BLUE LIGHT, VISION, AND THE EYE

By developing an experimental framework to distinguish beneficial blue light rays from harmful ones, Essilor has effectively created a new field in photobiology research.

The electromagnetic spectrum encompasses every possible wavelengths of radiation in our universe. At one end lie the tight, high-energy gamma rays that are so powerful that exposure to these rays can cause cancer in living creatures; while far away on the opposite end lie the long, low-energy frequencies that cause nothing more harmful than AM radio. Near the center of this vast continuum, sandwiched between ultraviolet and infrared energy, runs a very thin sliver of bandwidth that we see as visible light and colors—also known as optical radiation, which ranges from about 380 nanometers (nm) to 780 nm. (See Figure 1.)

Within optical radiation, the colors that are blue and bluish, from violet to turquoise, take up a lot of space, about 380 to 500 nm. They have tighter wavelengths and pack greater energy than greens, reds and yellows. Thus blue light is sometimes referred to as high-energy visible (HEV) light.

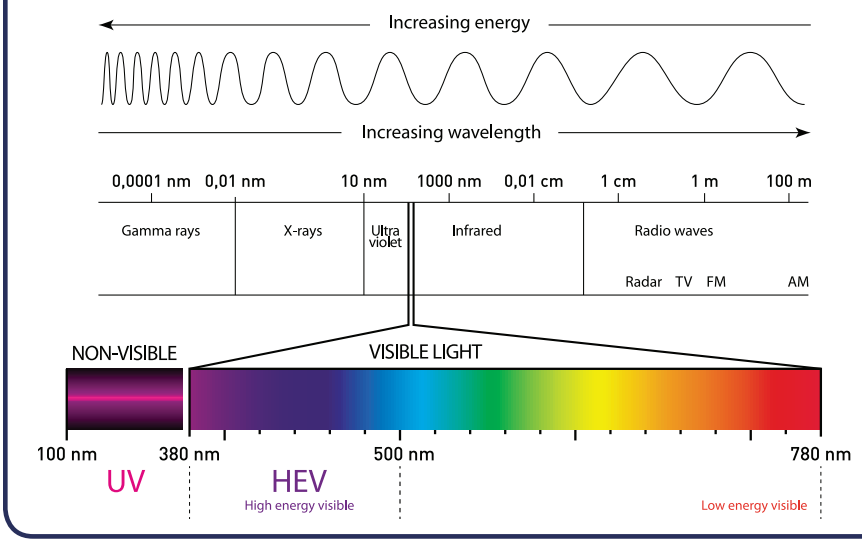
Blue light tends to occur at higher frequencies outdoors via sunlight and at lower ones indoors, where, until recently, most illumination was provided by incandescent light sources, which burn at higher red and yellow frequencies than the sun.

It is known that prolonged exposure to outdoor radiation (both visible and non-visible light) can result in cumulative damage to eye tissues, both anterior and posterior. Ultraviolet radiations are harmful to the cornea and crystalline lens and are associated with cataract development. HEV light is a known risk factor for age-related macular degeneration (AMD). It can induce and accelerate photochemical reactions and cell photodamage, largely mediated by the accumulation of reactive oxygen species in the retina, researchers believe.

And yet we also know that exposure to HEV light has a beneficial effect as well. It plays an important role in non-visual functions, such as circadian rhythms involving sleep-wake cycles, as well as cognitive, psychomotor, and hormonal balance.

Although they have a great deal in common, these two areas of scientific inquiry—the study of HEV light's positive effects on the one hand and its negative impact on the other—have up until now operated largely independently of each other. But recently, Essilor's R&D department, working in conjunction with the Paris Vision Institute, unveiled data that maps out a very precise retinal phototoxic spectrum within HEV radiation.[1] For the first time ever, researchers can measure the precise physiological conditions of illumination using an ***in vitro*** model. This paves the way for a whole new discovery of corrective lenses that filter out harmful HEV frequencies while allowing beneficial ones, to pass through to the eyes untouched.

