



Light-emitting diodes (LED) for domestic lighting: Any risks for the eye?

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ABSTRACT

Light-emitting diodes (LEDs) are taking an increasing place in the market of domestic lighting because they produce light with low energy consumption. In the EU, by 2016, no traditional incandescent light sources will be available and LEDs may become the major domestic light sources. Due to specific spectral and energetic characteristics of white LEDs as compared to other domestic light sources, some concerns have been raised regarding their safety for human health and particularly potential harmful risks for the eye. To conduct a health risk assessment on systems using LEDs, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), a public body reporting to the French Ministers for ecology, for health and for employment, has organized a task group. This group consisted of physicists, lighting and metrology specialists, retinal biologist and ophthalmologist who have worked together for a year. Part of this work has comprised the evaluation of group risks of different white LEDs commercialized on the French market, according to the standards and found that some of these lights belonged to the group risk 1 or 2.

This paper gives a comprehensive analysis of the potential risks of white LEDs, taking into account pre-clinical knowledge as well as epidemiologic studies and reports the French Agency's recommendations to avoid potential retinal hazards.

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1. Introduction

Artificial light sources, essential in the daily life of most of Human being consume around 2650 billion MWh/year, which represents almost 19% of the worldwide electricity production. The European Directive for the eco-design of Energy Using Products (2005/32/CE) recommends improving the energy performances of domestic use products in order to protect the environment. Consequently, decision was made to progressively suppress the least efficient light sources and replace them by either compact fluorescent lamps or by Light-Emitting Diodes (LED). By the first of September 2016, no more incandescent lights will be available in Europe for domestic lighting, and inorganic or organic LEDs could become the next generation light sources. Indeed, if white LEDs would replace other light sources, about 270 millions of tons of CO₂ per year would be saved, representing a tremendous ecologic gain and, with the growing improvement of LED 's light efficacy, their energetic and environmental benefits will not be disputable.

Yet, the potential risks of these new light sources need to be explored. Due to specific spectral and energetic characteristics of white LEDs as compared to other domestic light sources, some concerns have been raised regarding their safety for human health and particularly potential harmful risks for the eye. To conduct a health risk assessment on systems using LEDs, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), a public body reporting to the French Ministers for ecology, for health and for employment, has mandated a task group. This paper summarizes the ocular aspects of this task, giving a comprehensive and objective analysis of potential risks, and reports the French Agency's recommendations to avoid potential retinal hazards.

2. Light-emitting diodes, LEDs

2.1. Some physics and optics

Light is an electromagnetic radiation visible by the intact adult human eye in the range of 380–780 nm, spanning from violet to red light. Like all radiations, light carries energy, the shorter wavelengths being the most energetic ones. Radiometric quantities define energy-related parameters of optical radiation (Table 1 summarizes the definition of terms). Radiance is used to describe the “brightness” of a source, i.e., to quantify the amount of light emitted by a source [in W/(m² sr)] while irradiance is used to describe the power density on a receiving surface [in W/m²]. Photometric quantities take into account the visual effect of light and therefore indicate light levels that are spectrally weighted by the standard photometric visibility curve (photopic), which peaks at 555 nm for the human eye. such as the luminance (formerly referred to as “brightness”) as perceived by a human “standard observer”, measured in cd/m² and the illuminance (the light flux density on a receiving surface) measured in lux (luminance which is the ratio of the flux emitted by a source in a unit solid angle, divided by the area of the emitting surface). As a consequence, the smaller the emitting surface, the more concentrated the flux in the viewing direction and the higher the luminance. Because the eye has an optical system that images the world on the retina, the photometric quantity that is relevant in terms of real retinal illumination is the luminance of the objects that are viewed by a subject. Since the spectral distributions of different light sources vary widely, there is no simple conversion factor between photometric (either photopic or scotopic) and radiometric quantities. As both radiance and luminance describe the light source, it is

Table 1
Definition of terms.

Term	Unit	Definition
Luminous flux	Lumen lm	Evaluation according to eye sensitivity, of light quantity radiated in all space by a light source
Luminous intensity	Candela cd	Luminous flux emitted by solid angle unit
Luminance	Candela per square meter cd/m ²	Light surface density
Illuminance	Lux lx	Luminous flux received by a surface
Luminous efficacy	lumen/Watt lm/W	The theoretical maximum is 683 lm/W

worth noting that they do not vary with the viewing distance. Tables 2 and 3 gives examples of luminance and illuminance of natural light and some commonly used artificial lights.

The Correlated Color Temperature (CCT) of white light, used to define its shade, “hot” or “cold” after the associated feeling, is expressed in Kelvin. Warm-white lights present a yellow-orange tint and have a CCT below 3500 K (2700–2900 K for incandescent light sources). The cold-white lights are closer to the cool colors, like blue, and the associated CCT ranges from 5500 K and higher (6500 K for a standard daylight illuminant). The Color Rendering Index (CRI) is an index comprised between 0 and 100, which defines the ability of a light source to reproduce the various colors of objects illuminated by it, compared to a reference light source. By definition, daylight has a CRI of 100. In shops, school premises or offices, the IRC of lamps should always be greater than 80. Table 1 summarizes the main terms used to define light quantities. Tables 2 and 3 give some examples of luminances and illuminances corresponding to natural and artificial lights.

2.2. LED technology

A light-emitting diode is intrinsically monochromatic and its conversion efficiency depends on the emitting wavelength. The dominant wavelength emitted by the semi-conductor junction is mainly determined by the value of the energy gap between the conduction and valence bands. In addition, it can be shown that the emitted spectral line has a small Full Width at Half Maximum (FWHM) value depending on the junction temperature. The first commercialized light-emitting diode was red. Today, almost all saturated colors are achievable.

One of the key issues for LEDs to significantly penetrate the general lighting market is to obtain a “high power efficient white LED”. How LED can generate white light? There are today three methods to generate white light from a light-emitting diode:

Table 2
Example of luminance of natural and domestic lights.

Luminance examples (cd/m ²)	
Eye perception threshold	10 ^{−6}
Night sky	10 ^{−4}
Full moon, clear weather	2000
Fluorescent tubes	5000
White paper sheet under the sun, at 12:00, in summer	30 000
Glaring around	500 000
Carbon filament	700 000
Possible ocular lesions apparition around	250 × 10 ⁶
Xenon arc	400 × 10 ⁶

Table 3
Examples of illuminance of natural and domestic lights.

Illuminance examples (lx)	
Night sky	0,0003
75 W lamp at to 2 m	40
Public lighting	50
Very good artificial lighting	500
Outside, cloudy weather	15 000
Under the sun, during summer, at 12:00	100 000

- Combining a diode emitting at a short wavelength λ_1 with a phosphor emitting at a larger wavelength λ_2 (Fig. 1);
- Using a diode emitting in the near ultraviolet coupled with one or several phosphors;
- Using three diodes (at least) emitting at different visible wavelengths, which then combine themselves to produce white light.

When mixing several phosphors, the resulting correlated colour temperature (CCT) is related to the final mix.

Each of these methods presents advantages and drawbacks. The first method is the most commonly used today to produce high-brightness white LEDs. This method is based on the fact that two photons of complementary wavelengths (λ_1 “short” and λ_2 “long”) arriving simultaneously on the human eye will cause white light sensation. A diode generating a short wavelength is covered with a phosphor, which absorbs a few short wavelength photons to convert them into longer wavelength photons. For mass-production of white LEDs, blue diodes, based on InGaN or GaN crystals and combined with a yellow phosphor (YAG:Ce or similar) are used, producing LEDs with a CCT of 5500 K or higher. To produce “warm-white” with a CCT of about 3200 K, an extra layer of phosphor emitting red light is added. However, the extra layer significantly reduces the luminous efficacy of the LED. It should be noted that the blue-light component is always present in the LED spectrum.

The second method consists of using a short wavelength emitting diode (near ultraviolet) coupled to one or several phosphors, which convert the UV radiations into visible light. The same method is used in fluorescent lamps. The main advantage is to produce very high quality white light (good color rendering). This method intrinsically avoids direct emission of blue light.

Finally, the third method consists in using three light-emitting diodes, one for each fundamental color (red, green and blue). The additive synthesis of these three colors leads to a white light, which CCT depends on the relative weight of each color component. More than three sources are usually used today. It helps obtaining more color shades or to be more accurate in reaching a desired color point. It is therefore possible to add cyan, amber or red orange, the main goal being to improve the color rendering. This technique is often used for scenic and decorative lighting, rather than for general lighting as the involved equipment is much more expensive.

Nowadays, LEDs used for domestic lighting are producing white light with the first described method. Therefore, the risk assessment was made for this type of white LED systems. In Fig. 2, some examples of commercially available white LEDs are represented.

3. Interactions of light with biologic systems: mechanisms of light-induced damages

Interaction of radiation with biologic systems occurs through absorption, the radiant energy is transferred to the material in which the effect takes place. Two main mechanisms can be distinguished through which the absorbed radiant energy can take effect (Youssef et al., 2010; Organisciak and Vaughan, 2010).

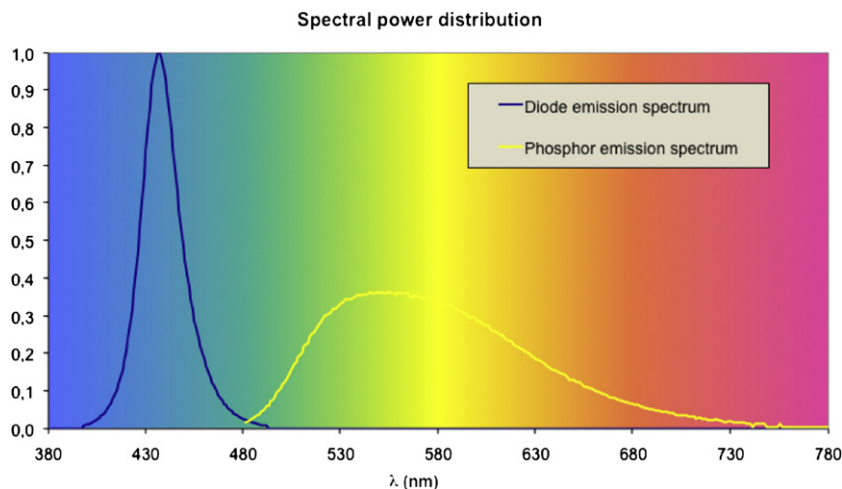


Fig. 1. Spectral representations of white light using LEDs. The mix of blue light emitted by the semi-conductor with yellow secondary emission from the phosphor produce white light.

- Heat: radiant energy is converted into movement of molecules (kinetic energy) such as vibration, rotation and translation. Thus, the temperature is increased. Here, the radiant energy (measured in Joules, J) absorbed per unit time (s) in a certain volume, determines the rise in temperature, i.e., the absorbed radiant power ($J/s = \text{Watt, W}$) per unit volume (m^3) or the (specific) absorption rate (W/m^3) is the determining factor. Photothermal damage occurs when the rate of light energy released by thermal deactivation is faster than thermal diffusion, inducing a raise of the tissue temperature. The duration of thermal exposure is usually between 0.1 and 1.0 s (Crochet et al., 2006). For visible light and infrared radiation reaching the retina, the depth of penetration depends on the incident wavelength, melanin (i.e., melanosomes in RPE cells and in choroid melanocytes) and hemoglobin or oxyhemoglobin (in choroidal vessels) being the primary absorbers with an ability to undergo very efficient non-radiative decay from their electronically excited states to the ground state (Marshall, 1970). At least 10°C in temperature rise induces to denaturation of many proteins in the retina resulting in thermal damage. Heat transfer through the retina is limited. The thermal damage is confined to the pigment epithelium, and damage to the retinal layers or to peripheral to the center of coagulation, arises secondarily from mechanical disturbances. Such mechanism is used for laser photocoagulation. However, retinal photothermal damages may also occur with exposure to high power flashes of light shorter than $\sim 20 \mu\text{s}$ (Delori et al., 2007).

- Photochemistry: radiant energy can cause excitation of atoms or molecules by moving the outermost (valence) electrons to higher orbital energy levels. This energy can subsequently be utilized in (photo-)chemical reactions yielding 'photoproducts'. The radiation needs to be within a certain wavelength range (the 'absorption band') for the excitation (the radiant energy is absorbed in discrete quanta, 'photons', which must match the energy required for the excitation). The (part of the) molecule that absorbs the radiation is dubbed the chromophore. Not every excited molecule will cause a chemical reaction: the energy may be lost through fluorescence (emission of radiation of longer wavelengths) or dissipated as heat. This implies that only a certain fraction of the absorbed radiant energy is oriented into the (photo-)chemical reaction: this is represented by the quantum efficiency (the number of photoproducts formed per photon absorbed; a ratio usually <1). Photochemical damage occurs when light is absorbed by a chromophore and leads to the formation of an electronically excited state of that molecule, which then undergoes either chemical transformation itself and/or interacts with other molecules leading to chemical changes of both interacting molecules or to a transfer of the excitation energy to the other molecules, which may then become chemically reactive. Radicals and reactive oxygen species (ROS) may thus be formed leading to photodynamic effect. Chromophores, which upon photoexcitation undergo intersystem crossing and produce free radicals and singlet oxygen, are known as photosensitizers. The retina

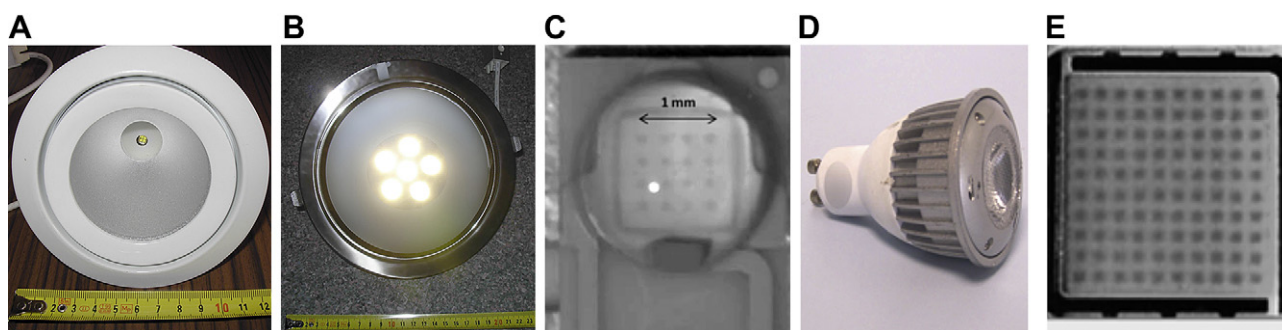


Fig. 2. Photographs of LED tested for the blue-light risk assessment A: 10 W downlight LED luminaire tested for the blue-light risk assessment. This luminaire falls into the risk group 2. B: 15 W indoor LED luminaire tested for the blue-light risk assessment. This luminaire falls into risk group 1. C: Close-up view of a high-brightness single-die white LED D: Directional LED lamp typically used as a replacement for a GU 10 halogen lamp. E: A multichip LED incorporating 100 dies.

contains endogenous photosensitizers, which can be excited by visible/infrared radiation reaching the retina (Table 4) (Glickman, 2002; Wu et al., 2006; Boulton et al., 2001). The outer retina, photoreceptors and retinal pigment epithelium (RPE), immediately adjacent to the choroidal blood supply, are thus highly oxygenated, potentially favoring conditions for photodynamic damage to occur (Yu and Cringle, 2005; Beatty et al., 2000).

