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IS LIGHT WITH LACK OF RED SPECTRAL COMPONENTS A RISK FACTOR FOR AGE-RELATED MACULAR DEGENERATION (AMD)?

Christoph Schierz

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CIE Central Bureau
Babenbergerstrasse 9
A-1010 Vienna
Austria
Tel.: +43 1 714 3187
e-mail: ciecb@cie.co.at
www.cie.co.at

IS LIGHT WITH LACK OF RED SPECTRAL COMPONENTS A RISK FACTOR FOR AGE-RELATED MACULAR DEGENERATION (AMD)?

Schierz, C.[1]
[1] Technische Universität Ilmenau - Lighting Engineering Group, Ilmenau, GERMANY
christoph.schierz@tu-ilmenau.de

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Abstract

Intense blue spectral light components pose a short-term risk to the retina, called blue light hazard (BLH). For this photochemically-induced retinal injury spectral weighting functions and applicable limit values are established. However, scientific evidence about blue light as a long-term risk factor promoting age-related macular degeneration (AMD) is less descriptive. Some studies indicate that a spectral weighting function seems to be similar to the function used for BLH. However, there are some scientific papers reporting good therapeutic results in patients with AMD by the use of a therapy called “photobiomodulation”. This indicates that red and near infrared (NIR) spectral components could be beneficial by counteracting blue light induced AMD. In order to describe the balance between the risk potential of blue and the protection potential of red/NIR spectral components an “AMD protection index” is proposed and is applied to various spectra of light sources including LEDs for comparison.

Keywords: Age-related macular degeneration, AMD, light hazard, photobiomodulation

1 Introduction: Age-related macular degeneration (AMD)

AMD is a disease affecting the photo receptors, the retinal pigment epithelial cells (RPE-cells), Bruch’s membrane and the choroid (for the structure of the retina and the differentiation of dry and wet AMD forms see Figure 1). This visual impairment of the central field of vision, the macula, starts from an age of about 50. Almost a quarter of the population above 65 are affected (Korb et al., 2014). The beginning of AMD is clinically recognisable by so called “drusen”, which are yellow fluorescent deposits located outside the RPE-cells, between the retinal pigment epithelium and Bruch’s membrane. The formation of drusen is favoured by the presence of the decomposition product lipofuscin. This is an accumulation of different, partly fluorescent biomolecules within so called lysosomes in the RPE-cells. Lysosomes are membrane-bound organelles which act as the cell’s waste disposal system.

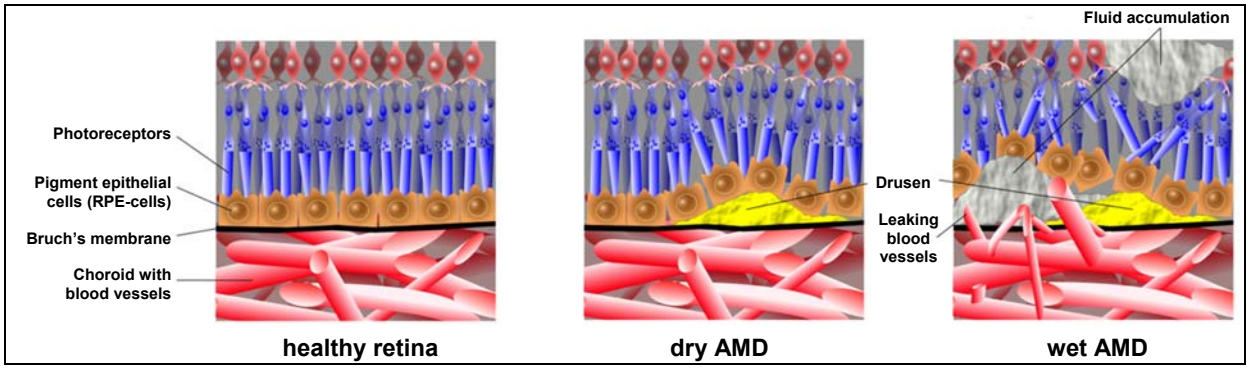

Figure 1 – Left: Schematic representation of a healthy retina. Light from above is partly absorbed within the photoreceptors (cones and rods) and, additionally, can get to the inside of the RPE-cells. Middle: With the dry form of AMD so called “drusen” develop. They are situated between Bruch’s membrane and the RPE-cells. Right: AMD can develop to the wet form with new, fragile blood vessels penetrating Bruch’s membrane and releasing fluids containing detrimental blood and inflammatory cells. Drusen, fluids, and scarring may result in blurred, distorted or inhibited vision in the central visual field.