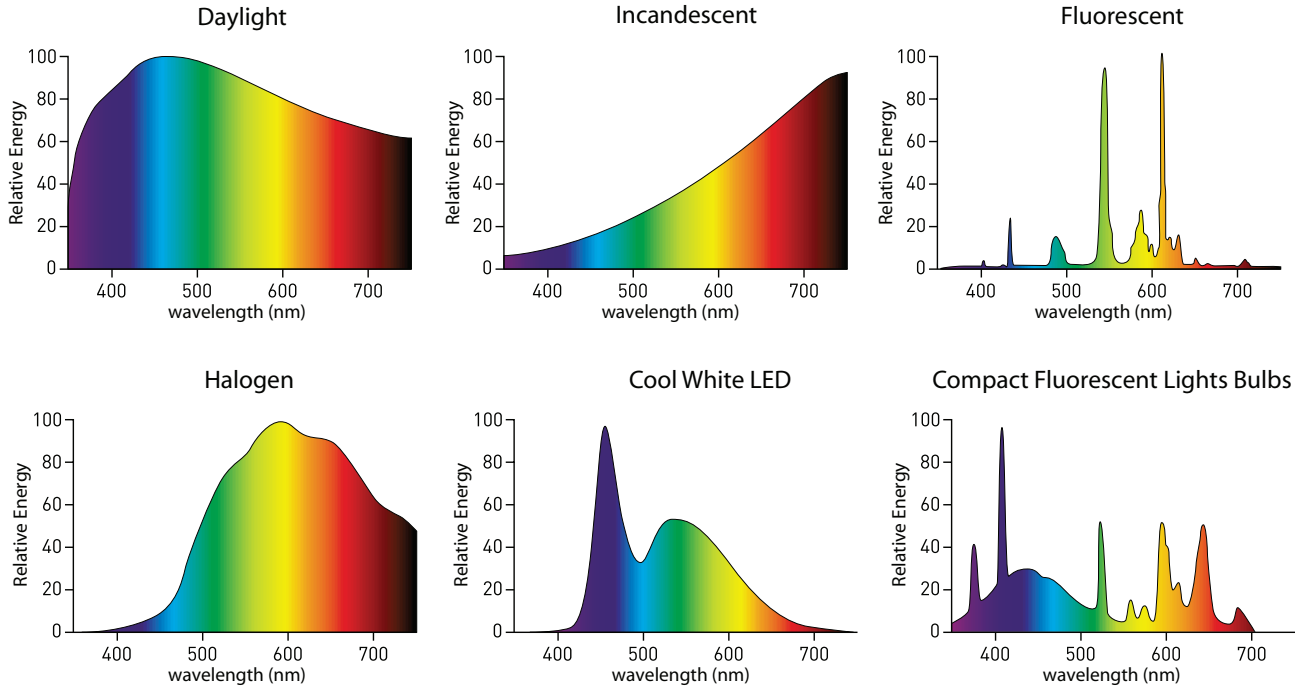
Figure 1. Electromagnetic spectrum and zoom on visible and blue light



Blue Light Sources

Every light source emits a spectrum that can be expressed as a function of a monochromatic wavelength and shown on a graph. For example, Figure 2 represents the spectra in the visible range of typical sunlight, an incandescent bulb, a fluorescent lamp, a halogen lamp, and a cool white light-emitting diode (LED).

Figure 2. Spectra of classical light sources



Depending on atmospheric conditions, time of day, geography, etc., the blue light portion of sunlight is 25-30% percent.

Existing artificial light sources are based on one of two processes: incandescence or luminescence. In incandescent light sources, that is, incandescent bulbs (of the Thomas Edison variety) and halogen lamps, a filament is heated and emits a light radiation.

