SCIENTIFIC REVIEWS

UDC 614/5: 644.36
DOI: 10.21668/health.risk/2017.4.14.eng

RISKS OF AGE RELATED MACULAR DEGENERATION AND LED LIGHTING

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Spectral structure of environmental light can have significant influence on risks of various eye diseases which can evolve quite early. The paper dwells on how age-related macular degeneration evolves and on a part which eye age pigment plays in the process. We discuss predictive models for age pigment accumulation and methodology of their creation. We created a predictive mathematical model for accumulated A2E age pigment quantity allowing for LED lighting peculiarities and its age-related perception. The model encompasses active oxygen forms generation evolving due to decrease in antioxidant cellular protection efficiency in a lighting environment with a higher blue light dose. It is shown that superoxide dismutase, catalase and glutathione peroxidase 1 (GRX 1) efficiency within 445 (plus minus 10 nanometers) range drops substantially in blue light; it increases risks of lower cellular resistance to effects exerted by non-compensated active oxygen forms. These processes which are rather long-term can lead to early age-related macular degeneration. Mathematical calculations prove that in the nearest future a share of patients aged 30–40 who suffer from age-related macular degeneration will grow drastically; it will eventually lead to an increased number of disabled people aged 50–60 whose disability is caused by eyesight disorders. It is shown that if we fail to discover any mechanisms aimed at lowering risks of early age-related macular degeneration evolvement in the nearest future, total costs required for solving eyesight disorders issue will grow substantially. Thus, in 2012 about 140 billion dollars were spent on the eyesight disorders issue all over the world; the sum is likely to reach 377 billion dollars in 2050.

Key words: *age-related macular degeneration, age pigment, antioxidant cellular protection, eye pathology prevention, lighting environment, LED lighting, blue light.*

Age-related macular degeneration (AMD) is a degenerative progressive disease of the retina macular area which plays the leading role in central vision loss among elderly people in developed countries who spend 80-90% of their time under artificial lighting. AMD holds the first place among diseases causing poor vision and, as a rule, leads to two-side damage (both eyes are damaged in 60% cases). As per data given by the WTO, this pathology prevalence amounts to 300 people per 100 thousand, 25-30 million people all over the world suffer from AMD. 25-40% of people older than 40 have this disease. This pathology is detected in 58% people who are older than 60. AMD evolvement becomes a more vital issue due to growth in elderly people share among overall population as well as due to the disease itself getting "younger", this process being induced by new computer and television technologies entering our lives and lives of your children [2]. Another problem here is overall lighting created mostly by artificial light sources. In Russia AMD is detected in more than 100 thousand people an-

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nually; 20% out of them suffer from the disease evolving into "wet" ("neovascular") form.

Economic consequences which neovascular AMD evolvement has are significant for patients, their families, and the public healthcare system (lower life quality, loss of independence, and disability). Assessment of economic losses caused by population disability is stated in the Orders by the RF Economic Development Ministry, the RF Social Development Ministry, the RF Ministry of Finance, as well as in the Order by the Federal State Statistic Service No. 113 dated April 10, 2012 "On Approval of methodology for calculating economic losses caused by population mortality, morbidity, and disability" [1].

AMD pathogenesis is known to be based on oxidation-reduction balance disorders in the eye retina. The main role in the process belongs to free radicals which appear in the retina structures under constant impacts exerted by active oxygen forms and light. Active oxygen forms appear due to influence exerted by external factors and the visual cycle as A2E (pyridinium bisretinoid) generates active oxygen forms under blue light influence when a certain pigment epithelium concentration is accumulated in the tissue culture [20].]. In the end the process causes cells death and age-related degradation evolvement in the eye retina, Stargardt disease, various retinopathies, and other dangerous eyesight diseases [9].

We can find lipofuscin in epithelium retinal pigment in the form of spherical particles of micron size; it has its own yellow fluorescence when being excited by blue light; this excitation leads to active intermediate oxygen forms occurrence.

Figure 1 shows the results of lipofuscin fluorescence distribution in the retina of people from various age groups.

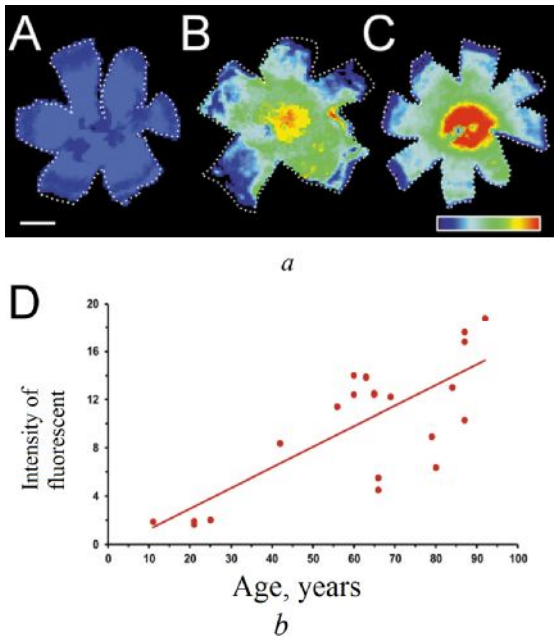


Figure. 1. Spatial distribution of lipofuscin fluorescence in a human eye:
a) fluorescent images of the overall retina pigment epithelium in patients from various age groups: A – 21-year old, B – 41-year old and C – 65-year old; images were taken via bio-luminescence system of image creation with radiation filter ranging from 575 to 650 nanometers (DC is red filter); b) measured overall intensity of lipofuscin fluorescence (DC red filter) grows with age (x axis is age (years); y-axis is fluorescence intensity [19]

A group of researchers estimated some risks calculated via multiple logistic regression analysis and considered genetic and ecological risk factors (smoking, primary hypertension, body mass index, and diabetes) for various age groups [14]. The scientists analyzed various age groups (<70, 70-79 and 80-89 years, and neogenetics as well) for risk variants with CFH genes (hu-

[1] On Approval of methodology for calculating economic losses caused by population mortality, morbidity, and disability: The Order by the RF Economic Development Ministry No. 192, the Order by the RF Social Development Ministry No. 323n, the RF Ministry of Finance No. 45n, The Federal State Statistic Service No. 113 dated April 10, 2012 (registered by the RF Ministry of Justice on April 28, 2012 No. 23983). Available at: http://www.consultant.ru/document/cons_doc_LAW_129302/ (06.07.2017).

man complement factor with genetic susceptibility to AMD and ARMS2 with age susceptibility). AMD probability is considered to increase due to three basic factors: CFH gene polymorphism (genetic marker is T1204C), 43 %; ARMS2 gene polymorphism (genetic marker is G205T), 36 %; and smoking, 20 %. Homozygotes as per changed (minor) alleles of CFH and ARMS2 genes run 50 times greater risk of AMD than basic alleles carriers [14].