The ROS have three major targets: 1) Cellular membranes leading to lipids peroxidation, which induce the formation of malonic dialdehyde, a potent mutagenesis compound; and to membrane disruption. The retina, which contains a large concentration of cell membranes, is particularly sensitive to oxidative stress. 2) Proteins and enzymes, modifying their structure and activity; 3) Nucleic acids, with mutations, oncogenesis and alteration of protein synthesis (Heil et al., 2010; Cadet et al., 2010). Moreover ROS induce premature senescent processes and modify the capacity of cells to react against other stress types.

Of the three types of optical radiation, UV radiation that carries the highest energy (UVA 315–400 nm, UVB 280–315 nm and UVC 100–280 nm) is photochemically most active. It is absorbed by certain common chromophores in organic molecules and aromatic rings; abundantly present in DNA and can therefore cause cell death and mutagenesis.

Three types of systems efficiently protect cells and tissues against physiologic oxidative stresses (Siu et al., 2008): 1) Non enzymatic molecules such as thiols, vitamins (E and C), carotenoids..., 2) Metallic ions scavengers and 3) Specific enzymes such as superoxide dismutase, catalase and glutathion-peroxidase... (Grimm et al., 2000b, c; Siu et al., 2008; Noell, 1980).

A third mechanism of potential light-induced damage is photomechanic (or photoacoustic). It occurs when the light energy is deposited faster than mechanical relaxation can occur. Pulses shorter than 1 ns induce tissue disruption by shear forces or by cavitation. Fluence rates needed to produce photomechanical damage can be obtained from sources such as intense pulsed lasers.

Depending on the wavelength, the absorbed energy and the exposure duration, two classes of photo-damages have been described in the retina (Gorgels and Van Norren, 1998; Harwerth and Sperling, 1971; Ham et al., 1979, 1976, 1978; Wu et al., 2006; Kremers and van Norren, 1989).

- Class I damage has an action spectrum that is identical to the absorption spectrum of the visual pigments and it appears after exposures of several hours to weeks to relatively low

irradiances, below 1 mW/cm², of white light. The initial damage is mainly located in the photoreceptors. Rhodopsin, which is dominant pigment in human retina has an absorption peak in vivo at 507 nm, which is in the green range (Pepe 1999; Grimm et al., 2000a). In monkeys, irreversible S (short wavelength) cone damages are observed upon illumination at 460 nm, while reversible damages of M (medium wavelength) and L (long wavelength) cones follow illumination at 520 and 630–720 nm respectively. Irreversible cone damage can thus be caused by blue-light illumination (Boulton et al., 2001).

- Class II damage has an action spectrum that peaks at short wavelength, in the range of blue light (400–480 nm), and this type of damage occurs under exposure to high irradiances of white light, above 10 mW/cm². The initial damage is generally confined to the retinal pigment epithelium (partly lipofuscin-mediated) but may then extend to the photoreceptors (Grimm et al., 2001; Hafezi et al., 1997; Gorgels and van Norren, 1995).

4. Light and the human eye: how does light reaches the retina

The whole sunlight spectrum is received by the eye. Radiations are either absorbed or transmitted by the different eye tissues before reaching the retina (Sliney, 2002, 2005). Table 4 summarizes the interactions of the different radiations wavelengths with eye tissues and more particularly with the pigments in the eye.

4.1. The cornea

All UVC (100–280 nm) are absorbed by the human cornea, which transmits radiant energy only at 295 nm and above. It however absorbs very efficiently UV radiations between 300 and 320 nm and about 30–40% of UVA radiations between 320 and 360 nm. Over exposure to UVA (315–400 nm) and to UVB (280–315 nm) may cause reversible lesions of the corneal epithelium, whilst exposure to UVC radiations (100–280 nm) can induce deeper lesions in the corneal stroma and Bowman membrane leading to corneal opacity and neovascularization. Upon prolonged repeated UV exposure, climatic droplet keratopathy, pterygium and conjunctival neoplasms as well as ocular melanoma may occur (Vajdic et al., 2002; Singh et al., 2004; Hu et al., 2008).

Infrared radiation (IR) has wavelengths ranging from 780 nm to 1 mm. IRA (from 780 nm to 1.4 μm) radiations are mostly absorbed by the cornea and IRB (from 1.4 to 3 μm) are mostly absorbed by the cornea, the aqueous humor and the vitreous humor (Fig. 3) (Sliney, 2002). Beyond 1.9 μm the cornea becomes the only absorber. Infrared usually only cause irritation but high energy (>30 J/cm²) may also cause deep stromal lesions and even perforations (Oliva and Taylor, 2005; Young, 2006; Gallagher and Lee, 2006). Long-term exposure to IRC may induce corneal lesions, particularly of the epithelium. Protection from sunlight is therefore highly recommended (Sliney, 2001, 2006).

4.2. The iris

The iris pigments contain melanin, which absorb all visible light wavelength. It also responds to light by constriction reducing therefore the light entry into the eye. When exposed to UV radiations, the pupil diameter is around 1 mm and it reaches 7 mm when exposed to infrared radiations. The mechanisms of pupillary reflex will be detailed in the paragraph dealing with retinal ganglion cells expressing melanospin. This mechanism is extremely important and efficient for protecting the retina against light damage.

Table 4

Tissue/molecule	Wavelength (nm)	Mechanism of interaction
Cornea	<300 and >800	Absorption/heat dissipation
Iris	Melanin : 300–700	Absorption/heat dissipation
Lens	Peak at 365 at 8 years Peak at 450 nm at 65 years	Absorption/heat dissipation
Retina	400–700 Rhodopsin : Peak at 507 SWS : Peak at 450 MWS: Peak at 530 LWS: Peak at 580	Photochemical damage type I: max at 507 nm Type II: max shorter wavelengths
RPE	Melanin: 400–700 nm	Absorption/heat dissipation Potential chemical damages
Lipofuscin	355–450 A2E: peak at 430–440	Photodynamic effect
Xanthophyll pigments	Lutein: Peak at 446 Xanthine: Peak at 455 Zeaxanthine: Peak at 480	Absorption/heat dissipation

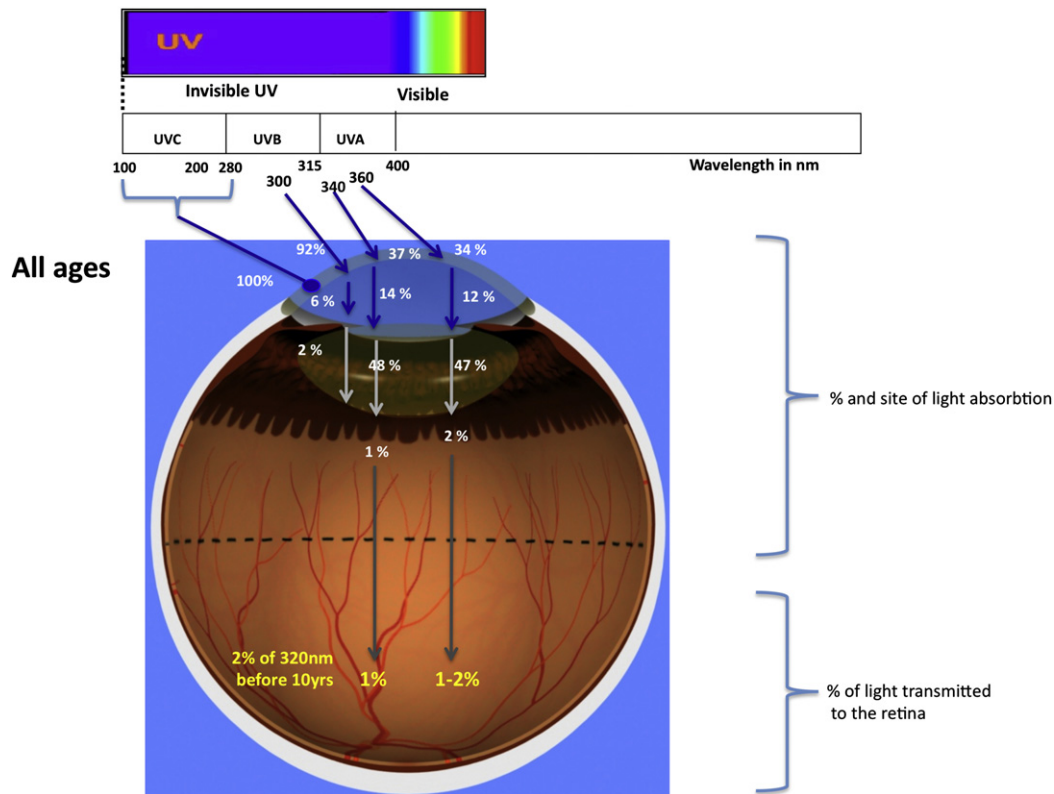


Fig. 3. Interaction of UV radiation and infrared radiation with the human eye (all ages).

4.3. The lens

The lens in the adult human eye absorbs strongly longer wavelength in the UVB (295–315 nm), and the full range of UVA (315–390 nm) and part of the near infrared wavelengths.

UV light induces cataract (Oliva and Taylor, 2005; Robman and Taylor, 2005; Asbell et al., 2005) and blue light may induce photodynamic damages in aging lenses. However, compounds that accumulate in the aging lens also act as antioxidant (Asbell et al., 2005; Robman and Taylor, 2005). Infrared radiations are also responsible for cataract (Roh and Weiter, 1994).

The absorption spectrum of the lens changes with age. In young children, more than 65% of blue light is transmitted to the retina. At around 25 years, only 20% of the light between 400 and 460 nm and 50% of wavelengths between 400 and 500 nm are transmitted (Fig. 4). With increasing age, the yellow filters of the lens increase and absorb most of the blue light. The peak of absorption of the lens is around 365 nm in the young adults and around 400 nm at 60 year-old (Figs. 4 and 5). The transmission of visible light is significantly reduced in older lenses, especially in the blue region of the spectrum (Fig. 6) (Gaillard et al., 2000; Bron et al., 2000; van de Kraats and van Norren, 2007; Kessel et al., 2010). In case of cataract surgery, yellow intraocular lenses are proposed to reduce retinal exposure to blue light (Dillon et al., 2004). However, to date no clinical comparative study has demonstrated the efficacy of these intraocular lenses to protect the retina from any retinal pathology.

4.4. The retina

Because the lens absorbs near UV and far infrared radiation (<400 and >800 nm), the cornea and the lens absorb infrared radiations above 980 nm, and the vitreous absorbs light above

1400 nm, up to 10 μm , the non-ionizing radiation reaching the retina is restricted to the so-called 'visible component' of the electromagnetic spectrum (390–780 nm), and some of the near infrared (Fig. 5) (Boettner and Wolter, 1962; Sliney, 2002, 2005). Particularly, the fraction of UV that reaches the retina is lower than 1–2%. Only in the young child (before age 8–10 years), a higher fraction of UV light at 320 nm reaches the retina (but can reach up to 8%) (Fig. 4). This window of transmission of UV light to the retina may explain the initial accelerated formation of lipofuscin in the young human retina by a photochemical process (Gaillard et al., 2011). This transmission band is gradually reduced when metabolites of tryptophan absorbing UV light accumulate in the lens. By the age of 20, only 0.1%, and by the age of 60 virtually no UV light reaches the retina except for aphakic individuals.

The peak of retinal absorption is between 400 and 600 nm whereas retinal transmission extends from 400 to 1200 nm. Rod photoreceptors, are present across the retina except for the very central region (the foveola), and provide scotopic vision. Their sensitivity range spans from 10 to 6 to 1 cd/m^2 with comparatively low resolution and high sensitivity, but lacking color information. In vitro, the peak of rods absorption is at 498 nm but, in vivo, taking into account absorption of the lens and macular pigment, their peak moves to 507–530 nm. Cone photoreceptors are responsible for day vision. Their sensitivity varies in a wide luminance ranging from 10^{-3} to $10^8 \text{ cd}/\text{m}^2$. The peak absorption of the different types of cones is represented in Table 4. In vitro, the maximal absorbance is around 420 nm for blue cones, 530 nm for green cones and 560 nm for red cones but in vivo, taking into account lens absorption and macular pigment, these peaks move to 450, 540 and 570 nm (Dartnall et al., 1983). Rod visual pigment is rhodopsin, which consists of opsin and the vitamin A aldehyde, 11-cis-retinal. Cone photopigments also consist of retinal associated with different opsins. Phototransduction is triggered by the photic conversion

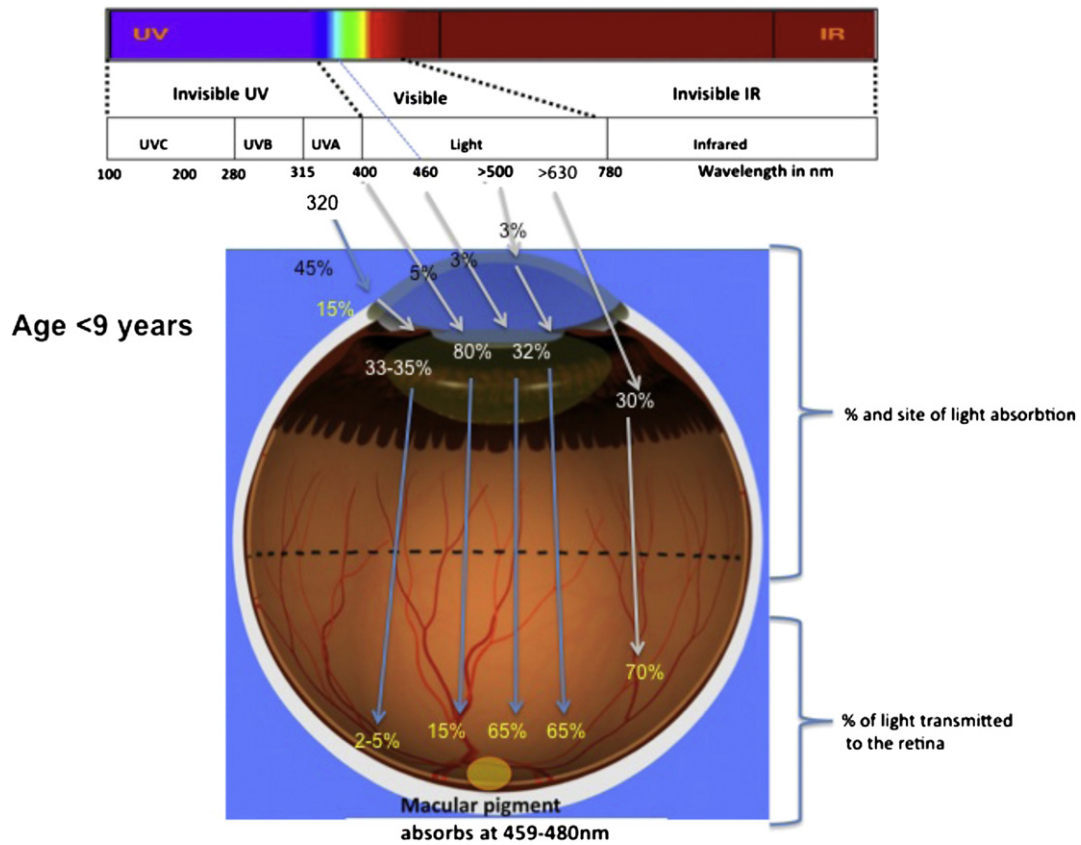


Fig. 4. Interaction of UVA radiation and visible light with a <9 years-old Human eye.

