Radioprotection 2019, 54(2), 141–147

https://doi.org/10.1051/radiopro/2019013

Available online at:
www.radioprotection.org

ARTICLE

Blue light hazard: does rat retina make relevant model for discussing exposure limit values applicable to humans?

S. Point* and M. Beroud

Emergency Lighting Design and Qualification Department, Cooper Sécurité SAS, rue Beethoven, BP 10184, 63204 Riom Cedex, France.

Received: 15 January 2019 / Accepted: 17 April 2019

Abstract – Recent scientific papers have drawn attention to potential blue light hazard associated with the use of LED lighting and the validity of exposure limit values of safety norms has been called into question. But can data coming from rat model experiments be extrapolated to human? This article provides some basic recommendations regarding rat retinal irradiance calculations and its potential extrapolation to human.

Keywords: blue light / LED / retina / exposure limit values

1 Context

In 1976, Ham, Mueller and Sliney demonstrated the possibility of photochemical injury to monkey retina under the action of a strong blue light applied during a relatively short time (from a few seconds to a few hours) (Ham *et al.*, 1976). This so-called Ham class damage (or class 2 damage) is characterized by the destruction of photoreceptors and of retinal pigmented epithelium under brief but strong retinal illumination (>10 mW/cm^2) (Youssef *et al.*, 2011). The action spectrum of such a damage, specific and greatest in the blue part of visible spectrum, is noted B(λ). Today, artificial light sources can be evaluated against this blue light hazard with protocols defined in an international standard (IEC, 2006). The evaluation protocol is based on 3 key elements:

- an action spectrum B(λ), (Fig. 1), which peaks at a 440 nm wavelength and describes the efficacy with which short visible wavelengths can produce photic injury on human retina;
- a maximum radiance dose of 1 million J/m^2/sr, that can also be expressed in term of radiant exposure. For example, for a human pupil of 3 mm diameter, the limit expressed in term of radiant exposure is 2.2 J/cm^2 (note that this value benefits from a safety factor of 5 by comparison to the value of radiant exposure for which damage can occur on human retina). From that maximal radiance dose, a maximal blue light effective radiance and a corresponding maximum exposure time can be derived;
- a risk group classification, built on maximal blue light effective radiance and maximal exposure time. Blue light effective radiance (noted L_b), measured on a lamp through a time-dependent field of view, must be compared to maximal blue-light effective radiance (noted L_{bmax}), which allows an association of the lamp under test with a maximum exposure duration and a risk group (Tab. 1).

Several standards dealing with design of lamps or luminaires (CENELEC, 2015; TSE, 2016) ask for an evaluation of LEDs against blue light hazard. For a summary of the measurement protocol, one can consult Point (2018). Evaluation of LEDs is justified by the fact that the peak of blue light emitted from LEDs is typically close to the maximum of the B(λ) action spectrum. However, not all LEDs pose the same risk regarding blue light hazard: risk assessment strongly depends on the intensity of the blue peak which can be modulated by the power of the source, by changing the correlated color temperature, or by the use of a frosted bulb. Moreover, applicable standards for self-ballasted LEDs (TSE, 2016), which define safety design requirements for LED bulb lamps available in mass market, only permit risk groups up to and including risk group 1, *i.e.* lamps that could expose an excess of the maximal radiance dose after minutes or hours of fixed observation at relatively short distance. For example, for luminaires like projectors or emergency lighting devices, risk group 2 is authorized but manufacturers and installers should respectively provide and respect an installation distance between lamp and position of potential observer to ensure the risk is decreased, by distance, to risk group 1. Thanks to these normative requirements, risk of acute exposure of users seems to be reasonably excluded, except in case of misuse of light technologies (Point and Lambrozo, 2017).