The experts calculated AMD risks basing on stepwise logistic regression for genetic and ecological risk factors applying three interrelated logistic regression equations:

$$\text{logit}\,(p^1) = \log\,(p^1/[1-p^1]) = \\ = b0 + b1\cdot\text{ARMS2} + b2\cdot\text{CFH},$$

$$\text{logit}\,(p^2) = \log\,(p^2/[1-p^1]) = b0 + \\ b1\cdot\text{smoking} + \\ + b2\cdot\text{bepertension} + b3\cdot\text{BMI} + b4\cdot\text{diabetes} + \\ b5\cdot\text{sex},$$

$$\text{logit}\,(p^3) = \log\,(p^3/[1-p^2]) = b0 + \\ b1\cdot\text{ARMS2} + \\ + b2\cdot\text{CFH} + b1\cdot\text{smoking} + b2\cdot\text{bepertension} \\ + \\ + b3\cdot\text{BMI} + b4\cdot\text{diabetes} + b5\cdot\text{sex},$$

where p^1 – is AMD risk allowing for genetic influence;

p^2 – is AMD risk allowing for environmental factors;

p^3 – is AMD risk allowing for both genetic and ecological impacts.

AMD probability for each risk parameter was calculated with the following equation: P = exp (logit[P])/(1 + exp [logit{P}]) allowing for the extent to which external factors could influence it. The authors gave a profound description of their risk assessment procedure; each factor significance was determined o the basis of the following patients data: 2,737 people (1204 were the control group; 1433, the focus one), including 166 neogenetics (52 were the control group; 114, the focus one). Single nucleotide polymorphisms (SNP) were detected in ARMS2 and CFH genes. The authors consider genetic and age risk factors to exert much less significant influence on AMD evolvement in neogenetics while environmental factors exert the same effect in people from senior age groups [20].

F.C. Delori et al. suggested mathematical models for assessing lipofuscin accumulation with age, rate of its accumulation, and spatial distribution in the retina allowing for melanin [12]. The researchers revealed that melanin concentration in pigment epithelium cells changes with age. Generalized results of their assessment are given in Figure 2.

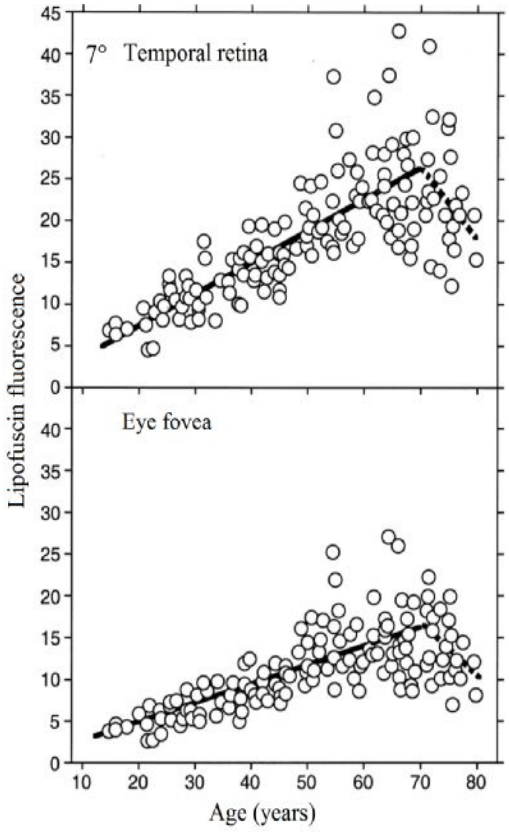


Figure 2. Lipofuscin fluorescence depending on age.Solid lines show linear regression equations at the age from 20 to 70 years (P <0.0001); broken lines show linear regression equations at the age from 70 to 80 years (p <0.12)

The following functional dependences for each age are suggested on the basis of regression analysis given in the paper [12]:

•F15 is fluorescence in young patients (starting from 15), with all the melanin located apically to lipofuscin;

•F65 is fluorescence in old people (older than 65), with their melanin evenly mixing with lipofuscin over the whole cell.

These fluorescences are calculated as per the following formulas:

$$F_{15} = \zeta\, d\, 10^{-[K_\Lambda + K_\lambda] D_{500}}$$

or

$$F_{65} = \frac{\zeta\, d \left\{1 - 10^{-[K_\Lambda + K_\lambda] D_{500}}\right\}}{\ln(10)\left[K_\Lambda + K_\lambda\right] D_{500}}.$$

Lipofuscin fluorescence grew linearly up to 70 years, but then it decreased. Accumulation rate was significantly slower in the fossa than on the temporal area; accumulations rates in vivo were higher than it was previously observed in microscope examinations. Fluorescence was by 40% lower in the fossa than at the 7 ° eccentricity and was asymmetrically distributed around the fossa. Fluorescence was maximum at "11 ° at the temple", 7 ° at the nose, "13 ° and higher", and "9 ° lower". Fluorescence at the same eccentricity was always lower as per the bottom meridian than as per any other one. Light absorption by melanin in pigment epithelium can explain differences between lipofuscin rates assessments in vivo and ex vivo. Decreasing fluorescence in older ages can be related to removal of atrophic cells in retinal pigment epithelium (RPE). Overall, spatial lipofuscin distribution coincides with rods spatial distribution and reflects, but does not predict, an age loss picture [12]. This statement has a very important consequence, namely, retina flare spot square which depends on a pupil diameter in this light environment should be smaller than a square of the macula with cones which are reliably protected with the yellow spot [5].

J.P. Greenberg in his work measured a qAF auto-fluorescence quantitative parameter of the retina ground in a healthy patient with the use of the standardized approach [25]. His goal was to detect standard data and determine factors which can influence lipofuscin accumulation in pigment epithelium cells and/or simulate AF observed signal in the retina ground images. AF images were obtained in 277 healthy people (age ranging from 5 to 60 years) using Spectralis confocal scanning ophthalmoscope (cSLO, 488 nanometers excitation, 30^0) equipped with an internal fluorescent etalon. Average level of grey for each image was calculated as a mean of eight pre-set areas and was gauged as per etalon zero light, optical carriers magnification and density as per standard data on lens transmission spectra. He also estimated correlation between qAF and age, sex, race/ethnic group, eyes color, refraction/axial length, and smoking status; he also examined measurement repeatability and qAF spatial distribution. The research involved application of linear regression equations for mixed effects which allowed for inter-subject correlations between eyes (Stata, College Station, TX). After tasting various models, he obtained the best linear diagram with the following exponential model:

$$\log(\text{qAFs}) = B0 + B1\ \text{factor}_1 + \ldots. + Bn\ \text{factor}_n + \text{Bage} \log(\text{age}),$$

where factor_1 и factor_n were a combination of binary and contiguous factors. Binary factors in the model included sex, race, and ethnic group.

Calculations revealed that qAF levels grew substantially with age; grew with the eccentricity rising from 108 to 158; were higher in women; were substantially higher in whites than in Latin Americans; were lowers in Asian people and Negros than in Latin Americans. There were no relations between an eye axis length and smoking. The authors came to the conclusion that qAF standard levels were a reference tool neces-

sary for interpreting qAF measurements in case of eyes diseases.