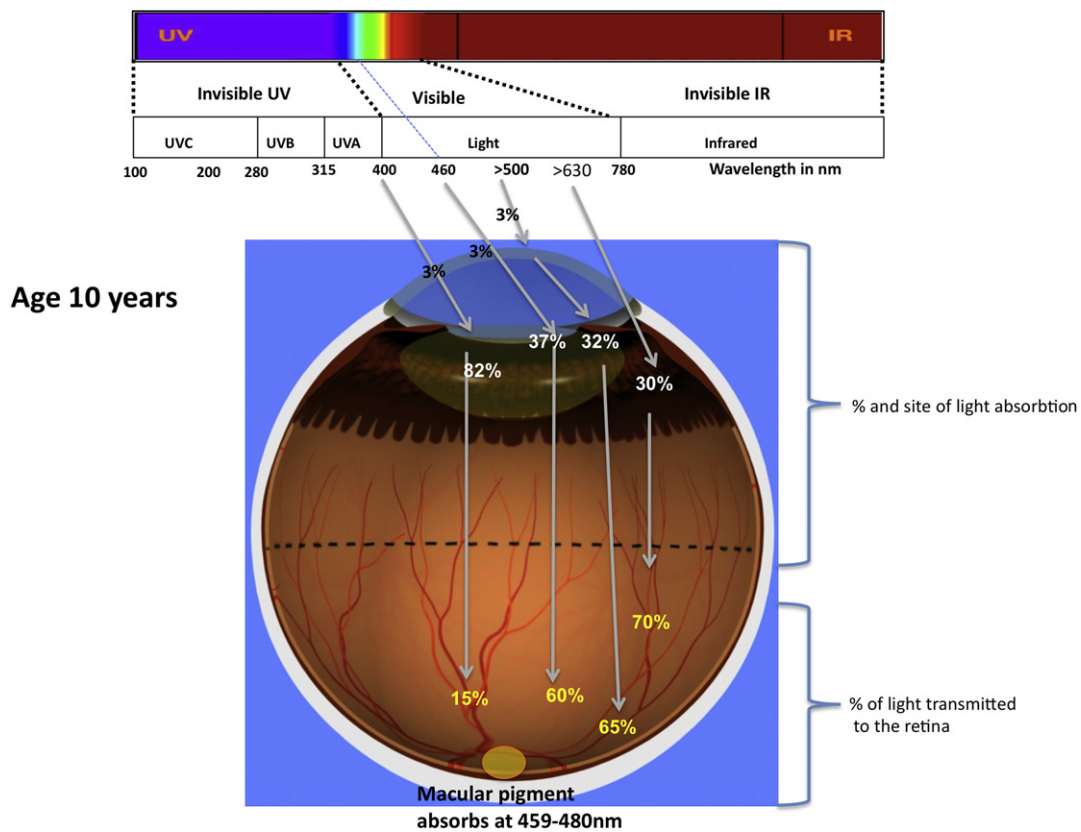


Fig. 5. Interaction of visible light with a >10 years-old Human eye.

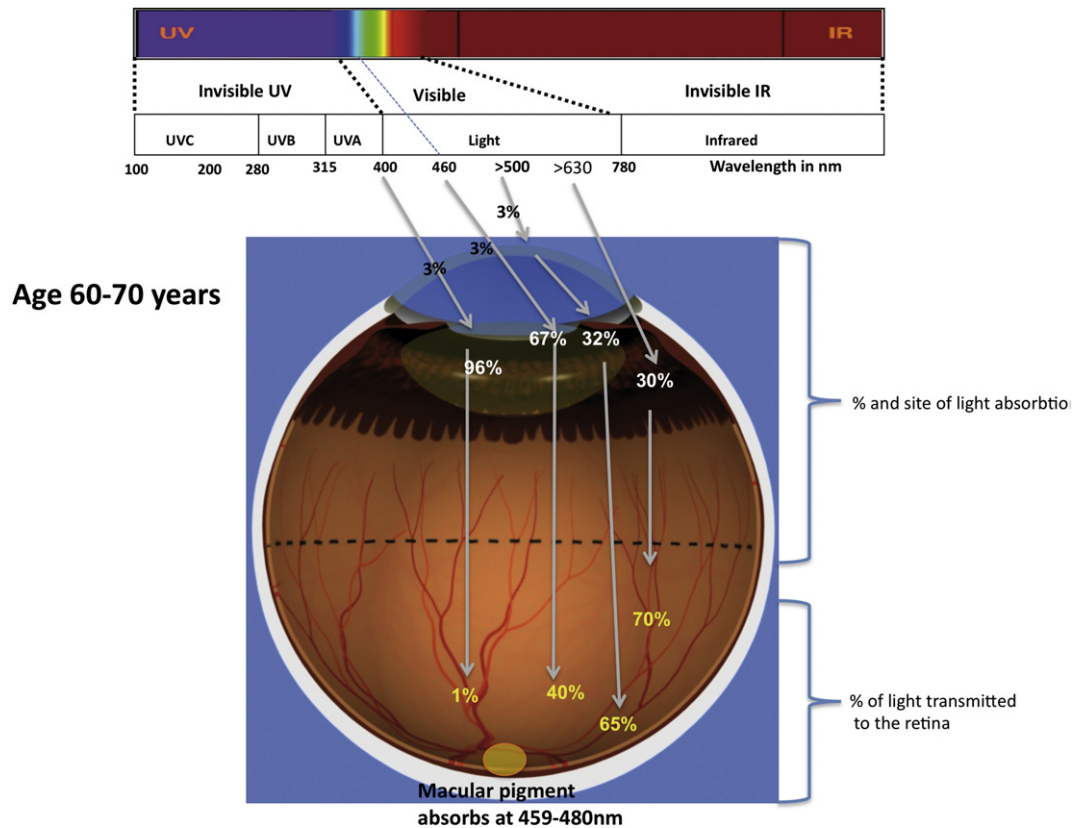


Fig. 6. Interaction of visible light with a 60–70 years-old Human eye.

of 11-cis-retinal to all-trans-retinal in rhodopsin. Activation of rhodopsin starts a cascade of events that leads to the closure of sodium/calcium channels, hyperpolarization of the photoreceptor membrane and a decrease in the intracellular calcium concentration (Pepe, 1999). The phototransduction system is modulated by several proteins (such as S-modulin [recoverin], S-antigen [arrestin], guanylate cyclase-activating protein, phosducin, and calmodulin) in a calcium-dependent manner, inducing light and dark adaptation. Rhodopsin is regenerated in the RPE through the visual cycle of retinoid metabolism (Bok, 1990). RPE cells are actively involved in the visual cycle as well as in the photoreceptor maintenance because they phagocytose every day the tips of the photoreceptor outer segments with intracellular disks containing the visual pigment for their constant renewal. Toxic by-products from the visual cycles accumulate in RPE cells such as lipofuscin that is highly light-sensitive (see below). Photochemical damage has been shown to occur through light interaction with the different pigments present in the outer retina (photoreceptors and RPE cells) (Table 4) opsins and with retinoids (Boulton et al., 2001).

4.4.1. Macular pigments

In the macula, yellow macular pigments located in the inner retinal layers are particularly concentrated in the fovea. The lutein and zeaxanthin efficiently absorb blue light between 400 and 500 nm (Landrum and Bone, 2001; Wooten and Hammond, 2002; Stahl, 2005; Whitehead et al., 2006). Lutein protects against oxidative damages and is a scavenger for singlet oxygen (Krinsky et al., 2003; Li et al., 2010; Davies and Morland, 2004.). They are concentrated in the macula of children, decrease with aging and can only be increased throughout life by nutrient intake. Nutrient supplements (containing macular pigments) have been shown to increase macular pigment density in older patients

already after a few months of intake and are therefore prone to reduce the progression risk of age-related macular degeneration (AMD) (Carpentier et al., 2009; Loane et al., 2008) through a reduction of oxidative light-damages.

4.4.2. Lipofuscin

Because retinal pigment epithelial cells are actively involved in the phagocytosis of oxidized photoreceptor outer segments and regeneration of visual pigments (Bok, 1990), debris accumulate with age. At their apical side, RPE cells contain intracellular melanin granules (eumelanin and pheomelanin) as well as many microperoxisomes and anti-oxidative enzymes, which play an important role in protective and anti-oxidative mechanisms. Particularly, melanin absorbs the excess of photons from 300 to 700 nm. In the RPE, lipofuscin forms a mixture of chromophores that accumulates with age and in several retinal disorders. Lipofuscin is a potent photosensitizer, that upon blue-light stimulation, induces photodynamic effects and subsequent photochemical processes (Boulton et al., 2004; Wang et al., 2006) eventually causing permanent damage to RPE and photoreceptors (Wassel et al., 1999). The major fluorescent component of lipofuscin, A2-E is formed in rod outer segments by a sequence of reactions that is initiated by the condensation of two molecules of all-trans-retinaldehyde with phosphatidylethanolamine (Sakai et al., 1996; Shaban and Richter, 2002). Its light absorption exhibits a peak between 430 and 440 nm and it results in ROS production under proper light stimulation (Reszka et al., 1995; Parish et al., 1998).

Interestingly, the age-induced changes in lipofuscin composition and structure increase its potential of photodynamic effect, resulting in higher ROS production upon illumination (Wu et al., 2010). Lipofuscin in aging eyes could potentially induce more oxidative damages upon blue-light illumination. Several other

native retinal chromophores including melanin, protoporphyrin, all-trans-retinal (Wielgus et al., 2010) and other lipofuscin components (Reszka et al., 1995; Wassel et al., 1999) have been suggested to act as photosensitizers (Yang et al., 2003; Godley et al., 2005). Contrarily to the skin, where melanin acts as a strong protective absorber, the role of melanin in the human retina remains imperfectly understood (Hu et al., 2008). Its combination with lipofuscin into melanolipofuscin granules is rather highly phototoxic.

The potential phototoxic retinal damage is thus expected to occur with wavelengths in the blue-light spectrum between 400 and 460 nm (blue-light hazard) (Ham, 1983; van Norren and Schellekens, 1990; Algere et al., 2006).

5. Retinal control of circadian cycle and pupillary reflex

Besides cones and rods, ganglion melanopsin cells, photopigments have been recently discovered in a subset of ganglion cells (ipRGCs, have been recently described containing melanopsin. They are 4 times more concentrated around the fovea as compared the other parts of the retina (Hattar et al., 2002; Hankins et al., 2008; Semo et al., 2010). These ganglion cells are a specific type of light-sensitive cells that do not only receive visual information issued from photoreceptors, but also direct light stimulation (Semo et al., 2010; Viénot et al., 2010). It was shown that the photoreceptor input can partly control circadian cycles and pupillary reflex, but that these functions can be driven normally solely by the melanopsin-sensitivity in the absence of photoreceptor input. Even if the melanopsin-ganglion cells are not required for circadian regulation, their absence reduces the circadian response by 40% (Panda et al., 2002; Panda, 2007; Ruby et al., 2002; Tsai et al., 2009). In humans, the peak of melanopsin stimulation and pupillary reflex in vivo is 480 nm (Brainard et al., 2008; Mure et al., 2009) as deduced from the light response of isolated ganglion cells. However, ipRGCs have an RPE-independent photo regeneration system, with a biphasic switch from melanopsin into meta melanopsin upon 480 nm activation and then return to its basal state at another longer wavelength (Mure et al., 2009). White and blue LED spectra have a strong imbalance between 460 nm and 480 nm; with a peak at 460 nm and a deep valley at 480 nm. The mechanisms by which melanopsin-retinal ganglion cells regulate circadian rhythms in humans are not yet fully understood. It was recently shown that they responded linearly to contrast changes of light stimuli, whereas they showed complicated responses to frequency changes with regard to the latency of response time. Melanopsin-ganglion cells may not have a simple response to the various frequencies of solar light (Fukuda et al., *in press*). To date, the potential consequences of the LED spectrum on sleep regulation and on pupillary reflex remain to be studied. Indeed, pupillary reflex shows two components, a rod-cone fast response, followed by the steady response from melanopsin-ganglion cells that are responsible for maintaining pupil size. If photosensitive ganglion cells are damaged or under-stimulated larger pupils could result in an increased retinal exposure to light. The pupil response to white LED exposure remains therefore to be evaluated in vivo.

6. Light and retinal pathology

As detailed above, the interaction of blue light with molecules constituting the retina or accumulating in the retina with aging or in pathological conditions is susceptible to induce damages to RPE cells, photoreceptor cells and to ganglion cells. The blue-light hazard has been identified more than 40 years ago. Noell et al. (1966) were among the first to recognize the potential photochemical damages induced in photoreceptor/RPE by blue light.

Many other studies have shown that the shortest wavelengths in the visible spectrum were the most dangerous ones for the retina and the mechanisms of light-induced damages have been reviewed previously by others (Wenzel et al., 2005; Wu et al., 2006). We will therefore not detail the mechanisms of light-induced retinal toxicity and damages.

Our aim is mostly to assess the ocular risks of new LED as compared to natural sunlight and to other artificial light sources.