2 Questions

In 1990, Van Norren and Schellekens (1990) demonstrated that rats were also susceptible to class 2 damage. Thus, it is possible to study the mechanisms of class 2 photochemical injury through experiments on rodent model, and many studies

*Corresponding author: sebastienpoint@eaton.com

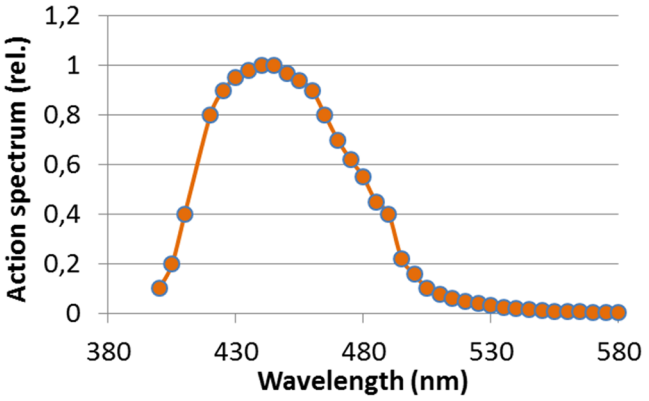

Fig. 1. B(λ) action spectrum.

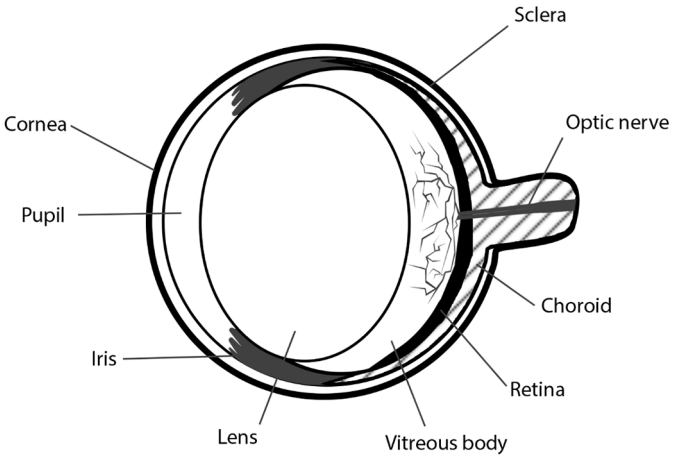

Fig. 2. Rat eye schematic view.

Table 1. Risk group classification.

Risk Group	RG0	RG1	RG2	RG3
Maximal exposure duration (s)	10 000	100	0.25	< 0.25
Maximal blue light effective radiance ($w.m^{-2}/sr$)	< 100	< 10 000	< 4 000 000	> 4 000 000

have been based on it. Despite the fact that normative requirements seem to have correctly protected general population from acute exposure to LEDs, in recent years, some concerns have been raised within public and in scientific community, because deleterious effects of light from white LEDs were demonstrated on rat retina, at low, domestic light levels (Shang *et al.*, 2013, 2017; Jaadane *et al.*, 2015, 2017; Krigel *et al.*, 2016). Subsequently, following some of these studies, authors asked, on the base of their results, for a reduction of the current limit of radiant exposure. However, discussions should be made based upon parameters used for radiant exposure calculations, in order to answer to the following questions:

– What are potential exposure calculation biases linked to the use of rat eye model, and are they under control?
– Are fundamental biometric differences between rat eye model and human eye model correctly taken into account?

This paper aims to answer the questions raised in the following discussion.

3 Discussion

3.1 What are potential exposure calculation biases linked to the use of rat eye model and are they under control?

On one hand, rats are inexpensive, easy-to-manage small animals that breed quickly and in quantity, are not aggressive and do not benefit from the same "sympathetic capital" with the public than other animals, which makes the ethical issues of experimentation less relevant. On the other hand, they are mammals; therefore, the biological mechanisms observed in these rodents are, in many cases, similar to observable biological mechanisms in humans. Regarding vision, the visual system of rat shares similarities to the system of human, and is composed of the eye, the optical nerve, the chiasma and the tract, the lateral geniculate body, the pretectal area, the superior colliculus and the visual cortex. These resemblances make them a convenient model for biological experiments regarding the biological effect of light on human.

A rat eye is, in a first approach, a 5.5 mm diameter ball (Fig. 2). The aqueous chamber is separated from the vitreous chamber by a large spherical posterior lens that occupies, in volume, two thirds of the intraocular cavity and is partially transparent to UVA radiation (Gorgels and Van Norren, 1992). The lack of well-developed ciliary muscle means that rats are not able to modify their lens shape and to accommodate. The determination of rat eye model is a full field of research (Lashley, 1932; Block, 1969; Massof and Chang, 1972; Hughes, 1979; Campbell and Hughes, 1981; Chaudhuri *et al.*, 1983; Remtulla and Hallett, 1985; Bawa *et al.*, 2013; Lozano and Twa, 2013) which is propitious to debate about lengths, curvatures and refractive index of different eye layers.