The above-mentioned models are true for predicting A2E, eye lipofuscin component, which starts to accumulate in pigment epithelium cells from the first visual cycle and the first sight. If we want to predict further AMD evolvement, it is very important to know lipofuscin primary accumulation over the first five years of life while the protective yellow spot and the ciliary muscle are developing.

In Figure 3 we can see age groups of patients examined in 1978. Patients were divided into two groups as per color temperature of a light environment which they were born in and spent their first five years of life.

The first group comprised people who were born and spent their first 5 years in a light environment with color temperature equal to 2700K (a light source being an incandescent lamp with a small blue light dose).

The second group were people who were born in a light environment with color temperature being equal to 4000K–6000K (luminescent lamps with great blue light dose) and spent their first 5 years of life under luminescent and incandescent lamps.

Nowadays children are born in a light environment with color temperature being more than 4000K, and they spend their first 5 years of life with LED toys and LED visual display units. They all get increased blue light dose at early stages of their life, and, consequently, high accumulated lipofuscin level which causes risks of early AMD occurrence.

E. Kitchel and M. Ed give an overview of evolution stages in causes for increased risks of AMD occurrence and an excessive dose of blue light in the sunlight spectrum here is considered to be an indentified risk factor for cataract and AMD [18]. Thus, 838 boatmen in Chesapeake bay who spent most of their time under bright sunlight on the

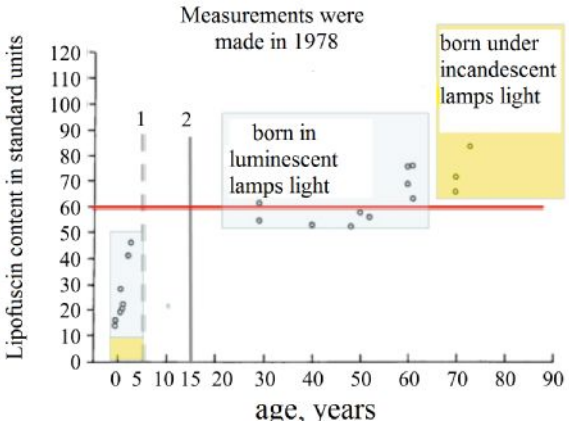


Figure 3. Lipofuscin content in overall RPE quantity depending on age [32]
(1: yellow spot develops by the age of 5, 2 is a moment when the ciliary muscle becomes fully developed).

water were examined, and scientists detected a significant correlation ($p = 0.05$) between their work during previous 20 years and grave cataract and yellow spot degradation. Patients suffering from AMD were much more susceptible to blue light than people from control groups but they were equally susceptible to ultraviolet radiation [13, 18].

Eye grounds were examined in 5,000 people aged from 43 to 84 and it allowed to detect a correlation between time spent outdoors (during age periods 13-19 years and 30 -39 years from 13 to 19 and from 30 to 39) and both early and "late" AMD occurrence [31].

To detect a correlation between blue light influence and wet AMD in patients with lower antioxidants level, researchers examined 4,753 people aged 65 and older (Figure 4). The eye retina was photographed in all the examined people. Participants were also asked how much time they usually spent under exposure to sunlight and gave their blood for antioxidant analysis. Blue light measuring was assessed via combination of meteorological data and questioning [26].

4,753 people aged 65 and older took part in the following research and data on

sunrays influence and antioxidants were available for 101 people with neovascular AMD among them and 218 with early AMD. The control group consisted of 2,117 people. Experts detected no correlations between blue light and neovascular or early AMD during the research. However, they detected a considerable dependence between blue light influence and a higher risk of wet AMD occurrence at low levels of vitamin C, zeaxanthin, and vitamin E, which were also related to early AMD stages with OR being about 1.4 or 40% [29]. Although it was impossible to detect causality between exposure to sunlight and neovascular AMD. Research results revealed that people in the general population should protect their eyes and follow the recommendations aimed at obtaining basic antioxidant nutrients.

Epidemiologists constantly argue over sunlight as a risk factor for yellow spot age-related degeneration. Meta-analysis of 14 integrated research revealed that experts came to a conclusion on a higher AMD risk under exposure to sunlight in 12 of them (OD 1.379). In six works researchers reported on significant risks but some experts consider they are not proven properly and not validated [17]. Some authors think that natural blue filtration loss after cataract surgery can be related to higher AMD prevalence [31]. All the above-said proves that experts create their models to predict

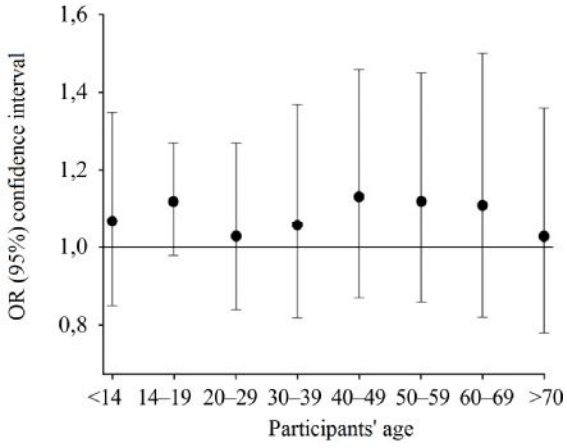


Figure 4. Odds ratio and confidence intervals of blue light exposure [29].

Characteristics of stages in age-related macular degeneration evolvement [12, 14, 18, 25, 32]

Parameter	Characteristics
Time stages in the process	The overall human lifecycle is divided into time stages as per criteria determined by AMD processes researchers
Stages particularity and sequence	Each stage is characterized with its particular amount of A2E accumulated amount. Accumulation rate is described with mathematical models on the basis of current time stage peculiarities
The process continuity	Results of the previous stage are the initial conditions for the next stage. A2E accumulation at a current stage is summed with A2E amount accumulated at the previous time stage

AMD evolvement at each stage of a person life cycle and also note what factors play significant role in the risk of its occurrence (table). Analysis of various models and AMD evolvement mechanisms allowed to reveal common methodological approaches to their design. Bearing hygienic science interests in mind (which hygienic measures are necessary for preventing negative trends in this or that process?), we can suggest a model which illustrates that AMD risks (with various gravity) occur at younger ages.

Given the determined target function of the hygienic approach, a mathematic model describing A2E stage accumulation for AMD prediction can be given as follows:

$$K_{\Sigma A2E} = \Sigma\,(A_i + B_i\,\Delta t_i),$$

where i – is a current stage number from the row: 1,2,3….n;

n – is a number of stages in a human lifecycle as per certain criteria (duration of being in a light environment of a maternity hospital, light environment at home, pre-school children facilities, school, educational establishments, working environment). From a hygienic point of view these criteria are: a) a time moment when protective elements in

the visual analyzer structure are fully formed which is related to age peculiarities (yellow spot and the muscle system of the accommodation apparatus are fully formed and functional); b) a time moment when age-related degradation processes occur;;

A_i – is A2E amount accumulated by a moment when i-stage starts; it is calculated as per the following formula

$$A_i = \Sigma\,(A_{i-1} + B_{i-1}\,\Delta t_{i-1});$$

Δt_{i-1} – is an i-stage duration;

B_i – is A2E accumulation rate at an i-stage.