6.1. Sunlight and retinal pathology

6.1.1. Acute exposure: solar retinitis

The visual impairment caused by a few minutes of direct looking into the sun or solar eclipse has been known for many years (Young, 1988); Eyes from patients who volunteered to stare at the sun prior to enucleation had various degrees of injury in the RPE cells 38–48 h later with only mild changes of the outer segments and inner segments of the photoreceptors. This explains the good vision shortly after exposure. The damage to the RPE was very similar to photochemical damages observed in the RPE in the monkey 48 h after exposure to blue (Ham et al., 1978); Whilst RPE and the blood retinal barrier restored rapidly, permanent degeneration of the photoreceptors was observed some time after the exposure (Tso and La Piana, 1975; Gladstone and Tasman, 1978). It is however important to remind that the inducing various degrees of visual disturbances and central scotoma. It is now well recognized that sunlight-induced retinal lesions result from chemical damages similar to those observed after blue-light exposure and not from thermal injury. Except in case of mental disorders, nobody stares at the sun and natural evicton reflex protects from sunlight burns. However, in some specific situations, increased retinal exposure may occur. At noon the snow illuminated by the sun may reach a luminance of 100 000 cd/m² and contrarily to what could be thought, it is not direct exposure but rather ground surface reflection that is the most important environmental exposure factor (Sloney, 2005). The overhead protection of the cornea by the upper lid protecting against direct exposure, decreased luminance conditions may increase peripheral exposure or exposure from ground reflections whilst increasing the lid opening. For example, prolonged exposure to hazy sky on fresh snow may induce over exposure and lesions. Pilots and soldiers exposed for several months in the desert have shown retinal lesions similar to solar retinitis. Whether cumulative chronic low intensity exposure to the sunlight may induce similar lesions remains to be demonstrated, even if such cases have been reported.

6.1.2. Chronic exposure: a link with age-related macular degeneration?

No consensus regarding any causal links between sunlight exposure and Age-Related Macular Degeneration (AMD) has emerged from epidemiologic studies. Oxidative stresses and sub clinical local inflammation have been demonstrated to be associated with aging processes in the retina (Xu et al., 2009) and smoking through benzo(a)pyrene toxicity was clearly shown to contribute to the development of AMD (Khandhadia and Lotery, 2010; Cano et al., 2010; Ding et al., 2009). No such aggravating effect could be demonstrated regarding sunlight exposure. However, in the Beaver Dam Eye study correlation between sunlight and 5-year incidence of early age-related macular changes, showed that leisure time spent outdoors while persons were teenagers (aged 13–19 years) and in their 30s (aged 30–39 years) was significantly associated with the risk of early age-related macular changes. People with red or blond hair were slightly more likely to develop early age-related macular changes than people with darker hair (Cruickshanks et al., 2001). The ten years incidence

study confirmed these findings. Indeed, while controlling for age and sex, exposure to the summer sun for more than 5 h a day during teenage and the 30 s led to a higher risk of developing increased retinal pigment abnormalities and early age-related macular changes as compared to those exposure for less than 2 h during the same period (Tomany et al., 2004). In another study, the effect of sun exposure was evaluated on 838 watermen. In this specific population, the relative exposure to blue light and UV was possible and showed as association between exposure and AMD signs. Compared with age-matched controls, patients with advanced age-related macular degeneration (geographic atrophy or disciform scarring) had significantly higher exposure to blue or visible light over the preceding 20 years but were not different in respect to exposure to UV-A or UV-B, suggesting that blue-light exposure could be related to the development of AMD, particularly in the more advanced ages (Taylor et al., 1992). These associations were not found in other studies such as in the French POLA study (Delcourt et al., 2001), but these studies were not designed to show such associations. Since animal retinal pathology resembling features observed in AMD can be induced experimentally by blue-light exposure, protection against blue light should be recommend at all ages. Considering new genetic factors for AMD, association with sunlight exposure and genetic markers should be interesting to study.

6.1.3. Blue light and glaucoma or other optic neuropathy

Osborne N and al showed that mitochondrial enzymes such as cytochrome and flavin oxidases absorb light and generate oxygen reactive species. Because ganglion cells are unprotected from visible light, they are directly exposed to such photo oxydative stimuli. In vitro, ganglion cells underwent a caspase-independent form of apoptotic death. Under light (400–700 nm) exposure and in vivo in the rat, only blue-light exposure induced signs of ganglion cell suffering (Osborne et al., 2008, 2010). Moreover, because melanopsin-ganglion cells participate in light-induced pupil response, patient with ganglion cell dysfunction owing to anterior ischemic optic neuropathy demonstrated global loss of pupil responses to red and blue light in the affected eye, suggesting that in those patients retinal illumination could be enhanced, increasing the blue-light hazard (Kardon et al., 2009).

Increasing evidences suggest that circadian disruption occurs in glaucoma and that it may enhance the neuropathy (Drouyer et al., 2008; Agorastos and Huber, 2011). However, to date no epidemiologic study has evaluated the correlation between sunlight or blue-light exposure and the progression or occurrence of glaucoma or other optic neuropathy.

7. Artificial light and ocular pathology

7.1. Ophthalmologic instruments

The risks of retinal damages in the operating room have been clearly recognized since about 20 years even if the first description was made in 1978 on animals. Operating microscopes can induce paramacular lesions, very similar to those induced experimentally by blue-light exposure (Azzolini et al. 1994–1995). Moreover, filtration of blue light significantly reduced, even if not suppressed the risks. Duration of illumination of the retina through dilated pupils increases the risk of retinal damages. In 1983, on a series of 133 patients, it was shown that at 6 months post surgery, visual acuity was significantly higher in patients operated with a fiber-optic light attenuated in the blue range as compared to a high-intensity tungsten filament microscope (Berler and Peyser, 1983). Thereafter, several reports identified blue-light output as the major risk for the retina as compared to red and UV ranges wavelengths

(Cowan, 1992). Limitation of surgical time, application of a pupil mask during prolonged surgery and limitation of luminance, have reduced such accidents.

7.2. Welder exposure

Arc welding exposes to UV as well as to blue light. Radiation in the UV range is absorbed mostly by the cornea and lens if welder are unprotected and gives rise to “arc-eye”, well known as an occupational hazard for welders. Even if very painful, the kerato-conjunctivitis is not expected to induce any permanent ocular damages. On the other hand, visible light, particularly in the blue range may expose to retinal photochemical damages (Mayer and Salsi, 1979; Naidoff and Sliney, 1974). Okuno et al. have evaluated blue-light hazard for various light sources and found that arc welding was among the highest effective radiances with corresponding permissible exposure times of only 0.6–40 s, suggesting that they may be very hazardous to the retina (Okuno et al., 2002). More recently, potential blue-light hazards from CO(2) arc welding of mild steel was evaluated. The effective blue-light radiance ranged from 22.9 to 213.1 W/(cm² sr). The corresponding maximum acceptable exposure duration was only 0.47–4.36 s, meaning that the total daily exposure to the welding arc without eye protection should not exceed this duration. Blue light retinal toxicity may therefore occur if welding is performed without appropriate protection (Okuno et al., 2010). Several case reports have been published stressing that welding should be performed in good background lighting and with permanent adequate protection since pupillary constriction in response to the striking arc should be too slow to block the initial surge of radiation.

8. Sunlight and artificial light: how to compare potential dangers?

8.1. Comparison of natural and artificial illumination in terms of photometric quantities

Human observers are exposed to a limited number of natural lights: the sun, the moon and flames. The sun, which provides natural daylight is by far the most intense. Its angular size is 0.5 degree of arc. Its luminance is 1.5×10^9 cd/m². It is at its maximum when the sun is directly overhead, and decreases with the height of the sun. Not only, the sun is a glaring source but it should never been viewed directly, except at sunset. Artificial light sources with luminances higher than 10 000 cd/m² are also glaring when they are viewed with the naked eye. Tables 5 and 6 give values of luminance of a few common daily used light sources. For this reason, lamps should always been integrated in a luminaire that shields the direct light. Previous work by Okuno et al. (2002) had revealed that the sun, arc welding, plasma cutting and the arc of discharge lamps were found to have extremely high effective radiances with corresponding permissible exposure times of only

Table 5
Values of luminance of a few common artificial light sources.

Artificial light sources	Luminance (cd/m ²)
Tungsten filament of a light bulb	10 000 000
Tungsten filament of a theater bulb	20 000 000
Carbon electric arc	160 000 000
Xenon arc	400 000 000
High-pressure mercury lamp	500 000 000
Sun through atmosphere	1 600 000 000
Flashes, for a few μ s	10 000 000 000

Table 6

Values of luminance of a few common sources.

Extended light sources	Luminance (cd/m ²)
White wall (at noon in March)	10 000
Fluorescent tube	10 000
Blue sky	5000
TV display	300
Computer display	150

0.6–40 s, suggesting that viewing these light sources is very hazardous to the retina (Okuno et al., 2002).

Extended artificial light sources, such as fluorescent tubes, have luminances around 10 000 cd/m² or 20 000 cd/m². The luminance of the clear and blue sky, which is an extended light source, does not exceed 5000 cd/m². It is only with a hazy atmosphere that the luminance of the sky increases around the direction of the sun. Outdoor, extended surfaces may be glaring. For instance, the luminance of a white wall facing South, of the sand or of the snow directly illuminated by the sun can reach 50 000 cd/m². In such cases, wearing protective ophthalmic glasses is recommended. Grade 3 ophthalmic glasses, which are the most common commercial items, transmit between 8% and 17% of the incident light and reduce the luminance of white surfaces to less than 10 000 cd/m².

In a LED, the chip that emits light is so small that, although the flux emitted may be moderate, the luminance may be extremely high. For example, for a LED that emits only a luminous flux of 212 lm, ANSES has measured an average luminance of 6.2×10^7 cd/m², which is much higher than regular domestic light sources. Moreover, in the near future, with the expected increase of luminous efficacy of LEDs, the luminance could become even higher. The fact that LED can have very high luminance without luminaire shielding the direct view of light because in some LEDs, luminaire and lamps and confounded, raises potential hazards concerns.

8.2. Comparison of the spectral power distribution of natural and artificial lights

Daylight is largely variable, depending upon the time of the day, the season, the latitude and the weather. Nevertheless, its variation follows regular laws in terms of spectrum and intensity. It has been shown that the relative spectral power distribution of daylight can be described using three principal spectral components, i.e., an average spectral component, a spectral component that reflects the relative content of short wavelengths versus long wavelengths, and a spectral component that reflects small spectral variations due to the state of the atmosphere. Consequently, direct light from the sun is enriched in long wavelength radiations, especially at sunset, while the blue sky is enriched in short wavelength radiations. As explained in Section 2, the color of natural or artificial lights is specified by the correlated color temperature, a scale that closely relates the color of the light emitted by a real source to the temperature of the blackbody that radiates light of the same color. Fig. 7 shows spectra of different artificial light sources that can be compared to sunlight spectra, plotted with the blue-light hazard function in Fig. 8. Spectra of different white LEDs are provided in the experimental sections for comparison. In the natural environment, due to daytime spectral variation of sunlight, human being are not supposed to be exposed to intense blue radiations from wakeup until late at night. Since cumulative exposure could potentially induce specific lesions, artificial light sources should not have high blue light contain.

8.3. State of adaptation of the retina, luminance threshold and glare

The eye continuously adapts to light, which allows humans to see along 12 decades of illuminance, from almost total darkness to highly luminous environments. Nevertheless, at a given time, vision is possible and comfortable only within a two or three decades range. Glare can lead to discomfort without impair visibility but it drives the observer to look away from the glaring source and it increases if the light source is facing the observer. Disability glare is due to the light scattering within the ocular media, which creates a veil that lowers any contrast and renders the task impossible to view. High luminance light sources generate a veiling glare the luminance of which decreases as the inverse of the angle between the direction of the point source and the direction of the gaze.

During dark adaptation, the absolute threshold reduces slowly with time. Several mechanisms are operating during adaptation. The pupil almost instantaneously contracts or expands. The rods and cones sensitivity changes slowly, increasing for instance neuronal coupling under dark adaptation reducing thereby visual acuity. At night, when the eye has adapted to dark environment, artificial light sources in the visual field such as car headlamps or isolated light bulbs may generate a veil that makes invisible low and moderate contrasts.

Visual sensitivity and sensitivity to adaptation depends upon the wavelength and upon the eccentricity of the target or of the light source. Visual sensitivity is maximum about 555 nm during daytime, and shifts to 507 nm in the dark and in the periphery of the visual field. Accordingly, in the periphery of the visual field a bluish light would become relatively more visible than a yellowish light at night but the risk of glare increases in parallel. As a first approximation, it is admitted that the spectral sensitivity to glare at night is maximum around 507 nm, the most efficient radiations for rods, but the mechanisms for glare are not fully understood. The high rod–rod coupling and the fusion of rod and cone information under mesopic conditions at the level of retinal ganglion cells could explain this blue light glaring effect. Anyhow, lights with a relative high content of blue, such as LEDs are liable to generate glare.

In the natural environment, the luminance of the sky is rather stable, about 5000 cd/m², white surfaces reach and their maximal luminance values in the middle of the day and usually in the summer, when eyes should be protected by sunglasses. The sun is never viewed directly except when it is at sunrise or at sunset when its luminance is about the same as the sky and its color temperature low or moderate. It is undoubtedly that when the luminance and the color temperature of the light are high blue-light hazard increases.

9. LED blue-light hazard risk assessment

In order to carry out a quantitative analysis of the blue-light risk, the ANSES working group selected a sample of products commercially available in 2010: LEDs, arrays of LEDs and LED-based luminaires.

- 1) Single-die high-brightness LEDs were arbitrarily selected: Six blue LED with a maximum emission wavelength between 435 nm and 460 nm, eleven cold-white LEDs with correlated color temperatures (CCT) between 5100 K and 8400 K, seven neutral-white LEDs with CCTs between 3800 K and 4000 K and ten warm-white LEDs with CCTs between 2600 K and 3400 K.
- 2) Two 10×10 arrays of cold white and warm-white LEDs of the abovementioned type.
- 3) Two multichip LEDs having 100 dies (10×10) having a flux of 7000 lm, in cold white and warm white.