3.1.1 Rat eye focal length

To reach the retina, light has to travel through the different layers of the eye. Figure 3 shows a schematic representation of the eye, from a geometrical point of view, as a succession of diopters and homogeneous isotropic media. For paraxial light rays, the focal length for the eye depends on:

– the refractive index n_0 of exterior medium (air, water...);
– the thickness e_1 and refractive index n_1 of the cornea, as well as radius of curvature of anterior face R_1 and posterior face R_2;
– the thickness e_3 and refractive index n_3 of crystalline lens, as well as radius of curvature of anterior face R_3 and posterior face R_4;
– the anterior chamber length e_2;
– the aqueous and vitreous index n_2 and n_4.

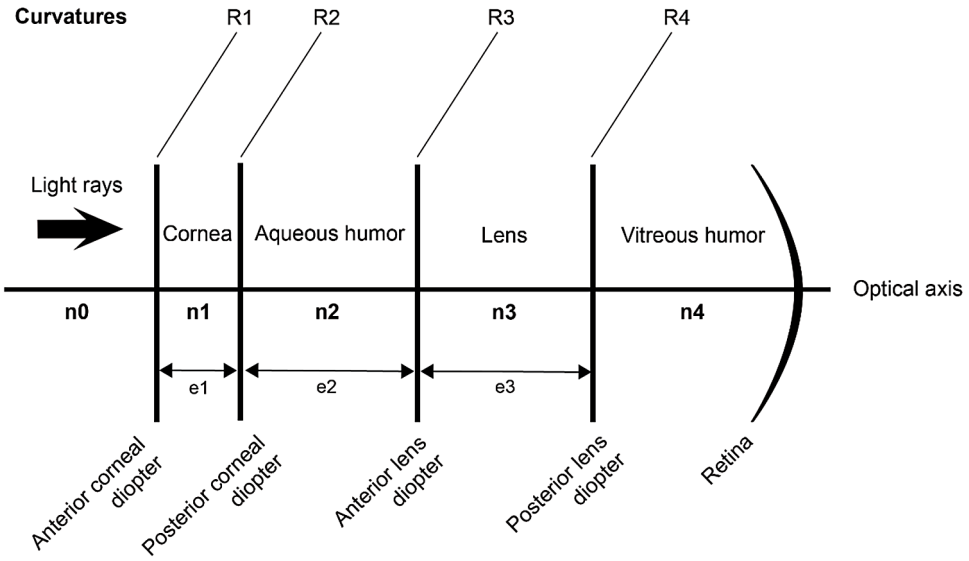

Fig. 3. Optical representation of the rat eye.

Table 2. Values of ocular parameters (used for focal length calculation) from different rat eye models.

Parameter	Thickness (mm)			Radius of curvature (mm)				Refractive index				Calculated focal length (this study)* (mm)
Author	Cornea e_1	Aqueous chamber e_2	Crystalline lens e_3	Anterior cornea R_1	Posterior cornea R_2	Anterior lens R_3	Posterior lens R_4	Cornea n_1	Aqueous n_2	Lens (Homogeneous model) n_3	Vitreous n_4	–
Block (1969) *Strain: Pigmented and albino rats*	0.25	0.88	2.80	2.75	2.50	1.85	1.72	1.38	1.34	1.61	1.34	3.498
Massof and Chang (1972) *Strain: Hooded rats*	0.25	0.87	3.87	2.78	2.53	1.11	1.42	1.374	1.344	1.433	1.347	6.660
Hughes (1979) *Strain: Dark Agouti rats*	0.260	0.621	3.710	2.965	2.705	2.340	2.340	1.380	1.337	1.683	1.337	5.748
Chaudhuri *et al.* (1983) *Strain: Long Evans rats*	0.156	0.708	3.814	3.051	2.959	2.535	2.441	1.3838	1.3346	1.6854	1.3349	5.726

*See calculation in Annexe A.