A2E evolvement generates active oxygen forms under exposure to blue light. Antioxidant protection efficiency is especially important at this stage (yellow spot formation for retina macula protection and superoxide dismutase efficient synthesis under exposure to excessive active oxygen forms). Thus, J.M. McCord et al. explains in his work that cells with insufficient superoxide dismutase content are extremely sensitive to oxygen intoxication [30].

Given all the above-stated, we suggest a model for predicting AMD evolvement at younger ages under exposure to excessive blue light dose in a light spectrum. This dose increases nowadays due to mass LED lighting implementation and its negative impacts only grow as it is installed now in maternity hospitals, pres-school children facilities, schools, at workplaces, and in private houses. The generalized model is given in Figure 5.

Potential functional resources of human organs are at least two times greater than our usual 60-80 years. But when hygienic rules are violated a human body degrades considerably faster in the contemporary environment. The brain can function for 200 years; eyes, lungs, and heart, up to 140 years; liver, up to 120 years; kidneys, up to 130 years; muscles, up to 150 year [8].

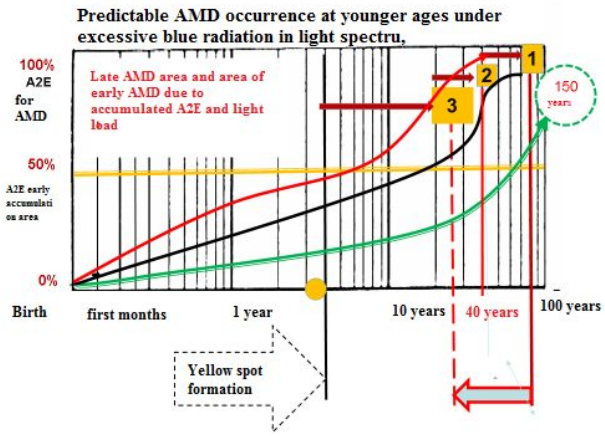


Figure 5. AMD occurrence rate.

A human body grows older because each its interaction with the environment causes a stress at this or that level. Stresses result in active oxygen forms which are to be compensated by antioxidant system.

Our model for A2E accumulation and predicting early AMD occurrence focuses on antioxidant system state as per its functional efficiency in a specific light environment. Mathematical models allowed for many influencing factors but they didn't contain calculations of antioxidant system state (superoxide dismutase and catalase) and its functional efficiency in a light environment created by artificial light sources with their spectra being different from the sunlight [12, 14, 18, 25, 32]. Let's expand on this point as it is important for getting better insight into AMD occurrence under LED light environment conditions.

Contemporary artificial lighting environment is created by lighting devices and visual display units. To detect regularities and crucial wave lengths (blue light doses) influencing the visual analyzed (A2E occurrence), we should consider overall spectra images of artificial light sources which create contemporary light environment (Figure 6).

As we can see from these graphs, all the contemporary artificial light sources have excessive radiation in blue light area (460 nanometers), a dip in blue-turquoise area (480 -

500 nanometers), as well as absence of light (380 nanometers), which participate in the visual cycle and rhodopsin production out of vitamin A.

Nowadays LED lighting is being implemented without any approval from ophthalmologists but it is even more alarming that lighting with the same spectra is used in visual display units and its "cyanotic" light influences faces and eyes of almost all children in Russia. And while chief Russian ophthalmologists are keeping their silence,

LED lighting producers claim that, as per SCHEER experts, low-intensity radiation levels are below a threshold of possible

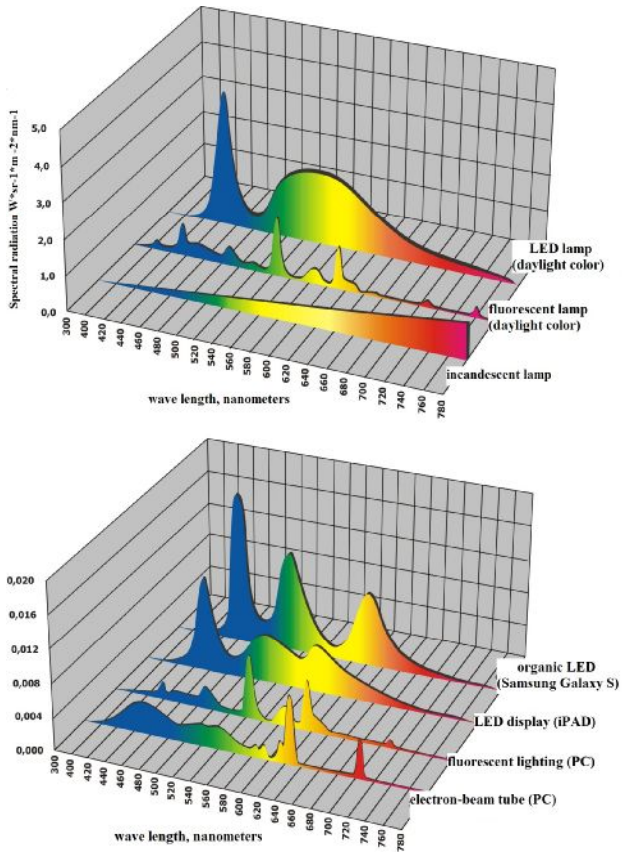


Figure 6. Overall light spectra images of various light devices.

damage to the retina which is determined as per Icnirp Guidelines: On limits of exposure to laser radiation of wavelengths between 180 nm and 1,000 μm [2] and Icnirp Statement: On Light-Emitting Diodes (Leds) And Laser Diodes: Implications For Hazard Assessment[3].

Nowadays Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) has published a preliminary report " Potential risks to human health of Light Emitting Diodes (LEDs)" dated July 6, 2017[4]. The section 6.5. "Basics of eye optics" contains the following conclusion: "Despite we don't have any reliable data for assessing risks to life safety when LED light sources are applied we can still be preoccupied with potential negative consequences caused by LED emissions especially in case of a susceptible population who already have early signs of the macula pathologic ageing. However, we should highlight that these problems arise due to the results obtained in experiments on animals or cells cultures models during which experts applied higher exposure levels than those which can possibly occur when LED light sources are used in everyday life. Impacts exerted by optical radiation coming from white LEDs can cause serious damage to the outer retina under high exposure levels. Spectral power distribution (SPD) and irradiation are risk factors which contribute into photochemical damage to the retina. To prevent this damage or to at least decrease it, one should use lower blue components for indoor lighting". The section 6.5.2.3 of the report titled "An eye posterior segment" contains the following experts' opinion: *"A spectrum emitted by white LEDs has photons with energies which are higher than the enzymes threshold which*

[2] Icnirp Guidelines: On limits of exposure to laser radiation of wavelengths between 180 nm and 1,000 μm. *Health Physics*, 2013, Vol. 105, no. 3, pp. 271–295.