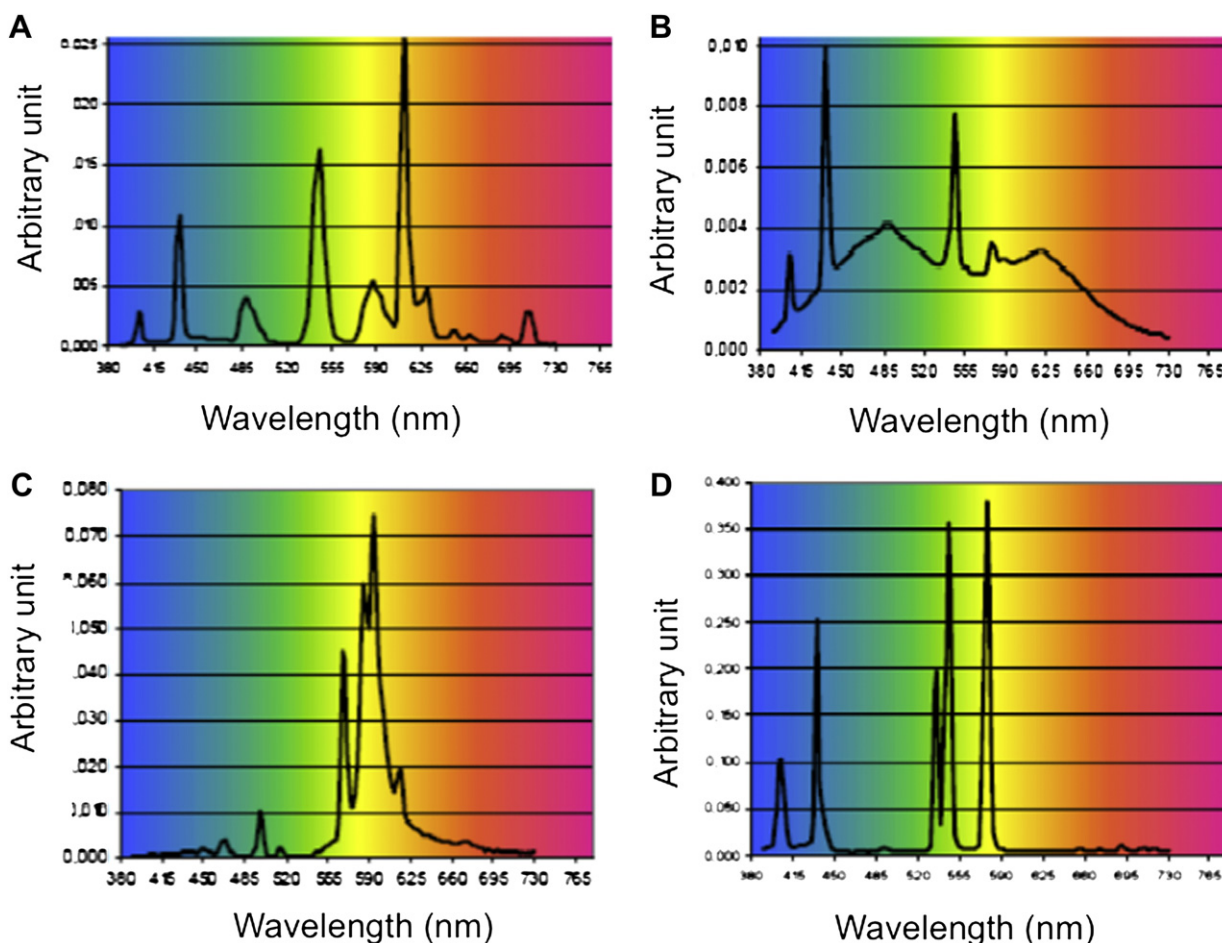


Fig. 7. Spectral power distributions of four different type lamps. A: Warm-white fluorescent tube (CCT = 3000 K) B: Cold-white fluorescent tube (CCT = 6500 K) C: High-pressure sodium (HPS) lamp used in outdoor public lighting D: Metal-halide lamp used for various outdoor lighting applications.

- 4) One cold-white LED associated with a 1 cm diameter collimator
- 5) One 3 W consumer lamp using one LED and having a GU10 socket base
- 6) One 10 W LED downlight luminaire, a 15 W LED downlight luminaire, and a small flash light using one LED.

These products are commonly used in lighting, signage and display applications.

9.1. Methodology

The blue-light risk assessment was carried out in compliance with the requirements of the EN 62471 standard. This standard, which concerns the photobiological safety of lamps and devices using lamps, recommends exposure limits for radiation from these light sources. It provides a system of classification based on radiance and irradiance. The standard considers all of the photobiological hazards that may affect the eye and the skin (thermal and photochemical hazards) from ultraviolet to infrared wavelengths and defines four risk groups according to the value of the maximum permissible exposure time.

For the blue-light risk, the classification is the following (Table 7):

Risk Group 0 (no risk) when the maximum exposure time is greater than 10 000 s.

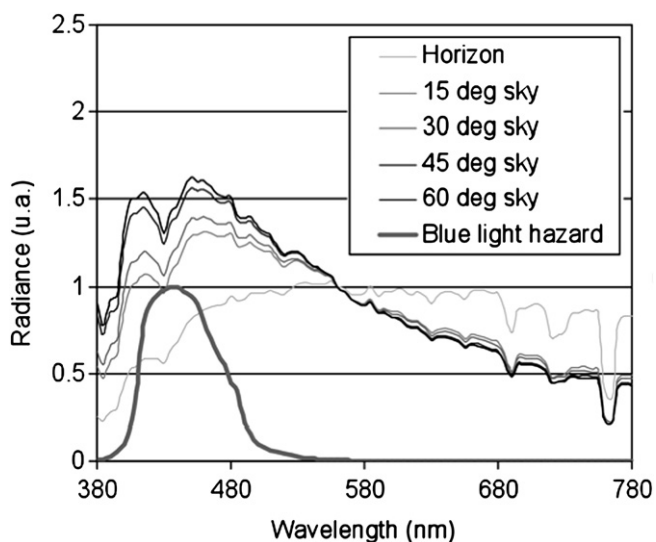


Fig. 8. Relative spectral radiance of sunlight, plotted with the blue-light hazard function. Measurements were obtained at various zenithal angles in terms of spectral radiance [in W/(m² sr)] and normalized at 560 nm.

Table 7

Risk group and blue-light risk exposure limit values (ELVs) of EN 62471, which defines a classification scheme for lamps and lamp systems, based on the amount of hazard present in the light emitted from the product. There are essentially four categories known as risk groups. As the risk group number increases, so too does the hazard present.

Maximal admissible exposure time (t)	Risk Groups
$t \geq 10\,000$ s	Risk Group 0
$100 \text{ s} \leq t < 10\,000$ s	Risk Group 1 (low risk)
$0.25 \text{ s} \leq t < 100$ s	Risk Group 2 (moderate risk)
$t < 0.25$ s	Risk Group 3 (high risk)

Risk Group 1 (low risk) when the maximum exposure time is between 100 s and 10 000 s.

Risk Group 2 (moderate risk) when the maximum exposure time is between 0.25 s and 100 s.

Risk Group 3 (high risk) when the maximum exposure time is less than 0.25 s.

It is important to note that to define the exposure limits, experiments were carried out on rabbits and some monkeys, exposed acutely to light (with different wavelength). Fundus examination was performed and the toxicity limit was reached when a white lesion was observed on the retina. Then, when this limit was determined, a 10-fold safety factor was added. The blue-light hazard limit is to protect against photo-maculopathy and is not based upon chronic light exposure. Knowing that photochemical damages can occur without macroscopically observed lesion, these standards should probably be revised using more sophisticated and precise methods to analysis retinal morphology and functions.

LEDs emitting visible light do not directly emit UV and IR radiation. Consequently, there is no risk associated with these radiations. In addition, the relatively low levels of luminous flux emitted by current state-of-the-art LEDs prevent them from presenting any

kind of thermal hazards. The blue-light risk is thereby the only one to consider when dealing with LEDs and LED systems.

The experimental procedure and the limit values of EN 62471 are consistent with the guidelines of ICNIRP (International commission on non-ionizing radiation). The blue-light risk assessment is based on evaluating an effective radiance using the blue-light phototoxicity function $B(l)$ which peaks at around 437 nm (see the black curve of Fig. 10). The $B(l)$ -weighted radiance should be determined and averaged in the effective field of view (FOV). The FOV is precisely defined by the standard and the ICNIRP guidelines. It increases with the exposure time in order to account for the spreading of the image of the light source on the retina as the eye moves. The minimum FOV is of 1.7 mrad for an exposure time of 0.25 s (limit between risk groups 2 and 3), 11 mrad for an exposure time of 100 s (limit between risk groups 1 and 2), 110 mrad for an exposure time of 10 000 s (limit between risk groups 0 and 1). The characterizations of the LED components (individual LEDs, arrays, multichip LEDs) were done using an imaging luminance-meter mapping the luminances (cd/m^2) of all the light-emitting areas of the device under test. Fig. 9 shows a luminance map of a cold-white LED measured with an input voltage of 3 V and a current intensity of 350 mA. In this example, the luminous flux emitted by the LED was 67 lm. Measured in the axial direction, this LED had a luminance of about $1.1107 \text{ cd}/\text{m}^2$, averaged in a $1.4 \times 1.4 \text{ mm}^2$ square effective source.

Besides, the spectral power distribution of the LED components was measured. The results given by the blue and white high-brightness LEDs selected by ANSES are shown in Fig. 10. The spectral power distribution was used to convert the luminance data in radiance data [$\text{W}/(\text{m}^2 \text{ sr})$] using the CIE standard photopic visibility function. The $B(l)$ -weighted radiance LB was determined from the average radiance L_e in the FOV using the following relationship (Sloney, 1994):

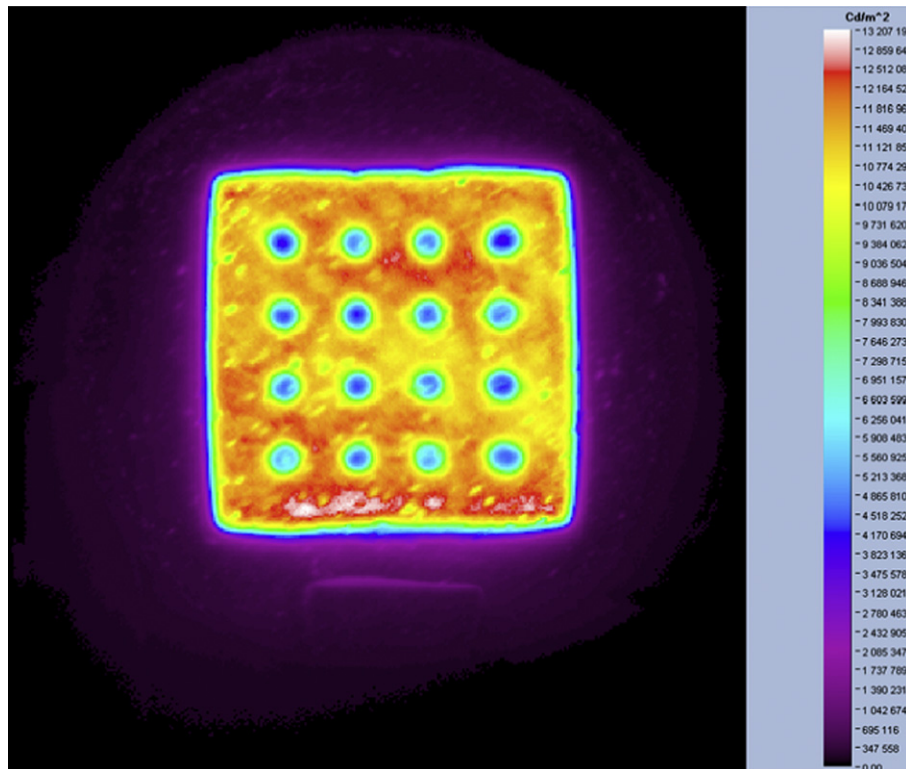


Fig. 9. Measured Luminance map of a cold-white LED operated at 350 mA and 3 V. The maximum luminance is about $1.3107 \text{ cd}/\text{m}^2$. This LED corresponds to the photograph of Fig. 2C.

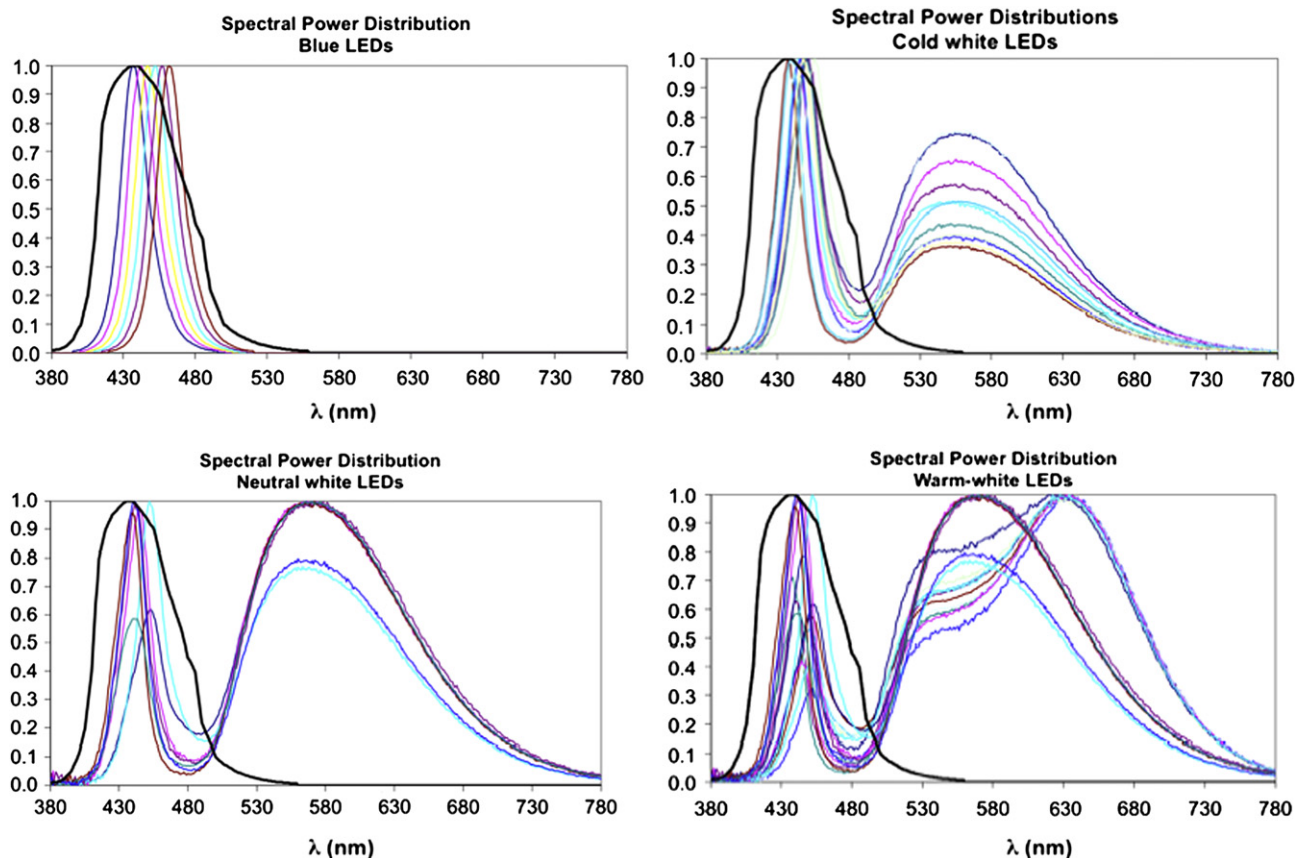


Fig. 10. Spectral power distributions of the studied LEDs. The black curve is the blue-light phototoxicity function $B(\lambda)$. The black curve is the blue-light toxicity function $B(\lambda)$.

$$L_B = B \cdot L_e$$

where B was computed from the spectral power distribution $S(\lambda)$ and the phototoxicity function $B(\lambda)$:

$$B = \frac{\sum_{\lambda} S(\lambda) B(\lambda) \Delta \lambda}{\sum_{\lambda} S(\lambda) \Delta \lambda}$$

The B factor represents the fraction of optical power emitted by a light source contributing to the blue-light risk. In the case of the sampled blue LEDs, the B factor lay between 0.71 for a peak emission wavelength of 460 nm and 0.92 for a peak emission wavelength of 435 nm.

