis could become an important element of preventive eyecare going forward.

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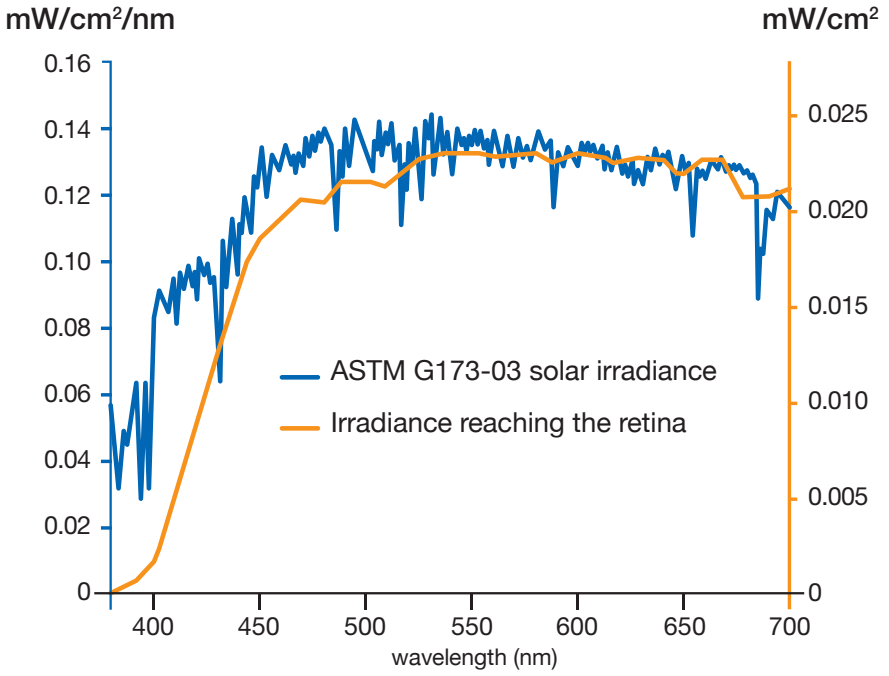

FIGURE 9. Calculated irradiances in the A2E experiment.

New Methods

A large body of prior research had demonstrated that blue light causes phototoxic damage to RPE cells and is far more damaging to those cells than green or yellow-red light.[46-49] In addition, it had been determined that blue-light-induced RPE cell death is mediated by apoptotic, rather than necrotic, processes.[46,47,50,51]

These studies, however, had a number of methodological limitations. For example, the cells typically used for in vitro experiments were from immortalized RPE cell lines (rather than freshly harvested RPE cells), and the culture media were not always entirely free of visible light chromophores. Nor were the experimental light levels normalized to approximate actual physiological conditions. Most importantly, all studies prior to the joint study between Essilor and the Paris Vision Institute work used broadband blue light illumination and so were not able to define the specific toxic sub-band(s) within the blue-violet spectrum.

Knowing this, scientists from Paris Vision Institute and Essilor used their respective areas of expertise to develop improved experimental techniques and overcome the limitations of prior studies. Instead of immortalized cell lines, they employed primary cultures of swine RPE cells grown in a cell medium free of visible light-absorbing chromophores. In addition, they devised a unique illumination system that allowed them to normalize light irradiances to sunlight retinal exposure. They were able to expose the RPE cells to extremely narrow (10-nm) spectral bands (across the range from 390 to 520 nm in 10-nm increments) with tight photometric control.

Before light exposure, the RPE cells were treated with A2E at different concentrations. (Because, again, A2E is a key photosensitive fluorophore in lipofuscin, A2E-loaded RPE cells are frequently used to model aging RPE cells.[18,47,49,52,53] Very recently, however, some authors have challenged the A2E model, proposing instead to measure lipofuscin directly. [Ablonczy Z, Higbee D, Anderson DM, Dahrouj M, Grey AC, et al. Lack of correlation between the spatial distribution of A2E and lipofuscin fluorescence in the human retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 2013 Jul 11.]) The A2E-containing cells were exposed to controlled doses of light in 10-nm bands at irradiance levels mimicking sunlight retinal exposure, and RPE cell damage was assessed by measuring cell viability, necrosis, and apoptosis (Figure 9).