[3] Icnirp Statement: On Light-Emitting Diodes (Leds) And Laser Diodes: Implications For Hazard Assessment. *Health Physics*, 2000, vol. 78, no. 6, pp.744–752.

[4] Potential risks to human health of Light Emitting Diodes (LEDs): Preliminary Opinion. *Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)*. 6 July 2017. Available at: https://ec.europa.eu/health/scientific_committees (10.09.2017).

protect from stress"[5].

Professor John Marshall in his new book "The Blue Light Paradox: Problem or Panacea", notes that:

- low-level long-term LED lighting (hours, days or months) causes damages to the retina;
- blue-violet light is more dangerous than other wave lengths;
- LEDs have high spectral peaks in blue range at levels which can exert cumulative impacts during human life;
- retina phototoxicity was shown in several research on wave lengths with high energy, blue-violet light, up to 455 nanometers [22].

Artificial light sources do exert malign impacts on the visual analyzer and it is clearly shown by new ophthalmologists' research on assessing myopia evolvement rate in countries where energy-saving lighting sources and computer technologies are implemented everywhere. Research performed in South Korea where compact luminescent and LED lamps are used everywhere had awful results: 96.5% of all the 19-year old men of call-up age suffered from myopia [24]. And it is only one step from myopia to early AMD occurrence as both these diseases evolve under low-intensive light. If light intensity doesn't do any damage to the retina, then "cyanotic" light spectrum can cause lower efficiency of the visual analyzer antioxidant protection.

Several researchers revealed that low-temperature 4,000K LED light is equal to 6,500K sunlight as per blue light dose [7]. Visual display units with 7,000K LED lighting are equal to 1,000K sunlight as per blue light. M.A. Ostrovskiy, the Russian Academy of Sciences Member (N.M. Emmanuel's RAS Biochemical Physics Institute) describes these processes as an eye-sight photobiological paradox which is that light carries visual information and is simultaneously a risk factor [6].

A combination of light and oxygen is a necessary condition for normal photoreceptor process functioning. But at the same time these are classic conditions, necessary and sufficient for occurrence and evolvement of destructive photochemical reactions in eyes structures as per free radical oxidation mechanism.

In M.A. Ostrovskiy's opinion, it is correct to spot out two functional eye systems: photoreception itself and protection from photo-damage danger. Focusing on an eye-sight photobiological paradox, we should point out that retinal is a key section in both photoreception and light damaging mechanisms. the visual cycle shown in Figure 7 underlies visual processes.

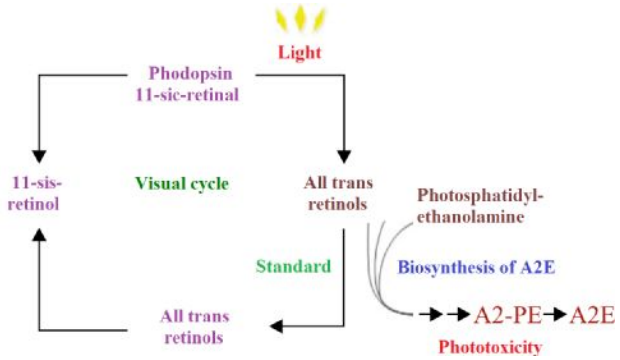


Figure 7. Visual cycle and photopathy danger

The visual cycle completely removes trans-retinal out of the photoreceptor membrane and then returns it back there but in 11-sic isomer form (Figure 7). Only this isomer is able to penetrate the chromophore center in a molecule protein section (opsin) and again create a covalent chemical bond with 296-lysine amino-acid residue in its seventh α-helix. All the above-said explains how rhodopsin regenerates, that is, returns

[5] Potential risks to human health of Light Emitting Diodes (LEDs): Preliminary Opinion. *Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)*. 6 July 2017. Available at: https://ec.europa.eu/health/scientific_committees/scheer/opinions_en#fragment1 (10.09.2017).

into its initial dark state with maximum optical photons absorption at a wave length equal to 500 nanometers and other lengths in the blue-turquoise spectrum part. Photon flux has a dip (minimal value at 500 nanometers) in this wave lengths range in case of LED light in comparison with the sunlight. Rhodopsin regeneration cycle is one of the key events in the retina dark adaptation process [6].

P.P Zak together with M.A. Ostrovskiy note that "Visual cycle results in so called A2E-phosphatidylethanolamine (A2EPE) formation in the membrane. Apparently, it is phototoxic by itself, but what is more important, it is just a predecessor of the next extremely toxic compound, namely pyridinium bisretinoid or A2E for short" [4]. Under exposure to blue light (<455 nanometers) this phototoxic compound, A2E, generates active oxygen forms. Phototoxicity mechanisms and a significant role which blue light plays in them are described in depths in M.A, Ostrovskiy's works.

The retina is a medium with great oxygen strain close to 70 mm Hg [11], and it creates perfect conditions for ROS oxidative stress evolvement (damage done to a cell due to oxidation). A spectrum (blue/turquoise balance) starts up the visual cycle during which rhodopsin decays and recovers with certain efficiency and A2E phototoxic compound occurs as a phosphor of lipofuscin granules which accumulate in pigment epithelium tissue culture. Under exposure to blue light and having reached certain concentrations, A2E is able to, on the one hand, develop detergent properties when it, for example, damages the outer mitochondrial membranes and activates cells apoptosis, and, on the other hand, to act as a photosensitizer of cell free-radical damage which can also led to its apoptosis. This paradox of light being both an information carrier and a potentially dangerous damaging factor, was solved as a sufficiently reliable multi-level system which protects against photopathy was created in the process of evolution. This system includes:

- ♦ photoreceptor membranes renewal;
- ♦ a set of endogenous antioxidants;
- ♦ a mechanism for the promptest free retinal removal out of a visual cell;
- ♦ eye optical filters system with a key role in it belonging to the lens which yellows with age in human and primates' eyes.

The next protection line is antioxidant. It includes vitamins E (α-tocopherol) and C (ascorbic acid), taurine, several antioxidant enzymes (superoxide dismutase, catalase, and peroxidase). Eye shielding pigments, or melanosomas, enhance this effect. A melanosoma is an organelle which consists of melanin and other light-absorbing pigments.