Fig. 11 shows the variation of the B factor with the correlated color temperature of the tested white LEDs. This figure shows that cold-white LEDs emitted about three to four times as much energy in the blue-light risk portion of the spectrum as warm-white LEDs did. For lamps and luminaires, the $B(\lambda)$ -weighted radiances were measured using a non-imaging radiance meter equipped with three different diaphragms in order to produce the FOV values defining the risk group boundaries. The devices were all tested at a viewing distance of 200 mm, which corresponds to the worst-case scenario of the EN 62471 standard. However, other measurements were also made at the distance corresponding to an illuminance of 500 lux, which the standard defines as the relevant distance for common lamps.

Although the luminous efficacy is favorable, calculation shows that the B factor is about 20 percent higher for the light emitted by a white LED than for daylight of the same correlated color temperature.

9.1.1. Assessment results with single-die high-brightness white LEDs and blue LEDs

The measured luminance map of each LED was processed in order to extract the luminance in the FOV corresponding to each exposure time ranging from 0.25 s to 10 000 s. Therefore, the $B(\lambda)$ -weighted radiances L_B were continuously estimated at all exposure times in this range. The intersect point of the L_B curve with the curve of the exposure limit determines the maximum permissible exposure time and accordingly, the risk group. Fig. 12 shows the L_B

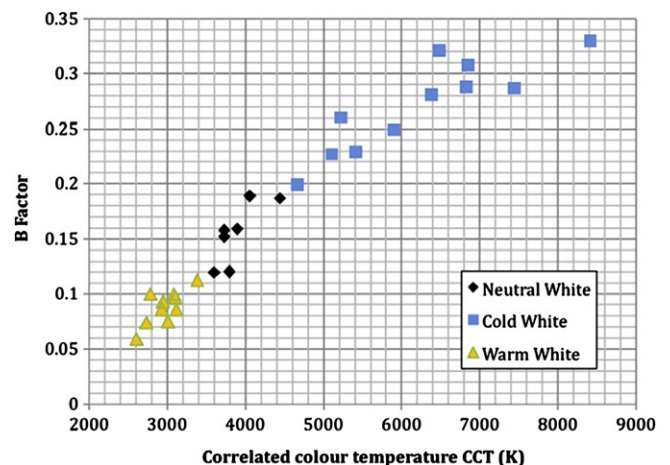


Fig. 11. Graph showing the B factor (fraction of optical power contributing to the blue-light risk) as a function of the correlated color temperature of the selected white LEDs.

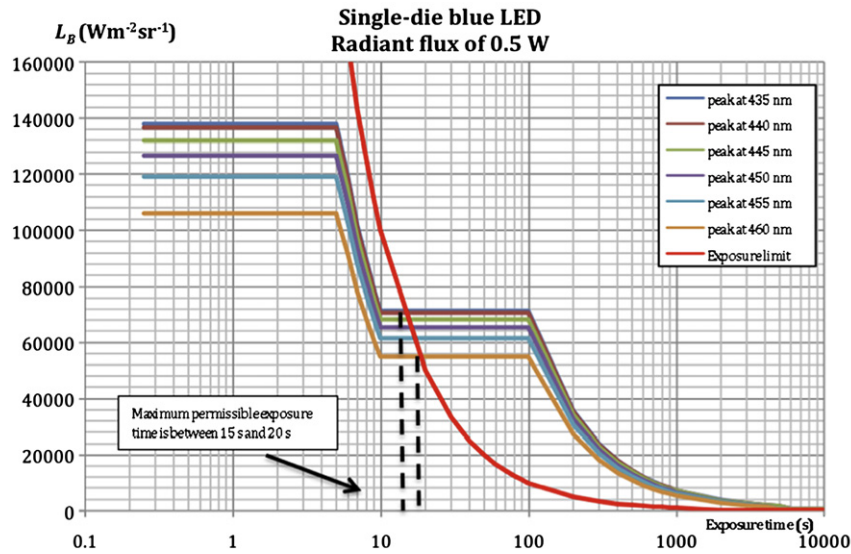


Fig. 12. Graph showing the variation of LB with the exposure time determined for six types of blue LEDs emitting a radiant flux of 0.5 W. The red curve is the exposure limit value. The intersect point corresponds to the maximum permissible exposure time, and, therefore, the risk group.

plots for the six blue LEDs chosen by the working group. In this example, the LEDs were operated such as they emitted a radiant flux of 0.5 W, which is about half the rated maximum value. The LB curves have a first plateau corresponding to a uniform luminance when the FOV is smaller than the light source. When the FOV is greater than the size of the effective light source, the luminance LB decreases as t^{-1} . The second plateau corresponds to a constant FOV when the exposure time is comprised between 10 s and 100 s (ICNIRP, 2006). After 100 s, the FOV increases again and the luminance LB decreases again as t^{-1} . In this example, the maximum permissible exposure times of these LEDs are between 15 s and 20 s. These values correspond to the Risk Group 2 (moderate risk) (Fig. 13).

The results obtained with all the single-die blue LEDs are shown in Table 8. These blue LEDs could be operated up to a radiant flux of 1 W. At this higher level, the risk assessment showed that the maximum permissible exposure time was about 3–4 s. The risk

group is still 2 but these limits are particularly short given the application of these LEDs in signage and display applications.

The analysis of the luminance data shows that risk group 3 (high risk) could be reached by such blue LEDs when their radiant flux exceeds 15 W, which seems unlikely to happen with single-die LEDs. On the opposite, it is possible to determine the maximum radiant flux of these blue LEDs to limit the risk group to 1. The maximum radiant flux would then be about 0.07 W.

The results of all the single-die high-brightness white LEDs are shown in Table 9.

When the cold-white LEDs studied here were operated at a luminous flux of 100 lm, the risk group was 0 (no risk) as the exposure limit value (ELV) was never reached. However, these cold-white LEDs were also operated at 200 lm (their maximum rated flux was near 300 lm). At 200 lm, all the cold-white LEDs fell into risk group 2 (moderate risk) with maximum permissible exposure times comprised between 40 s and 100 s.

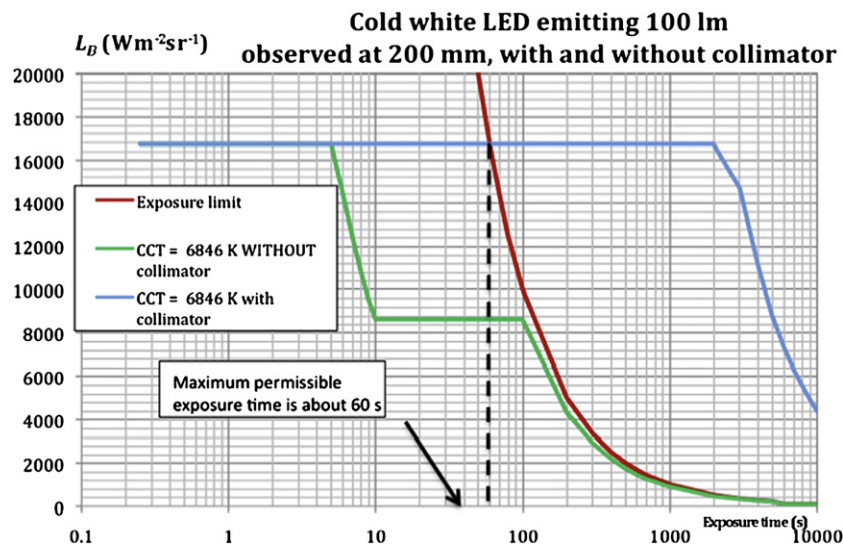


Fig. 13. Plot of the effective radiance LB of two identical cold-white LEDs, respectively used without any optical system and with a 10 mm diameter collimator, as a function of the exposure time. This graph shows that the exposure limit is never exceeded without the collimator (risk group 0). However, when the LED is used with the collimator, the exposure limits are exceeded after 60 s. Consequently, the LED with the collimator belongs to risk group 2.

Table 8

Results of the blue-light risk assessment carried out with the selected single-die blue LEDs.

Color	Radiant flux (W)	Radiance ($\text{Wm}^{-2} \text{sr}^{-1}$)	Maximum permissible exposure time at 200 mm (s)	Risk Group
Blue	0.07	21 000	100–10 000	1: low risk
	0.5	150 000	15–20	2: moderate risk
	1	300 000	3–4	2: moderate risk

Similarly, neutral-white LEDs operated at a luminous flux of 100 lm all fell in risk group 0. When operated at 200 lm, the ELV was reached at exposure times of about 100 s for CCTs equal or greater than 4000 K, meaning a risk group 1 (low risk).

Warm-white LEDs never exceeded the ELV and were all in risk group 0 (no risk), even when they were operated at a flux of 200 lm. These LEDs should reach a luminous flux of at least 500 lm to belong to risk group 1 (low risk).

None of the single-die LEDs studied here presented a high risk (risk group 3) corresponding to a maximum permissible exposure time less than 0.25 s. Blue LEDs and cold-white LEDs according to their CCT and their operating point may belong to risk group 2. Likewise, neutral-white LEDs may belong to risk group 1. On the contrary, warm-white LEDs studied here all belonged to risk group 0 (Table 10).

9.1.2. Assessment results with a multiple-die LED

A multichip LED incorporating 100 dies was studied (Fig. 1E). The emitting area had a size of $2.7 \text{ cm} \times 2.7 \text{ cm}$. Its rated electrical power was 100 W. Its luminous flux is 7000 lm. The average luminance of the emitting surface was about 3106 cd/m^2 . Two different CCTs were studied: 3000 K (warm-white) and 7000 K (cold white). The results are summarized in Table 11. The maximum permissible exposure time was between 200 s and 300 s in the case of cold-white color. In warm white, the maximum permissible exposure time was about 1300 s. Both warm-white and cold-white model are therefore in risk group 1.

Despite being a very powerful source, this multiple-die LED had a lower luminance than high-brightness single-die LEDs. Each of the 100 dies integrated in the device emitted a lower flux than the single-die LED studied above. However, the multiple-die technology is progressing quickly. It could produce components with much higher luminous fluxes and luminances in the near future.

The risk assessment was also performed at 2.1 m which is the distance corresponding to an illuminance of 500 lx. The results are shown in Tables 12 and 13. In this case, the ELV was never reached (risk group 0).

9.1.3. LED arrays

Arrays of LEDs are typical of various types of LED modules and LED luminaires used in indoor lighting. Square matrices consisting of 100 single-die high-brightness LEDs (10×10) were studied by

Table 9

Results of the blue-light risk assessment carried out with the selected LEDs.

Color	Luminous flux (lm)	Luminance (cd/m^2)	Maximum permissible exposure time at 200 mm	Risk group
Cold white	100	1.6107	ELV is not exceeded	0: no risk
	200	3.2107	50–100 s	2: moderate risk
Neutral white	100	1.6107	ELV is not exceeded	0: no risk
	200	3.2107	100–10 000 s	1: low risk
Warm white	100	1.1107	ELV is not exceeded	0: no risk
	200	2.2107		

Table 10

Results of the blue-light risk assessment carried out at 200 mm with a warm-white and a cold-white multiple-die LEDs.

Type	Luminance (cd/m^2)	Maximum permissible exposure time at 200 mm (s)	Risk group
10 × 10 multiple die 7000 lm Cold white (CCT ≈ 7000 K)	2.8106	200–300	1: Low risk
10 × 10 multiple die 7000 lm Warm white (CCT ≈ 3000 K)	2.8106	1000–1300	1: Low risk

the working group. The spacing between the LEDs was set at 5 mm. The overall source size was about $5.4 \text{ cm} \times 5.4 \text{ cm}$. Each LED emitted a luminous flux of 100 lm. The total luminous flux was 10 000 lm. At the distance of 200 mm, the risk assessment carried out on the array gave similar results as in the case of an LED considered individually. As a matter of fact, at this distance, the FOV corresponding to exposure times less than 500 s only covers an individual LED. The distance at which the illuminance reached 500 lx is equal to 2.5 m. At this distance, the risk assessment gives the results presented in Table 5. In this case, the ELV were never reached (risk group 0). In fact, the average luminance of the array was about 10 times less than the luminance of an individual LED. This example shows that it is not possible to transfer the risk group of an individual LED to a LED assembly (module, lamp or luminaire). However, if the observer of a LED assembly has a direct access to an individual LED at 200 mm, the risk group is necessarily equal or greater than the one of the individual LED. This is potentially the case in consumer applications for which the access distance is not restricted.

In conclusion, whatever the type of LED arrays or multiple-die LEDs, LED assemblies emitting a warm-white light ($2600 \text{ K} \leq \text{CCT} \leq 3400 \text{ K}$) with a luminance less than 2.2107 cd/m^2 were always found to belong to risk groups 0 and 1.

9.1.4. Single-die LED associated with an optical collimator

Collimators are optical systems design to reshape the beam emitted by a light source into a beam having a narrower solid angle. Collimators are widely-used in LED devices such as directional lamps and light fixtures (downlight luminaires, projectors, task lighting luminaires, flood lights, etc.). It is important to know that the luminance of a collimated beam of light cannot be greater than the luminance of the source itself. However, the source appears to be magnified by the collimator, leading to an increased effective size of source. In the case of an ideal collimator (the light source is placed at the focus of a perfect convergent lens), the effective size of the source is equal to the output surface area of the collimator. As a consequence, the averaged radiance LB will not decrease as fast when the exposure time increases. The maximum permissible

Table 11

Results of the blue-light risk assessment carried out at 2.1 m with a warm-white and a cold-white multiple-die LEDs.

Type	Average luminance (cd/m^2)	Maximum permissible exposure time at 2.1 m (illuminance of 500 lux)	Risk group
10 × 10 multiple die 7000 lm Cold white (CCT ≈ 7000 K)	2.8106	ELV is not exceeded	0: no risk
10 × 10 multiple die 7000 lm Warm white (CCT ≈ 3000 K)	2.8106	ELV is not exceeded	0: no risk

Table 12

Results of the blue-light risk assessment carried out at 2.5 m with an array of 100 warm-white and cold-white LEDs.