With increasing age a nearly linear increase of lipofuscin in the form of granules can be observed (Figure 2). For this reason it is also called “ageing pigment”. By 80 years of age lipofuscin can occupy up to 19% of the RPE cell volume (Pawlak et al., 2002). In addition to age, the main risk factors for AMD are believed to be smoking, genetic predisposition and having high blood pressure.

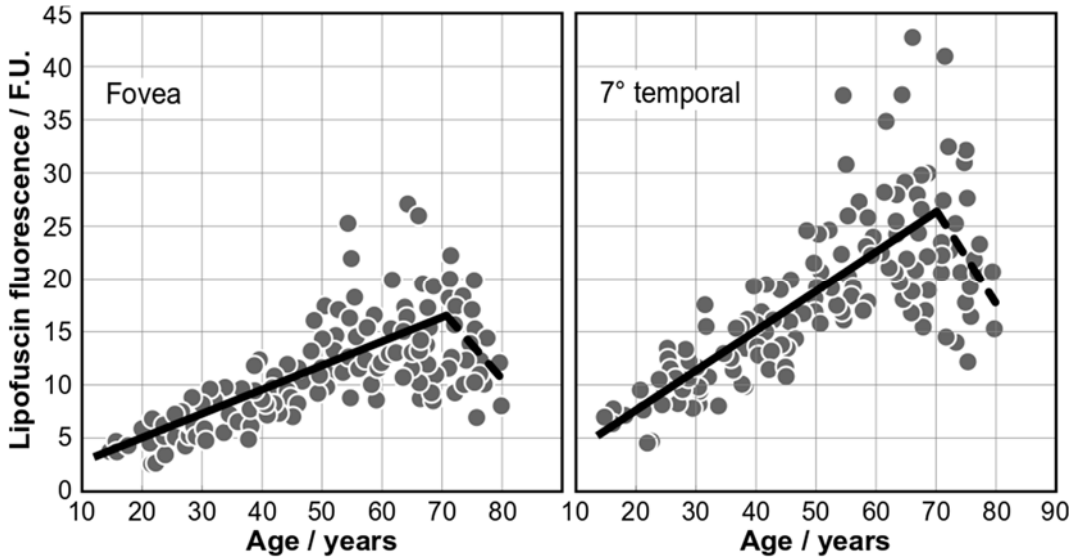

Figure 2 – Age-related accumulation of lipofuscin in the retinal pigment epithelial cells (RPE-cells) in the fovea (left) and 7° temporal to the fovea (right) by means of fundus fluorescence measurements. F.U. are relative fluorescence units corrected for lens absorption. Adapted from Delori, Goger, and Dorey (2001, Fig. 2).

2 Impact of blue spectral light components on AMD

Photochemically induced blue light hazard (BLH) destroys retinal photo receptors with relatively short exposure times. In contrast, in the longer term, chemical mechanism modified as a result of cumulative light effects may contribute to age-related macular degeneration (AMD) (Wu, Seregard, and Algvere, 2006). An epidemiologic study concludes that exposure to sunlight may be associated with the development of early AMD: Time spent outdoors while persons were aged 13 to 39 was significantly associated with this risk (Cruickshanks et al., 2001).