Results

The greatest damage followed exposure to the four 10-nm sub-bands within the blue-violet spectrum between 415 nm and 455 nm. In those test cells, morphological changes to RPE cells (cell rounding, loss of confluence, and decrease of density) were observed 6 hours after exposure (Figure 10). In addition to wavelength dependence, the toxic effect was A2E-dose dependent, with the greatest apoptosis rates occurring with 20 µM and 40 µM concentrations of A2E. In cells exposed to the narrow band

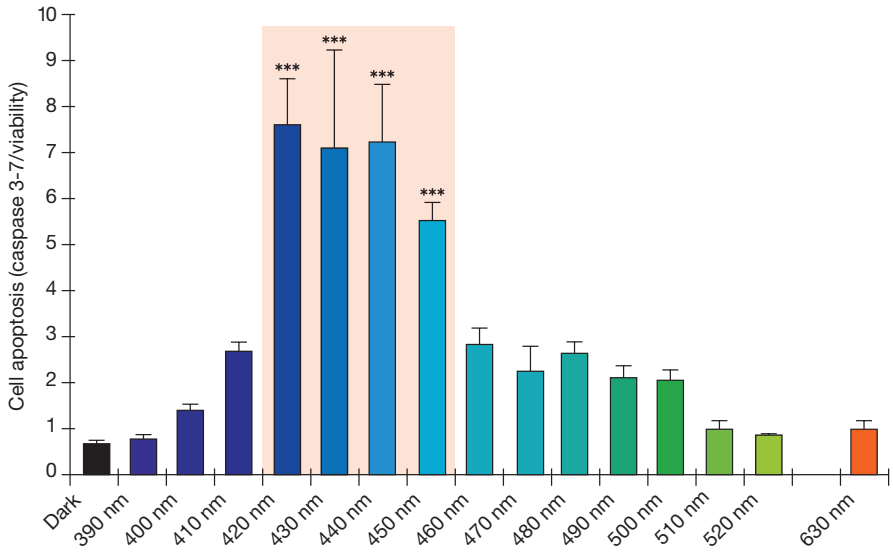

FIGURE 10. Phototoxic action (apoptosis) spectrum on A2E-loaded RPE cells and morphological changes of the RPE cells.
***$P < 0.001$ as compared to control cells maintained in the dark.**

of blue-violet light centered on 440 nm, though, there was a significant increase in apoptosis, even with 12.5 μM A2E, indicating the phototoxicity of those wavelengths.

The damage observed in the study was clearly apoptotic rather than necrotic. Irradiated RPE cells had necrosis rates no higher than those maintained in dark, irrespective of the A2E concentration, which is consistent with the experiments conducted in physiological light conditions.

Significance of these Findings

The A2E concentration dependence seen here demonstrates that the photodamage to RPE cells in this test system was not due simply to the high photon energy of short-wavelength blue-violet light. Rather, this apoptotic cell death represents blue-light phototoxicity specifically mediated by the photosensitizer A2E. This is significant because it provides evidence that the test system can be used as an in vitro model of the suspected mechanism of cell death in AMD.

The key learning from this series of experiments is that blue-light phototoxicity to RPE cells appears to be concentrated in a narrow band of wavelengths centered on 435 nm ± 20 nm. For the first time, the toxic wavelength range within the blue-violet spectrum has been identified in physiological sunlight conditions using an aging RPE model.

The data further suggests that selectively attenuating the hazardous portion of the blue spectrum (wavelengths from 415 nm to 455 nm) may provide protection for the retina without significantly affecting the igRGCs, whose primary action spectrum lies between 465 nm and 495 nm. This is in contrast to broad filtration of blue light ("blue blocking"), which has the potential to affect the regulation of the pupillary light reflex and other critical physiological functions. The establishment of a narrow phototoxicity spectrum paves the way for developing new ophthalmic filters that deliver *selective* photoprotection.

PREVENTIVE MEASURES

Given the probable role of blue-light phototoxicity in degenerative retinal diseases, selective photoprotection offers one potential means of helping eyes stay healthy longer. There may be added benefit to this in the world of blue-rich artificial light that is building around us due to the growing popularity of energy-efficient compact fluorescent lamps and LEDs.

Because these new lighting sources are more cost-efficient, energy-efficient, long-lasting, and environmentally friendly than incandescent and halogen bulbs, they are quickly becoming the next-generation light sources. By 2016, traditional incandescent light sources will, by law, no longer be available for domestic lighting in Europe.[3] LEDs are also becoming progressively more popular in backlit mobile phone, tablet, television, and computer displays.