Superoxide dismutase transforms active oxygen forms into hydrogen peroxide and then catalase transforms it into water. Undoubtedly, any disorders in the system "light spectrum - rhodopsin - antioxidant system" cause increased risks of light damage to the retina and pigment epithelium. SCHEER reports, section 6.5.2.3 "Posterior eye segment" contains experts' opinion that "a spectrum emitted by white LEDs has photons with energies higher than enzymatic threshold which protects from stress"[6]. We can also find a comprehensive analysis there which dwells on potential risks caused by white LEDs allowing for pre-clinic knowledge as well as epidemiologic research and reports by the French Agency for Preventing potential hazards for the retina via three systems [21]:

1) non-enzymatic molecules such as thiols, vitamins (E and C), carotinoids (vitamin

[6] Potential risks to human health of Light Emitting Diodes (LEDs): Preliminary Opinion. *Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)*. 6 July 2017. Available at: https://ec.europa.eu/health/scientific_committees/scheer/opinions_en#fragment1 (10.09.2017).

A);

2) metals ions absorbers;

3) specific enzymes such as superoxide dismutase (SOD) and catalase.

Superoxide dismutase (SOD) molecules can be found in all living cells exposed to oxygen-containing environment including epithelial retina cells (retinal pigment epithelium or RPE). Pigment epithelium in the human retina contains two different superoxide dismutase types [24]. Both CuZn- and Mn-containing SOD play their own role and can contribute greatly into removal of superoxide radicals which evolve in mitochondrias as an oxygen metabolism by-product [23].

1. Cytoplasmic (or cytosolic) superoxide dismutase (or SOD-1). It functions inside cells. A gene which is responsible for cytoplasmatic superoxide dismutase synthesis is located in the 21st chromosome, in 21q22.1 locus.

2. Mitochondrial superoxide dismutase (SOD-2). It is located in the mitochondrial matrix. A gene responsible for its synthesizing and functioning is in the 6th chromosome, 6q25.3 locus.

3. Extracellular superoxide dismutase (SOD-3). It can be found in the intercellular substance; a gene responsible for its synthesis and functioning is located in the 4th chromosome, 4p15.3-p15.1 locus.

Superoxide dismutases keep steady-state concentration of superoxide radicals at a certain level thus protecting cellular structures from their hazardous impacts. SOD-1 is in cytoplasm, SOD-2, in mitochondrias, and SOD-3 is an extracellular (intercellular) type. The first type is dimeric, while the two others are tetrameric (consisting of 4 equal sub-units). SOD-1 and SOD-2 contain copper in their active center and zinc as their structural component, while SOD-2 contains manganese in its active center. Genes responsible for these types are located correspondingly in the chromosomes 21, 6 and 4 (21q22.1, 6q25.3 and 4p15.3-p15.1). Cytoplasmic SOD-1 is a small protein with molecular weight 32.5 kDa, but molecular weight of mitochondrial SOD-2 is about 86–88 kDa. Extracellular SOD is the greatest superoxide dismutase, its molecular weight being 135 kDa.

As Hassan and Fridovich detected in 1977, enhanced superoxide dismutase synthesis occurred under increased facultative organisms exposure to oxygen when there was excessive peroxide radicals evolvement inside a cell. Intracellular superoxide dismutase concentration correlates with a cell resistance to oxygen intoxication [15].

A reaction catalyzed by SOD consists of two stages and involves transfer of an electron from one superoxide radical to another. A copper atom located in the SOD active center is an intermediate acceptor for this electron:

$$\text{СОД-Cu}^{2+} + \text{HO}^{*} \Rightarrow \text{СОД-Cu}^{+} + \text{O}_2$$

$$\text{СОД-Cu}^{+} + \text{HO}^{2*} \Rightarrow \text{СОД-Cu}^{2+} + \text{H}_2\text{O}_2.$$

Hydrogen peroxide (H_2O_2) is a basic source of the most toxic radicals in living systems, namely HO radicals. So, decrease in H_2O_2 will lead to lower HO radicals concentrations. H_2O_2, is removed by two enzymes: catalase and peroxidase.

Catalase enzyme cycle consists of the following stages:

$$\text{Cat-Fe}^{3+} + \text{H}_2\text{O}_2 \Rightarrow \text{Cat-Fe}^{5+} + 2\text{H}_2\text{O}$$

$$\text{Cat-Fe}^{5+} + \text{H}_2\text{O}_2 \Rightarrow \text{Cat-Fe}^{3+} + \text{O}_2.$$

Experts from the Institute for Biophysics and Cellular Engineering of the Belarus National Academy of Science assessed influence exerted by blue light on superoxide dismutase (SOD) activity and revealed that this activity aimed at active oxygen forms compensating in cells was significantly inhibited by it [3].

Figure 8 shows ranked results of the research. These data prove that photom flux in blue light range (450-465nm) exerts significant influence on (SOD) activity aimed at active oxygen forms neutralization. Superoxide dismutase (SOD) activity grows drastically under irradiation by light coming from a spectrally managed LED lamp with

blue+light blue (465-485nm) + yellow+red LEDs in its structure. As color temperature grows, superoxide dismutase (SOD) activity decreases.

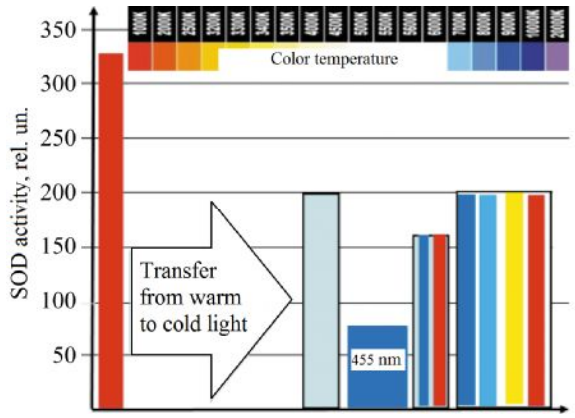


Figure 8. Changes in overall SOD activity in an organic object under lighting:
red LED 630nm-650nm; white light from luminescent lamp Philips TL-D36W/765 (6200K); blue LED 450nm-465nm; blue + red LEDs; blue + light blue (465nm-485nm) + yellow (590nm-595nm) + red LEDs.

Experiments made on laboratory animals are also interesting. Thus they revealed that if mice had SOD-2 deficiency, A2E level and lipofuscin accumulated in their RPE were high [28]. Some experts think SOD-2 is likely to play a positive role in early AMD prevention as it protects a mouse pigment epithelium from apoptosis caused by oxidation [27].

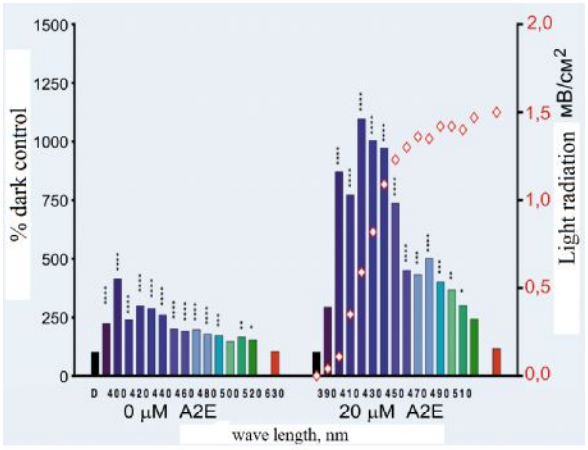
On May 1-5, 2016 at ARVO annual meeting in Seattle, Washington, there was a report entitled "Blue light decreases oxidative stress defenses in an in vitro model of AMD" [10]. Experts applied a specially designed lighting system which provided 10 nm wide lighting ranges in a blue-green range; they revealed that a narrow 415-455 nm range was the most toxic for EE-loaded RPE cells and was a sign of high oxidative stress (damage to a cell caused by oxidation). To get further insight into mechanisms related to this phototoxicity, experts then examined photomodulation of basic oxidative stress protections in the blue-green range of the visible spectrum. Light irradiation was standardized as per natural sunlight (6500K) which reached the retina after it had been filtrated by ocular structures (E_{max} <1.5 mW / cm ²).