Since lipofuscin and in particular its component A2E acts as photosensitizer it is potentially harmful. By means of light with increased blue spectral components it can generate free radicals inside the RPE-cells (Sparrow, Nakanishi, and Parish, 2000). Free radicals are aggressive oxygen molecules like hydrogen peroxide (H_2O_2), singlet oxygen ($^+O_2$) or superoxide (O_2^-). Free radicals are highly chemically reactive with their unpaired electron and are responsible for the formation of oxidative stress, which is considered to be destructive for RPE-cells and can lead to AMD. In addition, this process is leading to an increased loss of rods and cones, since RPE-cells are responsible for the regeneration of these photoreceptors as well as for the restoration of the associated photo-pigments by means of the “visual cycle” (Lamb and Pugh, 2004). The biomolecule A2E as part of lipofuscin is a degradation product of the rods. Apart from its toxic effects, A2E prevents the lysosomes from removing decomposition products which in turn promotes the formation of drusen (Finnemann, Leung, and Rodriguez-Boulan, 2002). As a result of the age dependent increase of lipofuscin, the risk for damage caused by short-wave light also increases with age. The yellowing of the eye lens with increasing age (van de Kraats, and van Norren, 2007; CIE, 2012) can counteract this process to a certain extent.

Arnault et al. (2013) could demonstrate that light with wavelengths between 415 nm and 455 nm could lead to changes within the RPE-cells if the concentration of A2E is increased. It is possible that other components of lipofuscin with other action spectra in the same spectral range (< 455 nm, blue-violet) are involved (Pawlak et al., 2002). In a clinical trial a certain

therapeutic success with blue-violet blocking eyeglasses was demonstrated (Colombo et al., 2017). By irradiating human RPE-cell cultures with blue screen light (449 nm) Moon et al. (2017) could show a substantial increase of reactive oxygen and a decline of survivability. Also with 458 nm the effect was significant; however, it could not be confirmed with 470 nm. Action spectra for oxidative stress (H_2O_2 production) and mitochondrial damage in A2E-loaded RPE-cells as well as the absorption spectrum of A2E are shown in Figure 3. These functions are situated in a similar spectral range to the one of blue light hazard (Figure 3). However, short time blue light hazard effects do take place within the photo receptors and not within the RPE-cells (Różanowska, and Sarna, 2005).

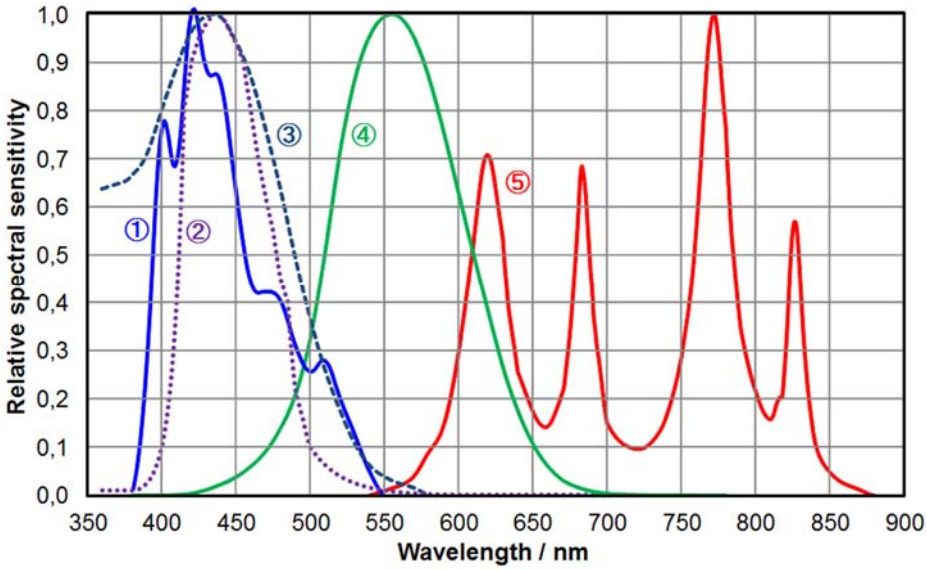

Figure 3 – Action spectra of different retinal light and IR effects:

- ① **Oxidative stress (H_2O_2 production) and mitochondrial damage in A2E-loaded RPE-cells, adapted from Marie et al. (2018, right curve of (B) in Fig. 1);**
- ② **Blue-light hazard function (CIE, 2002);**
- ③ **Absorption spectrum of A2E, adapted from Pawlak et al. (2002, Fig. 2);**
- ④ **CIE spectral luminous efficiency function V(λ);**
- ⑤ **Stimulation of RNA synthesis rate, adapted from Karu et al. (2005, curve (C) in Fig. 3).**