Color	Average luminance (cd/m ²)	Maximum permissible exposure time at 2.5 m (illuminance of 500 lux)	Risk group
10 × 10 LED array 10 000 lm Cold white	1.2106	ELV is not exceeded	0: no risk
10 × 10 LED array 10 000 lm Warm white	0.83 106	ELV is not exceeded	0: no risk

exposure time will thereby be shorter, with a possible change of risk group. For instance, a 10 mm diameter collimator associated with a cold-white single-die LED emitting 100 lm is classified in risk group 2, whereas the individual LED is classified in risk group 0 (Fig. 11 and Tables 14 and 15).

9.1.5. Results of blue-light risk assessment carried out on lamps and luminaires

A directional lamp (220 V, GU10 socket base) using a single LED with an optical collimator and two downlight luminaires using an array of LEDs and collimators were tested. A non-imaging radiance meter with the three FOV defining the boundaries of the risk groups was used. The assessment was performed at 200 mm and afterward, at the distance corresponding to an illuminance of 500 lx. The results are shown in Tables 13 and 14. The cold-white luminaire incorporating a single LED belongs to risk group 1 at the distance corresponding to 500 lx, whereas it is classified in risk group 2 at 200 mm.

It is therefore of primary importance to specify the distance at which the risk is assessed. According to the final use of the luminaire, an observer might be exposed at distances as short as 200 mm, which is not consistent with the risk group determined according to the EN 62471 requirements.

To conclude, this is the first time with LEDs that lighting devices in a risk group greater than 1 are available as commercial domestic lighting. More clearly, LED sources provide for the first time retinal exposures to violet, indigo and blue light at substantial levels compared to the past exposure to incandescent lights, so we cannot rule out a yet undiscovered risk for chronic day-long, life-time exposure. There is therefore the need for a regulation guideline to protect the population from potential light-induced hazards.

10. Anses opinion

On 25th October 2010, ANSES, has made public a report on "Lighting systems using light-emitting diodes: health issues to be considered" (<http://www.afsset.fr/index.php?pageid=2248&parentid=523>). Here is a sum up of the Opinion of ANSES.

Table 13

Results of the blue-light risk assessment carried out at 200 mm with an individual LED and the same LED used with an optical collimator.

Color	Average luminance (cd/m ²)	Maximum permissible exposure time at 200 mm	Risk group
Single-die LED Cold white 100 lm	1,6 107	ELV is not exceeded	0: no risk
Same LED with collimator of 10 mm diameter	1,6 107	60 s	2: moderate risk

Table 14

Results of the blue-light risk assessment carried out at the distance corresponding to an illuminance of 500 lx.

FOV (rd)	0.1	0.011	0.0017	Risk group
MR 16 Lamp – 1 LED – 3 W	115	2180	4021	1
Downlight luminaire 10 W/a unique four-die LED/Cool white	119	2088	23 715	1
Downlight luminaire 15 W/6 LEDs & collimators/Warm white	56	752	3806	0
Average luminance LB (W/m ² /sr) at the distance corresponding to an illuminance of 500 lx				

10.1. Photochemical risks of LEDs

10.1.1. Compliance with standards concerning glare

The radiance measurements show that certain LEDs currently on sale to the general public and potentially used in domestic lighting situations, for signage and guide lights, fall into Risk Group 2, whereas all the other light sources currently on sale to the public fall into either Risk Groups 0 or 1. The safe exposure limit times implied by placing these items in Group 2 vary from a few seconds for certain royal blue LEDs to a few tens of seconds for certain cold-white LEDs.

It is important to emphasize that other widely-used sources of lighting, particularly high-pressure gas discharge lamps (metal-halide lamps for outdoor lighting), are also in Risk Group 2. However, this last example is intended for clearly identified uses and can only be installed by professionals who are required to limit the exposure level for the population. With the arrival on the domestic lighting market of LEDs, light sources falling into Risk Group 2 thus become available to the general public, without details of the risk incurred appearing on the labeling.

With regard to glare-related risks, the standards lay down certain references covering visual ergonomics and safety. In LED lighting systems available on the market, the LEDs are often directly visible in order to avoid attenuating the level of brightness produced. This could lead to non-compliance with the requirements laid down in the standards.

10.2. Anses recommendations

- To ANSES recommends:
- To limit the sale of LEDs for domestic use or for the general public to LEDs falling into Risk Groups equal to or higher than 1 (when assessed at an observation distance of 200 mm);
- To force professionals designing lighting systems using LEDs to apply all standards concerning the quality of lighting;
- To clarify the IEC 62 471-2 standard ('Photobiological safety of lamps and lamp systems') for its application to lighting systems using LEDs,
- To adapt these standards to specific light-sensitive populations (children and aphakic or pseudophakic individuals).

Table 15

Results of the blue-light risk assessment carried out at 200 mm.

FOV (rd)	0.1	0.011	0.0017	Risk group
MR 16 Lamp – 1 LED – 3 W	831	4716	5763	1
Downlight luminaire 10 W/a unique four-die LED/Cool white	521	25 056	26 705	2
Downlight luminaire 15 W/6 LEDs & collimators/Warm white	1567	7047	9106	1
Average luminance LB (W/m ² /sr) at the distance of 200 mm				

10.3. Concerning use, information and traceability

ANSES recommends that consumer information about health risks related to the use of LED lighting systems be made available immediately pending the implementation of an appropriate regulatory framework. ANSES recommends:

- To avoid the use of light sources emitting cold-white light (light with a strong blue component) in places frequented by children (maternity wards, nurseries, schools, leisure centers, etc.) or in the objects they use (toys, electronic display panels, game consoles and joysticks, night lights, etc.);
- To ensure that manufacturers and integrators of LEDs carry out quality controls and qualify their products with regard to the different Risk Groups;
- To set up a clear, easy-to-understand labeling system for consumers, with a mandatory indication of the photobiological safety Risk Group on the packaging for all types of lighting.

11. Conclusions and future directions

Animal models commonly used to evaluate light-induced degeneration allow mechanisms analysis but are not relevant for human pathology. Rodents are mostly nocturnal and have rod rich retina without macula. Limited epidemiologic studies have correlated sun exposure to age-related macular changes, while other have not. On the other hand, light pollution is increasing exponentially in industrialized countries, with more sophisticated light sources, with specific spectra and high intensities.

LEDs will most probably become the main light sources. Beside blue LEDs that are used commonly for decorative purposes, white LEDs provide retinal exposures to violet, indigo and blue light at much higher levels than in previous light sources. This is the first time that the population will be exposed to such substantial blue light. Whether such retinal exposure will induce increased macular degeneration? Aggravation of glaucoma neuropathy? Perturbations of circadian cycles? Nobody can say today, but when analyzing all the knowledge that has been accumulating on blue-light hazards, we cannot rule out a yet undiscovered risk for chronic day-long, life-time exposure since photochemical damages may not induce any visible changes but cumulatively induce photoreceptors loss.

There is an urgent need for a better evaluation of potential light toxicity, depending on the different artificial light sources available, and upon chronic exposure of different populations to define clear guidelines for domestic light manufacturers.

References

- Agorastos, A., Huber, C.G., 2011. The role of melatonin in glaucoma: implications concerning pathophysiological relevance and therapeutic potential. *J. Pineal Res.* 50 (1), 1–7.
- Alvarez, P.V., Marshall, J., Seregard, S., 2006. Age-related maculopathy and the impact of blue light hazard. *Acta Ophthalmol. Scand.* 84 (1), 4–15.
- Asbell, P.A., Dualan, I., Mindel, J., Brocks, D., Ahmad, M., Epstein, S., 2005. Age-related cataract. *Lancet* 365 (9599), 599–609.
- Azzolini, C., Brancato, R., Venturi, G., Bandello, F., Pece, A., Santoro, P., 1994–1995. Updating on intraoperative light-induced retinal injury. *Int. Ophthalmol.* 18 (5), 269–276 (Review).
- Beatty, S., Koh, H., Phil, M., Henson, D., Boulton, M., 2000. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv. Ophthalmol.* 45 (2), 115–134.
- Berler, D.K., Peyser, R., 1983. Light intensity and visual acuity following cataract surgery. *Ophthalmology* 90 (8), 933–936.
- Boettner, E.A., Wolter, J.R., 1962. Transmission of the ocular media. *Invest. Ophthalmol. Vis. Sci.* 1, 776–783.
- Bok, D., 1990. Processing and transport of retinoids by the retinal pigment epithelium. *Eye* 4, 326–332.
- Boulton, M., Rozanowska, M., Rozanowski, B., Wess, T., 2004. The photoreactivity of ocular lipofuscin. *Photochem. Photobiol. Sci.* 3 (8), 759–764.
- Boulton, M., Rózanowska, M., Rózanowski, B., 2001. Retinal photodamage. *J. Photochem. Photobiol.* 64 (2–3), 144–161.
- Brainard, G.C., Sliney, D., Hanifin, J.P., Glickman, G., Byrne, B., Greeson, J.M., Jasser, S., Gerner, E., Rollag, M.D., 2008. Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J. Biol. Rhythms* 23 (5), 379–386.
- Bron, A.J., Vrensen, G.F., Koretz, J., Maraini, G., Harding, J.J., 2000. The ageing lens. *Ophthalmologica* 214 (1), 86–104.
- Cadet, J., Douki, T., Ravanat, J.L., 2010. Oxidatively generated base damage to cellular DNA. *Free Radic. Biol. Med.* 49 (1), 9–21.
- Cano, M., Thimmalappula, R., Fujihara, M., Nagai, N., Sporn, M., Wang, A.L., Neufeld, A.H., Biswal, S., Handa, J.T., 2010. Cigarette smoking, oxidative stress, the anti-oxidant response through Nrf2 signaling, and age-related Macular Degeneration. *Vis. Res.* 50 (7), 652–664.
- Carpentier, S., Knaus, M., Suh, M., 2009. Associations between lutein, zeaxanthin, and age-related macular degeneration: an overview. *Crit. Rev. Food Sci. Nutr.* 49 (4), 313–326.
- Cowan Jr., C.L., 1992. Light hazards in the operating room. *J. Natl. Med. Assoc.* 84 (5), 425–429.
- Crochet, J.J., Gnyawali, S.C., Chen, Y., Lemley, E.C., Wang, L.V., Chen, W.R., 2006. Temperature distribution in selective laser-tissue interaction. *J. Biomed. Opt.* 11 (3), 34031.
- Cruickshanks, K.J., Klein, R., Klein, B.E., Nondahl, D.M., 2001. Sunlight and the 5-year incidence of early age-related maculopathy: the beaver dam eye study. *Arch. Ophthalmol.* 119 (2), 246–250.
- Dartnall, H.J.A., Bowmaker, J.K., Mollon, J.D., 1983. Human visual pigments: microspectrophotometric results from the eyes of seven persons. *Proc. Royal Soc.* 220, 115–130.
- Davies, N.P., Morland, A.B., 2004. Macular pigments: their characteristics and putative role. *Prog. Retin. Eye Res.* 23 (5), 533–559.
- Delcourt, C., Carrière, I., Ponton-Sanchez, A., Fourrey, S., Lacroux, A., Papoz, L., POLA Study Group, 2001. Light exposure and the risk of age-related macular degeneration: the Pathologies Oculaires Liées à l'Age (POLA) study. *Arch. Ophthalmol.* 119 (10), 1463–1468.
- Delori, F.C., Webb, R.H., Sliney, D.H., 2007. Maximum permissible exposures for ocular safety (ANSI 2000), with emphasis on ophthalmic devices. *J. Opt. Soc. Am. A Opt. Image Sci. Vis.* 24, 1250–1265.
- Dillon, J., Zheng, L., Merriam, J.C., Gaillard, E.R., 2004. Transmission of light to the aging human retina: possible implications for age related macular degeneration. *Exp. Eye Res.* 79 (6), 753–759.
- Ding, X., Patel, M., Chan, C.C., 2009. Molecular pathology of age-related macular degeneration. *Prog. Retin. Eye Res.* 28 (1), 1–18.
- Drouyer, E., Dkhissi-Benyahya, O., Chiquet, C., Wolde Mussie, E., Ruiz, G., Wheeler, L.A., Denis, P., Cooper, H.M., 2008. Glaucoma alters the circadian timing system. *PLoS One* 3 (12), e3931.
- Fukuda, Y., Tsujimura, S.I., Higuchi, S., Yasukouchi, A., Morita, T. The ERG responses to light stimuli of melanopsin-expressing retinal ganglion cells that are independent of rods and cones. *Neurosci. Lett.*, in press.
- Gaillard, E.R., Merriam, J., Zheng, L., Dillon, J., 2011. Transmission of light to the young primate retina: possible implications for the formation of lipofuscin. *Photochem. Photobiol.* 87 (1), 18–21.
- Gaillard, E.R., Zheng, L., Merriam, J.C., Dillon, J., 2000. Age-related changes in the absorption characteristics of the primate lens. *Invest. Ophthalmol. Vis. Sci.* 41 (6), 1454–1459.
- Gallagher, R.P., Lee, T.K., 2006. Adverse effects of ultraviolet radiation: a brief review. *Prog. Biophys. Mol. Biol.* 92 (1), 119–131.
- Gladstone, G.J., Tasman, W., 1978. Solar retinitis after minimal exposure. *Arch. Ophthalmol.* 96 (8), 1368–1369.
- Glickman, R.D., 2002. Phototoxicity to the retina: mechanisms of damage. *Int. J. Toxicol.* 21 (6), 473–490.
- Godley, B.F., Shamsi, F.A., Liang, F.Q., Jarrett, S.G., Davies, S., Boulton, M., 2005. Blue light induces mitochondrial DNA damage and free radical production in epithelial cells. *J. Biol. Chem.* 280 (22), 21061–21066.
- Gorgels, T.G., Van Norren, D., 1998. Two spectral types of retinal light damage occur in albino as well as in pigmented rat: no essential role for melanin. *Exp. Eye Res.* 66, 155–162.
- Gorgels, T.G., van Norren, D., 1995. Ultraviolet and green light cause different types of damage in rat retina. *Invest. Ophthalmol. Vis. Sci.* 36, 851–863.
- Grimm, C., Remé, C.E., Rol, P.O., et al., 2000a. Blue light's effects on rhodopsin: photoreversal of bleaching in living rat eyes. *Invest. Ophthalmol. Vis. Sci.* 41, 3984–3990.
- Grimm, C., Wenzel, A., Hafezi, F., Reme, C.E., 2000b. Gene expression in the mouse retina: the effect of damaging light. *Mol. Vis.* 6, 252–260.
- Grimm, C., Wenzel, A., Hafezi, F., Yu, S., Redmond, T.M., Remé, C.E., 2000c. Protection of Rpe65-deficient mice identifies rhodopsin as a mediator of light-induced retinal degeneration. *Nat. Genet.* 25, 63–66.
- Grimm, C., Wenzel, A., Williams, T., Rol, P., Hafezi, F., Remé, C., 2001. Rhodopsin-mediated blue-light damage to the rat retina: effect of photoreversal of bleaching. *Invest. Ophthalmol. Vis. Sci.* 42, 497–505.
- Hafezi, F., Marti, A., Munz, K., Reme, C.E., 1997. Light-induced apoptosis: differential timing in the retina and pigment epithelium. *Exp. Eye Res.* 64, 963–970.
- Ham Jr., W.T., 1983. Ocular hazards of light sources: review of current knowledge. *J. Occup. Med.* 25 (2), 101–103.
- Ham, W.T., Mueller, H.A., Sliney, D.H., 1976. Retinal sensitivity to damage from short wavelength light. *Nature* 260, 153–155.