In luminescent light sources, which include compact fluorescent lamps (CFL), fluorescent bulbs, and LEDs, the atoms of a gas or a semiconductor are excited via a discharge or a carrier recombination, leading to the emission of visible radiation.

Luminescent light sources tend to contain a greater portion of blue light. For example, compact fluorescent lamps contain 26% blue light, and cool white LEDs emit at least 35%. By contrast, traditional incandescent lamps emit only 3% blue light.

Until recently, traditional artificial light was provided mostly by incandescent lamps. However, such older light sources are now being rapidly replaced by products based on LEDs, which have a longer lifetime, lower energy consumption, and less negative environmental impact. In Europe, it is predicted that by 2016 traditional incandescent light sources will no longer be available for domestic lighting. Leaders in the lighting industry believe that by 2020, more than 90% of all light sources worldwide will be based on solid state lighting products and LEDs. We can see this all around us as luminescent light sources progressively conquer office environments, TV screens, computer monitors, mobile phones, tablets, etc.

This trend significantly increases exposure to these new LED-based artificial light sources, consequently elevating the proportion of total blue light that reaches the eye.

Blue Light and Vision

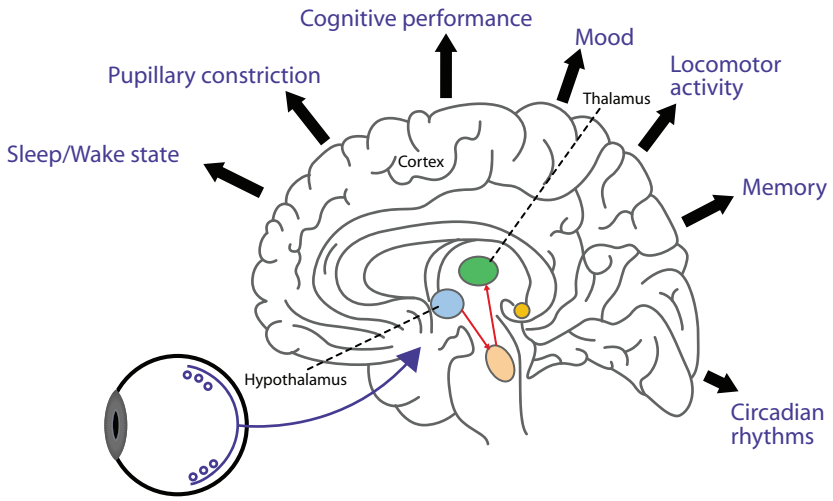
To function properly, rod and cone photoreceptors must constantly regenerate. Retinal pigment epithelium (RPE) cells play a critical role in this regeneration. Without RPE cells, rods and cones cannot survive. Several retinal pathologies can be linked to RPE and photoreceptor degeneration, including AMD, retinitis pigmentosa, and Stargardt's disease.

Over the last 20 years, many studies have linked the role of sunlight exposure to the prevalence of AMD. For example, the EUREYE study found significant associations between blue light exposure and neovascular AMD in individuals having the lowest antioxidant levels.[2] Another study performed on 838 fishermen in the Chesapeake Bay area showed patients with advanced AMD had been exposed to high levels of blue light over the preceding two decades.[3]

Furthermore, granules that accumulate in the RPE cells in the early stages of AMD are made up of a substance called lipofuscin. Lipofuscin is produced by an incomplete phagocytosis of the photoreceptor's outer segments and can be activated by specific protons, with a maximum absorption in the blue spectral range.

How does this occur? During very prolonged or extreme light exposure, an accumulation of all-trans-retinal (ATR) can occur in the photoreceptor outer segments (POS). The ATR is photosensitive to light ranging from violet to blue, with an absorption profile decreasing from 400 nm to 500 nm. When the antioxidant defenses begin to falter, as they do in advanced age, this ATR photoactivation can induce an oxidative stress

Figure 3. Non-visual biological functions controlled by light



in the POS. When the POS are oxidized, they cannot be correctly phagocytized by RPE cells. This incomplete intracellular digestion generates lipofuscin granules in the RPE. The end result of all these processes is RPE degeneration and photoreceptor death.