3 Photobiomodulation (PBM) and AMD

Anecdotal reports of health improvements by a therapy called “photobiomodulation” (PBM) seem to indicate that low-level red and near infrared (NIR) radiation can counteract the development of AMD. From literature the current status of knowledge about red and NIR spectral components as a protective factor has been assembled (see Table 1). Even though the data base is sparse, the results are promising. The radiation of human RPE-cells with red LEDs of 670 nm peak wavelength resulted in an increased removal of decomposition products in the cells (Fuma et al., 2015). In a study involving patients with dry AMD the radiation of the retina with red LED-light (a combination of 590 nm, 670 nm, and 790 nm) led to a reduction of drusen size (Merry et al., 2017). Additionally, visual performance in terms of acuity and contrast sensitivity could be improved. This was also the result of a study of 203 patients with wet AMD by means of radiation from a laser diode with 780 nm (Ivandic, and Ivandic, 2008).

Several studies with albino rats, which have been exposed to additional oxidative stress, demonstrate several beneficial effects of red LED-light with 670 nm (see Table 1): The induced histopathologic alterations could be attenuated and the retinal cells were stabilised and protected against light-induced damage. The beneficial effect of red light was present, regardless of whether it was applied before, during or after a detrimental intense white light exposition (Albarracin, Eells, and Valter, 2011; Chu-Tan et al., 2016).

The success of PBM is not based on a thermal effect, but can be explained by molecular mechanisms within the mitochondria of the pigment epithelium cells. Mitochondria are

organelles which are responsible for the cell's energy and metabolism regulation. The photoacceptor for red light and near IR radiation is the enzyme "cytochrome c oxidase" (COX). It is part of the respiratory chain which is located in the inner membrane of RPE-mitochondria. This electron transport chain acts as radical scavenger and counteracts oxidative stress. Action spectra with four maxima at 620 nm, 675 nm, 760 nm, and 830 nm are presented by Karu, and Kolyakov (2005). One of them is shown in Figure 3 as ⑤.

To sum up the validity of PBM, the conclusion of Geneva (2016) can be quoted: "Given the promising pre-clinical results and the equally promising first few translations to human patients, we should expect a growth in the field of photobiomodulation applied to treat common retinal conditions such as age-related macular degeneration…"

Table 1 – Studies about light treatments of the retina by means of photobiomodulation (PBM).

References	Species	Light treatment				Remarks
		Spectrum	Intensity	Exposure time	Treatment effect	
Albarracin et al. (2011)	54 albino rats	670 nm, LED	600 W/m^2	3 min, daily at 9 AM, for 5 consecutive days	Attenuation of histopathologic alterations	Light damage: 24 h with 18 W cool white FL, 1000 lx at bottom of cage
Albarracin et al. (2013)	60 albino rats	670 nm LED	600 W/m^2	3 min, daily at 9 AM, for 5 consecutive days	Increased stability of photoreceptors in cond. of oxidative stress	Receptor damage: Rats placed in hyperoxic environment (75% oxygen)
Qu et al. (2010)	8 groups of albino rats	670 nm LED	50 mW (?)	30 min, 3 h before, and 0, 24 and 48 h after LD	Protects retinal cells against light-induced damage	Light damage (LD): 3 h of 1800 lx and 2700 lx, respectively.
Chu-Tan et al. (2016)	55 albino rats	670 nm LED	600 W/m^2	5 days at 9 AM for: 3 min, 6 min, 12 min, or 30 min	Increased prevention of cell death (assessed by DNA fragmentation)	After treatment: 24 h exposure to 750 lx, 1000 lx, or 1500 lx light from cold-white FL
Di Marco et al. (2014)	44 albino rats	670 nm LED	250-300 W/m^2	3 min for 7 days	Reduction of cell death	Light damage before treatment: 24 h with FL, 1000 lux.
Natoli et al. (2010)	24 albino rats	670 nm LED	600 W/m^2	3 min, daily at 9 AM, for 5 days	Normalisation of gene expression which was reduced by LD	Light damage before treatment: 24 h with FL, 1000 lux.
Olmo-Aguado et al. (2016)	62 Wistar rats	630 nm LED	16,5 W/m^2, 5,5 W/m^2	1 h 24 h	Attenuation of insults due to raised intra-ocular pressure (IOP)	Induction of experimental ischaemia by increasing IOP for 60 min.
Begum et al. (2013)	29 mice	670 nm LED	19 W/m^2	6 min, daily at 6 AM and 6 PM, for 14 days	Increase in cytochrome c oxidase (COX)	Aged mice, at room illumination of 50 lx.
Fuma et al. (2015)	Cultured human RPE-cells	670 nm LED	38,9 W/m^2	250 s for 4 days, twice per day	Reduction of reactive oxygen species production	Additional effect: Enhancement of phagocytic activity.
Ivandic et al. (2008)	203 AMD patients	780 nm semi-conductor laser diode	75 W/m^2	40 s, four treatments (two treatments per week)	Improvement in visual acuity, reduction of edema, bleeding, distorted vision, scotoma, and colour blindness	Application: Transconjunctivally to the macula
Merry et al. (2017)	42 human eyes with dry AMD	590 nm + 670 nm + 790 nm LEDs	670 nm: 500–800 W/m^2	670 nm: 88 s	Improvement in visual acuity and contrast sensitivity, reduction in drusen volume	590 nm at 4 mW (?), and 670 nm at 0,6 mW (?) for 35 s, with 2,5 Hz, 250 ms on,150 ms off.
Rodriguez-Santana et al. (2008)	1 AMD patient	904 nm pulsed laser	45 kJ/m^2/day (?)	Fractioned daily radiant exposure	Several positive clinical outcomes (e.g. visual acuity, ocular fundes, intraocular pressure...)	Note: Time schedule and application method is unclear