- Ham Jr., W.T., Ruffolo Jr., J.J., Mueller, H.A., Clarke, A.M., Moon, M.E., 1978. Histologic analysis of photochemical lesions produced in rhesus retina by short-wave-length light. *Invest. Ophthalmol. Vis. Sci.* 17 (10), 1029–1035.
- Ham, W.T., Mueller, H.A., Ruffolo, J.J., Clarke, A.M., 1979. Sensitivity of the retina to radiation damage as a function of wavelength. *Photochem. Photobiol.* 29, 735–743.
- Hankins, M.W., Peirson, S.N., Foster, R.G., 2008. Melanopsin: an exciting photopigment. *Trends Neurosci.* 31 (1), 27–36.
- Harwerth, R.S., Sperling, H.G., 1971. Prolonged color blindness induced by intense spectral lights in Rhesus monkeys. *Science* 174 (4008), 520–523.
- Hattar, S., Liao, H.W., Takao, M., Berson, D.M., Yau, K.W., 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295 (5557), 1065–1070.
- Heil, K., Pearson, D., Carell, T., 2010. Chemical investigation of light induced DNA bipyrimidine damage and repair. *Chem. Soc.*
- Hu, D.N., Simon, J.D., Sarna, T., 2008. Role of ocular melanin in ophthalmic physiology and pathology. *Photochem. Photobiol.* 84 (3), 639–644.
- ICNIRP, 2006. Guidelines on Limiting Exposures to Non-ionizing Radiation, ICNIRP 7/99; Adopted by EU in Directive 25/EC.
- Kardon, R., Anderson, S.C., Damarjian, T.G., Grace, E.M., Stone, E., Kawasaki, A., 2009. Chromatic pupil responses: preferential activation of the melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex. *Ophthalmology* 116 (8), 1564–1573.
- Kessel, L., Lundeman, J.H., Herbst, K., Andersen, T.V., Larsen, M., 2010. Age-related changes in the transmission properties of the human lens and their relevance to circadian entrainment. *J. Cataract Refract. Surg.* 36 (2), 308–312.
- Khandhadia, S., Lotery, A., 2010. Oxidation and age-related macular degeneration: insights from molecular biology. *Expert Rev. Mol. Med.* 12, e34 (Review).
- Kremers, J.J., van Norren, D., 1989. Retinal damage in macaque after white light exposures lasting ten minutes to twelve hours. *Invest. Ophthalmol. Vis. Sci.* 30 (6), 1032–1040.
- Krinsky, N.I., Landrum, J.T., Bone, R.A., 2003. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. *Annu. Rev. Nutr.* 23, 171–201.
- Landrum, J.T., Bone, R.A., 2001. Lutein, zeaxanthin, and the macular pigment. *Arch. Biochem. Biophys.* 385 (1), 28–40 (Review).
- Li, B., Ahmed, F., Bernstein, P.S., 2010. Studies on the singlet oxygen scavenging mechanism of human macular pigment. *Arch. Biochem. Biophys.* 504 (1), 56.
- Loane, E., Nolan, J.M., O'Donovan, O., Bhosale, P., Bernstein, P.S., Beatty, S., 2008. Transport and retinal capture of lutein and zeaxanthin with reference to age-related macular degeneration. *Surv. Ophthalmol.* 53 (1), 68–81.
- Marshall, J., 1970. Thermal and mechanical mechanisms in laser damage to the retina. *Invest. Ophthalmol.* 9, 97–115.
- Mayer, M.A., Salsi, M.S., 1979. Rayonnements ultraviolet, visible et infrarouge. Mesure-Evaluation des risques. INRS, Cahiers de Notes Documentaires 96 (3), 403–413.
- Mure, L.S., Cornut, P.L., Rieux, C., Drouyer, E., Denis, P., Gronfier, C., Cooper, H.M., 2009. Melanopsin bistability: a fly's eye technology in the human retina. *PLoS One* 4 (6), e5991.
- Naidoff, M.A., Sliney, D.H., 1974. Retinal injury from a welding arc. *Am. J. Ophthalmol.* 77, 663–668.
- Noell, W.K., Walker, V.S., Kang, B.S., Berman, S., 1966 Oct. Retinal damage by light in rats. *Invest. Ophthalmol.* 5 (5), 450–473.
- Noell, W.K., 1980. Possible mechanisms of photoreceptor damage by light in mammalian eyes. *Vis. Res.* 20 (12), 1163–1171.
- Okuno, T., Ojima, J., Saito, H., 2010. Blue-light hazard from CO₂ arc welding of mild steel. *Ann. Occup. Hyg.* 54 (3), 293–298.
- Okuno, T., Saito, H., Ojima, J., 2002. Evaluation of blue-light hazards from various light sources. *Dev. Ophthalmol.* 35, 104–112.
- Oliva, M.S., Taylor, H., 2005. Ultraviolet radiation and the eye. *Int. Ophthalmol. Clin.* 45 (1), 1–17.
- Organisciak, D.T., Vaughan, D.K., 2010. Retinal light damage: mechanisms and protection. *Prog. Retin. Eye Res.* 29 (2), 113–134.
- Osborne, N.N., Li, G.Y., Ji, D., Mortiboys, H.J., Jackson, S., 2008. Light affects mitochondria to cause apoptosis to cultured cells: possible relevance to ganglion cell death in certain optic neuropathies. *J. Neurochem.* 105 (5), 2013–2028.
- Osborne, N.N., Kamalden, T.A., Majid, A.S., del Olmo-Aguado, S., Manso, A.G., Ji, D., 2010 Dec. Light effects on mitochondrial photosensitizers in relation to retinal degeneration. *Neurochem. Res.* 35 (12), 2027–2034. Epub 2010 Oct 7.
- Panda, S., Hogenesch, J.B., Kay, S.A., 2002. Circadian rhythms from flies to human. *Nature* 417 (6886), 329–335.
- Panda, S., 2007. Multiple photopigments entrain the Mammalian circadian oscillator. *Neuron* 53 (5), 619–621.
- Parish, C.A., Hashimoto, M., Nakanishi, K., Dillon, J., Sparrow, J., 1998. Isolation and one-step preparation of A2E and iso-A2E, fluorophores from human retinal pigment epithelium. *Proc. Natl. Acad. Sci.* 95, 14609–14613.
- Pepe, I.M., 1999. Rhodopsin and phototransduction. *J. Photochem. Photobiol. B.* 48, 1–10.
- Reszka, K., Eldred, G., Wang, R.H., Chignell, C., Dillon, J., 1995. The photochemistry of human retinal lipofuscin as studied by EPR. *Photochem. Photobiol.* 62, 1005–1008.
- Robman, L., Taylor, H., 2005. External factors in the development of cataract. *Eye (Lond)* 10, 1074–1082.
- Roh, S., Weiter, J.J., 1994. Light damage to the eye. *J. Fla. Med. Assoc.* 81 (4), 248–251.
- Ruby, N.F., Brennan, T.J., Xie, X., Cao, V., Franken, P., Heller, H.C., O'Hara, B.F., 2002. Role of melanopsin in circadian responses to light. *Science* 298 (5601), 2211–2213.
- Sakai, N., Decatur, J., Nakanishi, K., Eldred, G.E., 1996. Ocular age pigment A2-E an unprecedented pyridinium bis-retinoid. *J. Am. Chem. Soc.* 118, 1559–1560.
- Semo, M., Gias, C., Ahmado, A., Sugano, E., Allen, A.E., Lawrence, J.M., Tomita, H., Coffey, P.J., Vugler, A.A., 2010. Dissecting a role for melanopsin in behavioural light aversion reveals a response independent of conventional photoreception. *PLoS One* 5 (11), e15009.
- Shaban, H., Richter, C., 2002. A2E and blue light in the retina: the paradigm of age-related macular degeneration. *J. Biol. Chem.* 277 (3), 537–545.
- Singh, A.D., Rennie, I.G., Seregard, S., Giblin, M., McKenzie, J., 2004. Sunlight exposure and pathogenesis of uveal melanoma. *Surv. Ophthalmol.* 49 (4), 419–428.
- Siu, T.L., Morley, J.W., Coroneo, M.T., 2008. Toxicology of the retina: advances in understanding the defence mechanisms and pathogenesis of drug- and light-induced retinopathy. *Clin. Experiment. Ophthalmol.* 36 (2), 176–185.
- Sliney, D.H., 1994. Ocular hazards of light. In: T. Tibbitts, T.W. (Ed.), *International Lighting in Controlled Environments Workshop*, pp. 183–189. NASA-CP-95-3309.
- Sliney, D.H., 2001. Photoprotection of the eye – UV radiation and sunglasses. *J. Photochem. Photobiol.* 64, 166–175.
- Sliney, D.H., 2005. Exposure geometry and spectral environment determine photo-biological effects on the human eye. *Photochem. Photobiol.* 81 (3), 483–489.
- Sliney, D.H., 2002. How light reaches the eye and its components. *Int. J. Toxicol.* 21 (6), 501–509.
- Sliney, D.H., 2006. Risks of occupational exposure to optical radiation. *Med. Lav* 97 (2), 215–220.
- Stahl, W., 2005. Macular carotenoids: lutein and zeaxanthin. *Dev. Ophthalmol.* 38, 70–88.
- Taylor, H.R., West, S., Muñoz, B., Rosenthal, F.S., Bressler, S.B., Bressler, N.M., 1992. The long-term effects of visible light on the eye. *Arch. Ophthalmol.* 110 (1), 99–104.
- Tomany, S.C., Cruickshanks, K.J., Klein, R., Klein, B.E., Knudtson, M.D., 2004. Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Arch. Ophthalmol.* 122 (5), 750–757.
- Tsai, J.W., Hannibal, J., Hagiwara, G., Colas, D., Ruppert, E., Ruby, N.F., Heller, H.C., Franken, P., Bourgin, P., 2009. Melanopsin as a sleep modulator: circadian gating of the direct effects of light on sleep and altered sleep homeostasis in *Opn4*(–/–) mice. *PLoS Biol.* 7 (6), e1000125.
- Tso, M.O., La Piana, F.G., 1975. The human fovea after sungazing. *Trans. Sect. Ophthalmol. Am. Acad. Ophthalmol. Otolaryngol.* 79, OP788–OP795.
- Vajdic, C.M., Kricker, A., Giblin, M., McKenzie, J., Aitken, J., Giles, G.G., Armstrong, B.K., 2002. Sun exposure predicts risk of ocular melanoma in Australia. *Int. J. Cancer* 101 (2), 175–182.
- van de Kraats, J., van Norren, D., 2007. Optical density of the aging human ocular media in the visible and the UV. *J. Opt. Soc. Am. A Opt. Image Sci. Vis.* 24 (7), 1842–1857.
- van Norren, D., Schellekens, P., 1990. Blue light hazard in rat. *Vis. Res.* 30 (10), 1517–1520.
- Viénot, F., Bailacq, S., Rohellec, J.L., 2010. The effect of controlled photopigment excitations on pupil aperture. *Ophthalmic Physiol. Opt.* 30 (5), 484–491.
- Wang, Z., Keller, L.M., Dillon, J., Gaillard, E.R., 2006. Oxidation of A2E results in the formation of highly reactive aldehydes and ketones. *Photochem. Photobiol.* 82 (5), 1251–1257.
- Wassell, J., Davies, S., Bardsley, W., Boulton, B., 1999. The photoreactivity of the retinal age pigment lipofuscin. *J. Biol. Chem.* 274, 23828–23832.
- Wenzel, A., Grimm, C., Samardzija, M., Remé, C.E., 2005. Molecular mechanisms of light-induced photoreceptor apoptosis and neuroprotection for retinal degeneration. *Prog. Retin. Eye Res.* 24 (2), 275–306.
- Whitehead, A.J., Mares, J.A., Danis, R.P., 2006. Macular pigment: a review of current knowledge. *Arch. Ophthalmol.* 124 (7), 1038–1045.
- Wielgus, A.R., Chignell, C.F., Ceger, P., Roberts, J.E., 2010. Comparison of A2E cytotoxicity and phototoxicity with all-trans-retinal in human retinal pigment epithelial cells. *Photochem. Photobiol.* 86 (4), 781–791.
- Wooten, B.R., Hammond, B.R., 2002. Macular pigment: influences on visual acuity and visibility. *Prog. Retin. Eye Res.* 21 (2), 225–240.
- Wu, J., Seregard, S., Algvere, P.V., 2006. Photochemical damage of the retina. *Surv. Ophthalmol.* 51 (5), 461–481.
- Wu, Y., Yanase, E., Feng, X., Siegel, M.M., Sparrow, J.R., 2010. Structural characterization of bisretinoid A2E photocleavage products and implications for age-related macular degeneration. *Proc. Natl. Acad. Sci. U S A* 107 (16), 7275–7280.
- Xu, H., Chen, M., Forrester, J.V., 2009. Para-inflammation in the aging retina. *Prog. Retin. Eye Res.* 28 (5), 348–368.
- Yang, J.H., Basinger, S.F., Gross, R.L., Wu, S.M., 2003. Blue light-induced generation of reactive oxygen species in photoreceptor ellipsoids requires mitochondrial electron transport. *Invest. Ophthalmol. Vis. Sci.* 44 (3), 1312–1319.
- Young, A.R., 2006. Acute effects of UVR on human eyes and skin. *Prog. Biophys. Mol. Biol.* 92 (1), 80–85.
- Young, R.W., 1988. Solar radiation and age-related macular degeneration. *Surv. Ophthalmol.* 32, 252–269.
- Youssef, P.N., Sheibani, N., Albert, D.M., 2010. Retinal light toxicity. *Eye (Lond)* 29 [Epub ahead of print].
- Yu, D.Y., Cringle, S.J., 2005. Retinal degeneration and local oxygen metabolism. *Exp. Eye Res.* 80 (6), 745–751.