When this AMD model was applied in vitro, it was detected that antioxidant protection deteriorated after exposure to blue light and it could make for concomitant increase in active oxygen forms quantity. These results prove that blue light can act as ROS inductor and ROS elimination process inhibitor which will result in greater oxidative stress and, consequently, cells death. These results give better knowledge needed for preventing oxidative stress caused by blue light during retina photo-adjustment and AMD.

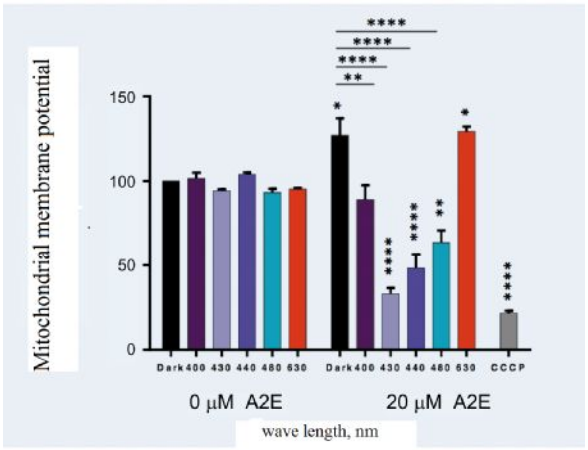
Figure 9 (a, b, c, d, and e) shows generalized results of influence exerted by blue light on:

- hydrogen peroxide from A2E concentration;
- mitochondria potential;
- superoxide dismutase (SOD-2);
- catalase;
- glutathione peroxidase 1, also known as GPX1.

Glutathione peroxidase functions at hydrogen peroxide detoxification and is one of the most important human antioxidant enzymes; it is expressed everywhere in many tissues where it protects cells from oxidative stress. It is located inside cells, in cytoplasm and mitochondrias and catalyzes reduction of other organic hydroperoxides such as lipid peroxides, to corresponding spirits. GPX1 usually uses glutathione (GSH) as a reducing agent, but glutathione synthetase (GSS), just as in cerebral mitochondrias, can also act as a reducing agent instead of γ-glutamylcysteine. A protein coded by this gene protects from CD95-inducted apoptosis in cultivated breast cancer cells and inhibits 5-lipoxygenase in blood cells, and its



a



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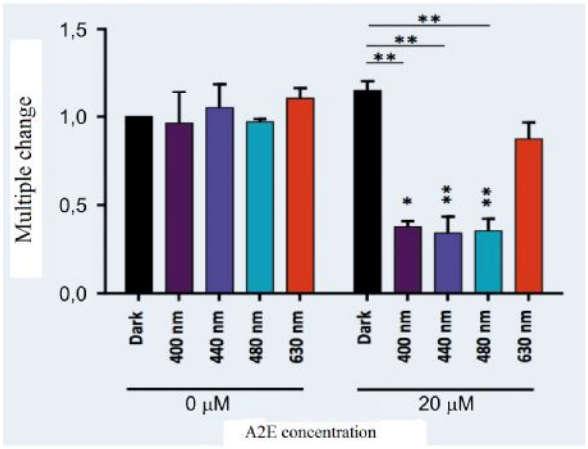
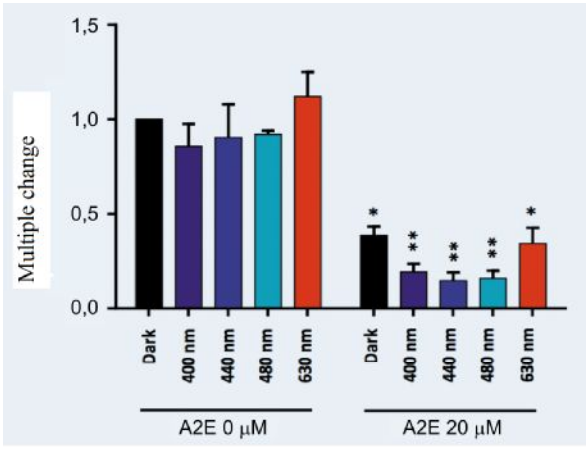
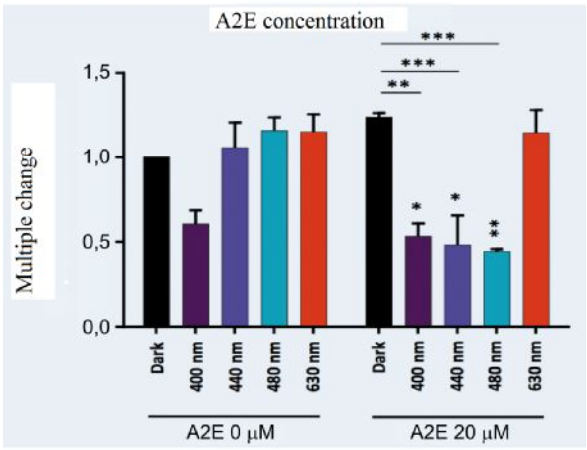


c



d



e

Figure 9 (a, b, c, d, and e). Influence exerted by blue light on hydrogen peroxide from A2E concentration; mitochondrial potential; superoxide dismutase (SOD-2); catalase; glutathione peroxidase 1: *a* – high hydrogen peroxide content was detected in blue-violet spectrum after 15-hour irradiation with A2E presence in comparison with dark control and red lighting, especially between 415-455 nm (average ± s.e.m, n = 4); *b* – mitochondrial membrane potential decerased significantly after blue-violet light impacts at 440 nm in cells loaded with A2E (average ± s.e.m, n = 3); *c* – Low SOD-2 antioxidant protection expression СОД-2; *d* – catalase; *e* – glutathione peroxidase-1

excessive expression postpones endothelial cells death and increases resistance to toxic problems, especially oxidative stress.

Lower SOD-2 mRNA, catalase, and GPX1 expression was observed after 15-hour exposure to blue light in cells loaded with A2E in comparison with untreated control elements or cells loaded with A2E which were exposed to red light (average ± s.e.m, n = 3).