4 Proposal for an "AMD protection index"

In order to compare the potential of different light sources with regard to positive or negative effects on AMD a tentative "AMD protection index" is proposed. It is intended that this index represents the "oxidant – antioxidant balance" within the RPE-cells. The "weights" which can be placed on each side of the "beam-balance" are the photobiological quantities B_{AMD} and R_{AMD} calculated as spectrally weighted radiances:

$$B_{\mathrm{AMD}} = \int_{360\ \mathrm{nm}}^{880\ \mathrm{nm}} S_\lambda(\lambda) \cdot \bar{b}_{\mathrm{AMD}}(\lambda) \cdot \mathrm{d}\lambda \tag{1}$$

$$R_{\mathrm{AMD}} = \int_{360\ \mathrm{nm}}^{880\ \mathrm{nm}} S_\lambda(\lambda) \cdot \bar{r}_{\mathrm{AMD}}(\lambda) \cdot \mathrm{d}\lambda \tag{2}$$

where

B_{AMD}	is the photobiological quantity (balance weight) for negative effects;
R_{AMD}	is the photobiological quantity (balance weight) for positive effects;
$S_\lambda(\lambda)$	is the spectral distribution of the light source radiation;
$\bar{b}_{\mathrm{AMD}}(\lambda)$	is the action spectrum for negative effects;
$\bar{r}_{\mathrm{AMD}}(\lambda)$	is the action spectrum for positive effects.

The construction of an AMD protection index follows the principle of Michelson contrasts (hence the selection of the letter C):

$$C_{\mathrm{AMD}} = \frac{R_{\mathrm{AMD}} - f_{\mathrm{ZA}} \cdot B_{\mathrm{AMD}}}{R_{\mathrm{AMD}} + f_{\mathrm{ZA}} \cdot B_{\mathrm{AMD}}} \tag{3}$$

where

C_{AMD}	is the proposed AMD protection index with values between -1 and +1;
f_{ZA}	is a factor for zero adjustment.

The more positive the AMD protection index is, the better the light protects against AMD; the more negative the index is, the riskier is the light for AMD. However, since at present it is not possible to know where the equilibrium between blue and red spectral components could be, a zero adjustment factor f_{ZA} has been introduced. Until the knowledge of the best choice of the action spectra and of the equilibrium with a reasonable value for f_{ZA} is available, the AMD protection index should only be used for relative comparisons. For the calculations presented in Section 5, the action spectra ① and ⑤ of Figure 3 have been chosen and f_{ZA} was selected to give the daylight illuminant D45 an AMD protection index of zero. The reasoning behind this is the result from epidemiology that sunlight may present a risk for AMD (Cruickshanks et al., 2001) and therefore daylight with $T_{\mathrm{cp}} > 4500$ K should get negative index values.