As LEDs and other blue-rich solid state light sources become more important in domestic and workplace lighting, and as people spend more and more time staring at TV, computer, and mobile phone screens, blue light exposure will gradually increase, and its ocular hazards may become more problematic.

From Science to Solution

Efforts have been made to develop prophylactic and therapeutic methods to protect retinal cells from phototoxic damage. In cataract surgery, yellow intraocular lenses that block both UV and blue light (< 500 nm) have been introduced to reduce retinal phototoxicity in pseudophakic eyes; however, the clinical value of these lenses is debatable, as they block both hazardous wavelengths and those that most effectively activate the ipRGCs.[54,55]

The use of small-molecule compounds is also being investigated as a treatment method to modulate the visual cycle and reduce lipofuscin accumulation in RPE cells.[56,57] The most viable preventive approach, however, may simply be wearing spectacle lenses that are able to stop hazardous blue light from entering the eye.[58,59] Blue-light blocking glasses have existed for years and are recommended for patients with retinal diseases; but current lenses absorb a very large portion of the blue-light spectrum, distorting colors, reducing scotopic vision and possibly interfering with nonvisual ipRGC-controlled functions. Also, the absorptive technology makes the lenses appear yellowish (absorbing blue).

Based on the discovery of the precise spectrum of RPE-toxic blue light, Essilor has developed a new No-Glare lens, Crizal® Prevencia™, a unique narrow-range blue light filter that selectively attenuates the hazardous portion of blue-violet light (415 nm to 455 nm) while remaining transparent to other wavelengths of visible light. Designed to reduce exposure to potentially harmful blue light, Crizal® Prevencia™ No-Glare lenses also protect eyes from UV light coming through the front or reflecting off the back surfaces of the lenses. This new lens can benefit everyone by reducing exposure to the phototoxic wavelengths of blue-violet light.

Optometrists and Eye Protection

There is scientific evidence to support the finding that high-energy blue light is harmful to the retina and that reducing exposure to the most toxic wavelengths of this light is likely to be beneficial.

Today, optical dispensing is becoming more doctor-driven, with optometrists no longer hesitant to discuss eyewear and make specific spectacle lens recommendations to patients in the chair. This is fortunate because the exam room is the ideal place to educate patients about the nature of blue light hazard and to explain how spectacle lens wearers can better protect themselves from it. In recommending selective filtering of phototoxic wavelengths, clinicians have an ideal opportunity to perform a truly beneficial function—protecting vision for a lifetime—even if the patient has simply come in for a refraction and new glasses.

This role will become ever more important as LED and compact fluorescent lighting find their way into more homes and workplaces—and as blue rich digital screens come to occupy even more of our days and evenings.

Crizal® Prevencia™ No-Glare lenses, which cut the hazardous blue light in the 415 nm to 455 nm band by 20% and provide protection from back-side UV reflection, can be beneficial for patients at all ages. It is important for clinicians prescribing Crizal® Prevencia™ No-Glare lenses to gain the support and commitment of their staff members, who can contribute tremendously to communication with patients. Once staff members understand the nature of blue light hazard and its association with ocular health, they can bolster the doctor's recommendation and help patients understand the importance of blue-light protection for the eye.

CONCLUSIONS AND FUTURE DIRECTIONS

Certain wavelengths in the blue-violet range are now known to be detrimental to the retina, and cumulative blue-light damage is implicated in retinal disorders such as AMD. The most hazardous blue wavelengths for retinal pigment epithelium, as determined by the joint work of Essilor and the Paris Vision Institute, fall in the narrow band between 415 nm and 455 nm. This is relatively distinct from the spectral band that is responsible for critical physiological functions such as the pupillary light reflex and circadian entrainment.

For spectacle lenses to protect the retina, this means that in addition to protecting against UV wavelengths, attenuation of high-energy blue-violet light in the 435 ± 20 nm band is of value. But for normal physiologic functioning, lenses must block this light without reducing transmission in the chronobiological spectral band.

Furthermore, patient acceptance may be limited when lenses are visibly colored and distort color perception, as is the case with most blue absorber lenses. To enhance vision and support color perception, lenses should offer high transmittance of all visible light wavelengths outside the UV and phototoxic blue bands.

Crizal® Prevencia™ No-Glare lenses offer selective photofiltering and superior clarity of vision, taking blue blocking lenses and eye protection to the next level.

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