Preventative Measures

AMD is a serious worldwide problem, one expected to worsen as life expectancies increase and mean population ages continue to rise. The worldwide AMD population was roughly estimated at 100 million people in 2012, and if demographic trends continue at current rates, this number will double in the next 30 years.

While great advances have occurred over the past 10 years in the treatment of AMD, especially in the field of anti-vascular endothelial growth factor (VEGF) injection therapy, the longevity of treatment benefits remains frustratingly short, and there seems to be no endpoint to the frequent intra-vitreal injections required to maintain it. Any measures that could be taken to prevent the onset of this blinding disease would no doubt be enthusiastically welcomed by the ophthalmic community.

One area in which preventative measures might be particularly effective is dry AMD, where anti-oxidative dietary supplements, containing lutein or zeaxanthin, have yielded positive results.

Another degenerative disease in which preventative options would be welcome is retinitis pigmentosa. Like AMD, retinitis pigmentosa is characterized by RPE and photoreceptor degeneration. Progressive rod atrophy causes a slow peripheral vision loss in both eyes. Cones are also affected at later stages of the disease. No treatment solutions for this disease in advanced stage have yet been commercialized.

Stargardt's disease is an inherited juvenile form of macular degeneration that causes progressive central vision loss. The pathological features of Stargardt's include the accumulation of fluorescent lipofuscin pigments in the RPE and the degeneration of photoreceptors.[4,5] Some ***in vivo*** studies on Stargardt's disease models suggest that light exposure increases the formation of lipofuscin granules. For instance, researchers have observed that mice kept in dark environments demonstrated almost no lipofuscin deposits.

Beyond the lack of therapeutic treatments for patients suffering from degenerative retinal diseases, a dearth of preventative solutions coupled with a generally late diagnosis explain the irreversible and numerous negative effects on vision.