5 Influence of CCT, CRI and peak wavelength on the AMD protection index.

For orientation, initial calculations of the relative impact on AMD for different light source spectra (LEDs, fluorescent lamps, Planckian radiator and daylight) are performed by means of the AMD protection index given in Equation (3). Although, generally, lower correlated colour temperature T_{cp} (CCT) is associated with higher a AMD protection index (Figure 4), there are considerable differences between different types of light sources. For example at 3000 K, due to the lack of red spectral components, LEDs or fluorescent lamps have a lower AMD protection index than a Planckian radiator (e.g. halogen incandescent lamp) with the same colour temperature. This also applies for LEDs imitating the sun spectrum (e.g. SunLike, Seoul Semiconductor; see Figure 4). Figure 5 shows the impact of specific LED properties for a fixed CCT of 4000 K: The higher the CIE 1974 general colour rendering index R_{a} (CRI) and the LED peak wavelength are, the better the AMD protection index will be. The lack of red spectral components is even more elucidated with the special colour rendering index R_9, which describes the light source accuracy for colour fidelity of red objects. The R_9 correlates better with the AMD protection index than the CRI (compare left and right in Figure 5).

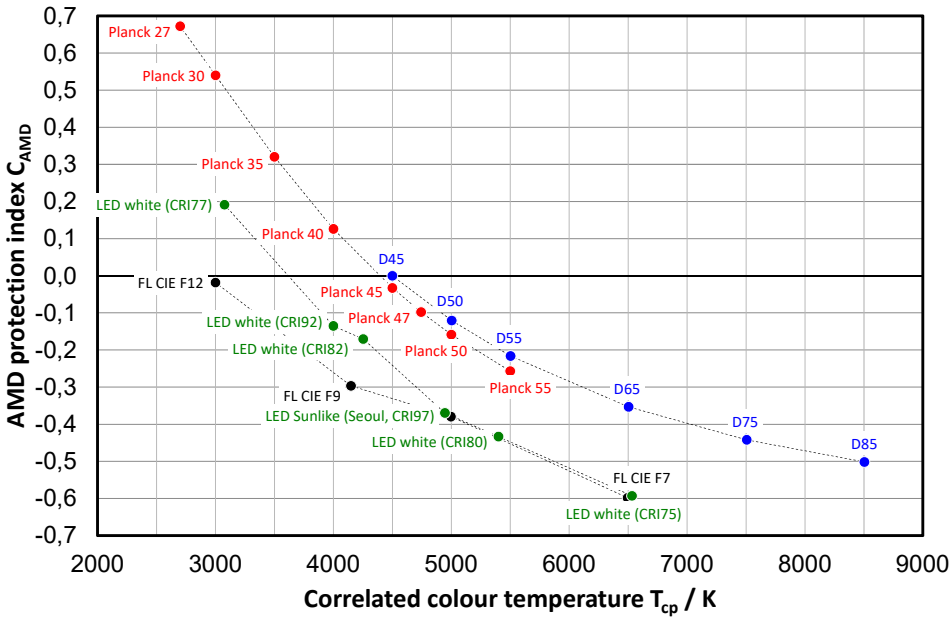

Figure 4 – Association of the correlated colour temperature T_{cp} with the AMD protection index for several light sources like daylight illuminants (blue), Planckian radiators (red), fluorescent lamps (black), and LEDs (green). The underlined value and the underlined values in Figure 5 correspond to the same LED spectrum.