Peri-nuclear clustering and globular forms were observed in mitochondrias of cells irradiated with blue-violet light (430-400nm) and their membrane potential became significantly lower in RPE cells falling down to nearly mitochondrial dysfunction. Low expression of basic antioxidant enzymes was detected after exposure to blue light at A2E presence, and high hydrogen peroxide content was detected in cells exposed to blue light between 415 and 455 nm, and it allows to consider blue light an indentified AMD risk factor.

O.V. Basharina states in her work that impacts exerted by ultraviolet light (240-390 nm) in specific doses (4.5-15.1) * 10^2 J/m2 at pH 6.3, (1,.5-45,.3) * 10^2 J/m2 at pH 9.0 and (l.5-i-22, 6) *10^2 J/m2 at pH 11.5) cause higher superoxide dismutase activity. greater ultraviolet light doses induce the enzyme inactivation [1].

Analysis of all the above-mentioned data proves that antioxidant protection (superoxide dismutase) reaches its maximum efficiency under certain light doses and when this level is exceeded, metal-containing protective enzymes become inactive.

So, spectral structure of the environment adults and children live in can have significant influence on early AMD occurrence risks and other eye diseases risks.

Excessive blue light dose is a difference between doses under LED lighting against hygienically safe sunlight at a preset lighting level. Given all the detected drawbacks in white LEDs (a blue crystal covered with yellow phosphor) and their negative influence on the human visual analyzer [7], no wonder, that Russian experts have already designed a concept of semi-conductor white light sources with a biologically adequate radiation spectrum.

A biologically adequate light spectrum is a set of photon fluxes which form a controlling signals matrix providing harmonized functioning of the visual analyzer cells, human hormonal system, and normal brain functioning.

Biologically adequate lighting environment is an environment created by semiconductor white light sources with a biologically adequate light spectrum aimed at minimizing human health risks at all the stages in his or her life cycle. This definition is created on the basis of all the above-stated and working experience in formulating scientific grounds for the design of semi-conductor white light sources with biologically adequate light spectrum. As experts from "ELTAN" Ltd worked on a project " Development of an industrial technology for manufacturing energy-efficient LED white light sources with biologically adequate radiation spectrum", they synthesized a white light spectrum without any peaks within 460nm range and dips within 480 nm range. Figure 10 shows a measured spectrum of the designed lamp.

This spectrum doesn't have any drawbacks detected in a standards white LED spectrum. The developed technology is protected by patents issued in Russia, Europe, Korea, the USA, and China, and it has made foreign LED manufactures to increase quality of light coming from their LEDs. And countries where teenagers myopia has the highest levels have reached certain success in synthesizing semi-conductor white light emitters with a spectrum which is equal to a spectrum of hygienically safe sunlight.

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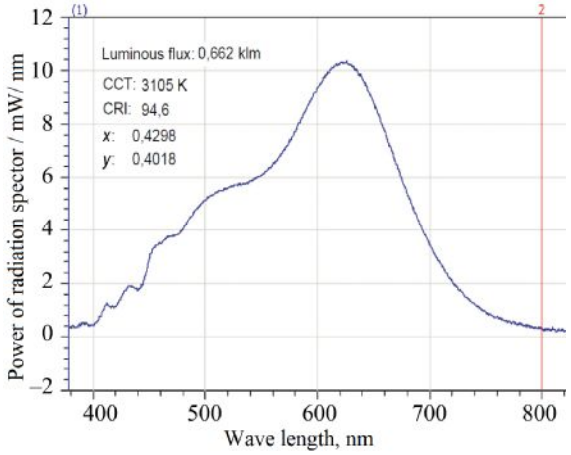

Figure 10. A light spectrum of a semiconductor source with biologically adequate white light spectrum -3105K, designed by "ELTAN" Ltd experts.

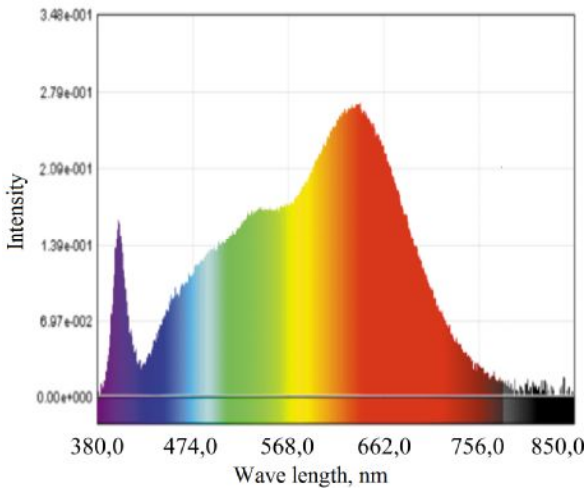

Figure 11. White light spectrum at 3000K emitted by a LED from Xenoled II range.

foreign LED manufactures to increase quality of light coming from their LEDs. And countries where teenagers myopia has the highest levels have reached certain success in synthesizing semi-conductor white light emitters with a spectrum which is equal to a spectrum of hygienically safe sunlight. LEDs belonging to the second generation and developed in Japan and Korea (with blue light dips and peaks in their spectrum not exceeding parameters of hygienically safe sunlight) are now penetrating European light techniques market. EuroLighting GmbH (Germany) increases its activities in selling ALLIX LEDs manufactured in Korea. White LEDs with sunlight spectrum are protected with patents in Europe, Korea, the USA, and China. This new LED is available in two ranges: Xenoled I and Xenoled II. The difference between them is that Xenoled I has a blue chip as its base but LEDs from Xenoled II range employ a crystal which emits violet light and phosphors of many colors. These SMD LEDs have high CRI up to 98, and there are no blue peaks in their spectrum within 450nm-460nm and dips within 480nm range (Figure 11).

A peak occurrence in the spectrum of the LEDs from Xenoled II range requires providing additional constructional protection in the LED lamp. But all in all LEDs from this range emit almost sunlight and blue peaks hazard is significantly reduced in them. Semi-conductor light sources which emit white light with a biologically adequate spectrum can be applied as light sources creating healthy lighting environment for children and adults provided that they are given relevant hygienic certificates with ophthalmologists participating in the procedure.

Conclusions: 1. To make advance predictions for early AMD occurrence risks it is advisable to create mathematical models aimed at assessing safety of new artificial light sources which are to be installed in educational and medical facilities. 2. Existing mathematical models for predicting A2E eye lipofuscin level don't allow for impacts exerted by blue light on antioxidant protection efficiency and color temperature of the lighting environment starting from birth and over the first 5 years of life. 3. We should allow for peculiarities and a period of being in a lighting environment with various artificial sources which differ as per spectra and color temperature when we create a set of prevention activities for people from different age groups. 4. Mass implementation of LED

lighting and visual display units with lighting having excessive blue light dose with peaks within 450nm-460nm range and dips within 480nm range will lead to greater risks of AMD occurrence by the age of 30-40 years already, and it in its turn will cause greater expenses of state budgets in the nearest future due to population disability related to eye diseases and eyesight loss.

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Received: 31.08.2017
Accepted: 15.12.2017
Published: 30.12.2017