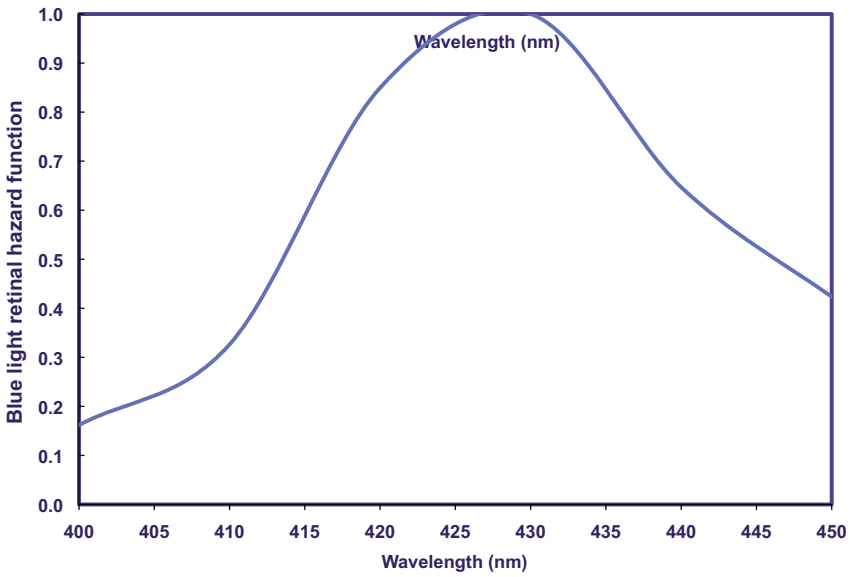
Blue Light and Non-visual Functions

While it is obvious that light regulates the visual process, photons received by

KEY TAKEAWAYS

- Essilor is the first ophthalmic industry player to conduct *in vitro* photobiology research with 10 nm ranges of HEV exposure.
- For the first time, the most toxic wavelength range within blue light is identified in physiological sunlight conditions using a swine AMD cell model.
- Wavelength-dependent apoptosis (cell death) is evidenced, associated to lifelong cumulative toxicity.
- RPE cell apoptosis is evidenced between 415 nm and 455 nm (435 +/-20nm), the Blue-Violet range.
- Preventative solutions are necessary to slow down the continuous aging and pathological process.
- The innovation of the photobiology research, carried out by Paris Vision Institute and Essilor, is based on 4 aspects:
  1. Use of an *in vitro* model of AMD and aging using A2E photosensitization on primary swine RPE cells.
  2. Calculation of physiological sunlight exposure at retinal level.
  3. Sophisticated LED-fibered cell illumination device to scan blue spectral range.
  4. RPE cell exposure to 10 nm illumination bands in physiological sunlight conditions.

Figure 4. Relative blue spectral function efficiency, blue light risk function



the eye can also affect many non-visual biological functions. These non-visual irradiance detection tasks are triggered by a third photoreceptor, discovered in 2002, called intrinsically photosensitive retinal ganglion cells, or ipRGC. These cells contain a melanopsin associated pigment.[6] Melanopsin pigment absorbs around 480 nm ± 15 nm, (about what we see as turquoise) which is now commonly known as the "chronobiological spectral band."

Non-visual photoresponse is essential for circadian rhythms in many non-visual functions, encompassing sleep/wake state (melatonin synthesis), pupil light reflex, cognitive performance, mood, locomotor activity, memory, and body temperature, among other bodily functions. (See Figure 3.)

Chronobiological disruptions can cause sleep disorders, gastrointestinal disorders, depression, anxiety—and even increased risks of cancer for shift workers, according to studies (HAS-French Haute Autorité de Santé 2012 report).

Thus, it is now widely believed that exposure to blue light within the chronobiological spectral band should be maintained to ensure a good synchronization and regulation of non-visual biological functions.

Experimental Model

The achievement of Essilor and the Paris Vision Institute has been to establish an ***in vitro*** experimental model that produces accurate, reproducible photobiology results. This model consists of an illumination device that allows researchers to convey light on very restricted, narrow wavelengths, parsing the visual light spectrum into 10-nanometer bands. Each band is guided by an optic fiber toward a cell incubator, which contains swine cells. This allows researchers to precisely control the degree of illumination for each wavelength.

Researchers have extracted from this ***in vitro*** model a formula to calculate blue light risk. It describes the biological risk linked to the photochemical degradation of RPE cells when the retina is exposed within certain blue light ranges. (See Figure 4.)

Moreover, the newly established selective photo-toxicity spectrum creates the starting points for two very practical areas of research: the invention of selective photo-protection ophthalmic filters and the calculation of how well these filters function.

Summary

The 4-year rigorous research work, jointly released by scientists from Essilor's R&D department and Paris Vision Institute, shows that RPE cell apoptosis is specifically amplified in a 40 nm narrow range within the Blue-Violet light spectrum, from 415 nm to 455 nm, centered at 435 nm. The identification of this precise "toxic band" represents the heart of this scientific discovery.

Thus, we now have specific criteria for selective photo-protection. Essilor has developed a truly new category of ophthalmic lenses—Crizal® Prevencia™ No-Glare lenses. This new technology can simultaneously selectively filter harmful light—Blue-Violet and UV light—while passing through all beneficial light and still maintaining lens transparency.

Furthermore, the unique illumination system is currently being used to measure the cell protection brought by various blue filtering lenses. Hence, for the first time, lens protective efficacy can be evaluated under ***in vitro*** physiological sunlight conditions, based on objective measurements of cell viability.

This evidence, though preliminary, strongly suggests that new filters could aid in preventing patients from premature AMD onset, and possibly other diseases as well.

References

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