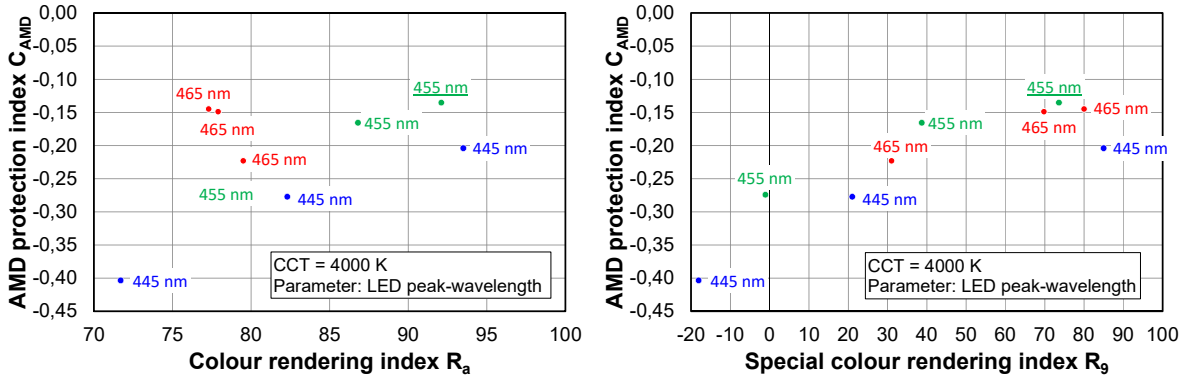

Figure 5 – Association of the CIE 1974 general colour rendering index R_a (left) and the special colour rendering index R_9 (right) with the AMD protection index for several phosphor converted white LEDs with a fixed CCT of 4000 K but with different blue peak wavelengths. The underlined values and the underlined value in Figure 4 correspond to the same LED spectrum.

6 Conclusions

This paper serves the purpose to give a short overview of the state of knowledge about the mechanisms connecting light to AMD . The idea that light with lack of red spectral components could be a risk factor for AMD comes from the first reports about a successful therapy called “photobiomodulation”. This therapy shows good results by using red and NIR radiation which acts as antagonist to the detrimental effects of blue spectral components. Taking into account molecular processes, a preliminary proposal for possible spectral weighting functions for risk and protective light effects could be found and an “AMD protection index” could be derived.

However, it should be noted that the available scientific basis does not allow drawing a final conclusion. Although scientific indications suggest a reasonable suspicion of beneficial red light and NIR effects, there is a need for further research. A scientific confirmation can only be reached when scientific studies of independent research groups come to the same reproducible results, and when the overall scientific picture supports the existence of a causal connection which is also valid in everyday situations. Some open problems are the following:

- Photobiomodulation is still not a topic of mainstream biology and medicine. Even in case photobiomodulation has proven its value, the question remains as to whether therapeutic approaches can be adapted to everyday lighting applications as prevention measures for healthy people.
- The selected action spectra are not generally acknowledged and do not take account of all beneficial and detrimental light effects on RPE-cells. They have been determined from cell studies and not from studies with eyes of living humans.
- It is as yet unknown what a healthy balance between blue light and red/NIR light is (problem of zero adjustment).
- It is not clear if the thresholds for the light effects in question are below or above light levels of normal daily life and if linearity of effects can be reasonably assumed.

Nevertheless, if the precautionary principle is taken into account, the following conclusions for AMD prevention should be drawn:

- Lower correlated colour temperatures (T_{cp}) are preferable;
- higher colour renderings (R_a) are preferable, especially a higher R_9 index;
- higher blue peak wavelengths for white LEDs are preferable;
- LEDs and FL exhibit an insufficient red component at 670 nm.

In regard to future light source developments spectral components < 460 nm should be avoided, and components > 600 nm should be encouraged. In this regard, it has to be discussed if the use of energy optimising measures solely based on the luminous efficiency function (e.g. lm/W) should be superseded by measures with more comprehensive efficiency functions.

Also IR and partly red absorbing windows have to be questioned. Initial calculations with glazing transmissions used for the definition of CIE indoor daylight illuminants (CIE, 2009) showed no substantial change of the AMD protection index. May be the use of a more extensive glazing database would be more informative.

Finally, it should be noted that blue spectral components < 450 nm could also have beneficial health effects. This is indicated for example by the success in the treatment of dermatitis (Becker et al., 2011). However, lighting systems supporting the effects of intrinsically-photosensitive retinal ganglion cells (i.e. non-image-forming effects) are still possible, because these effects have an action spectrum with maximum at 490 nm (CIE, 2018).

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