Table 2 reports values of refractive indexes, cornea and lens thicknesses and curvatures, anterior chamber lengths as reported successively by Block (1969), Massof and Chang (1972), Hughes (1979) and Chaudhuri *et al.* (1983) and finally our calculations of rat eye focal lengths created from this literature, where $n_0 = 1$ (air). Table 3 shows the variety of focal lengths as used in the literature dealing with rat retinal irradiance and blue light hazard.

3.1.2 Rat eye pupil size

Block (1969) reports that for rats, the maximal myosis under urethane anaesthesia and bright light is 0.2 mm. Same author mentions a range of normal values between 0.4 to 1.2 mm. This is in agreement with the pupil size that Sliney chose himself for his calculation (d = 0.5 mm).

In the case of atropinized eye, according to Block (1969), pupil size can reach 4.5 mm. This value is in good agreement with pupil size values of atropinized rat eyes measured by Van Norren and Schellekens (1990) and Van Norren and Gorgels (2011) (d = 5 mm). This last value has been used in calculations to model the retinal irradiance of eyes by Jaadane *et al.* (2015, 2017). Also, for possible values of rat pupil size, for non-anaesthetized animals, a range from 0.4 mm (under bright light) to 5 mm (atropinized eye) shall be considered.

Table 3. Values of focal length for rat eye model extracted from literature.

Studies	Used focal length (mm)
Jaadane *et al.* (2015)	2.4
Campbell and Hughes (1981)	4.5
Sliney (1984)	3.3 to 4.7
Gorgels and Van Norren (1992); Jaadane *et al.* (2015)	5.25

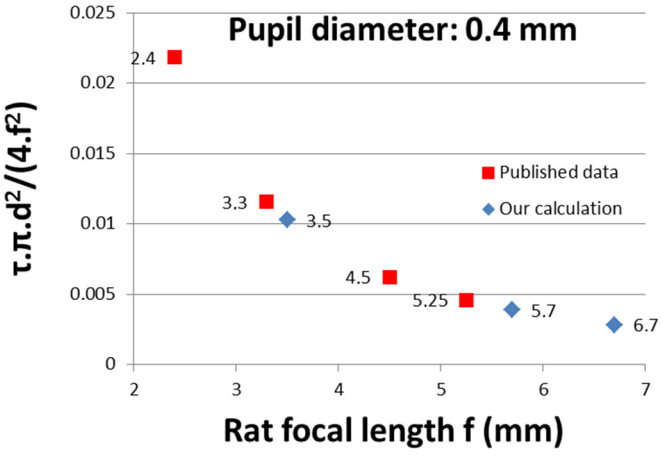

Fig. 4. Calculated values of $\tau.\pi.d^2/(4.f^2)$ for values of rat focal length in Tables 2 (our calculation) and 3 (published data) at a 0.4 mm rat pupil diameter.

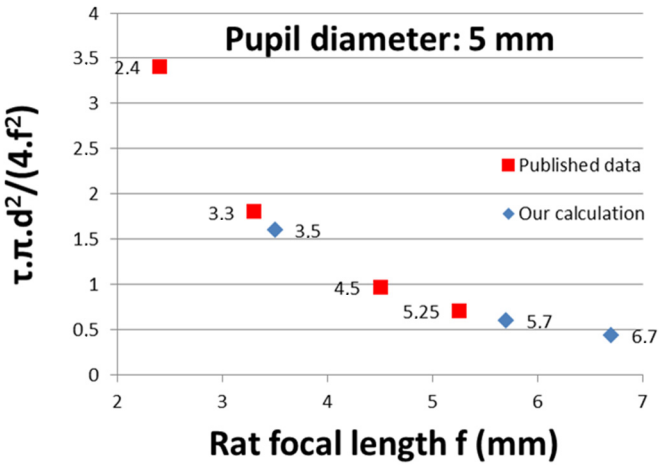

Fig. 5. Calculated values of $\tau.\pi.d^2/(4.f^2)$ for values of rat focal length in Tables 2 (our calculation) and 3 (published data) at a 5 mm rat pupil diameter.

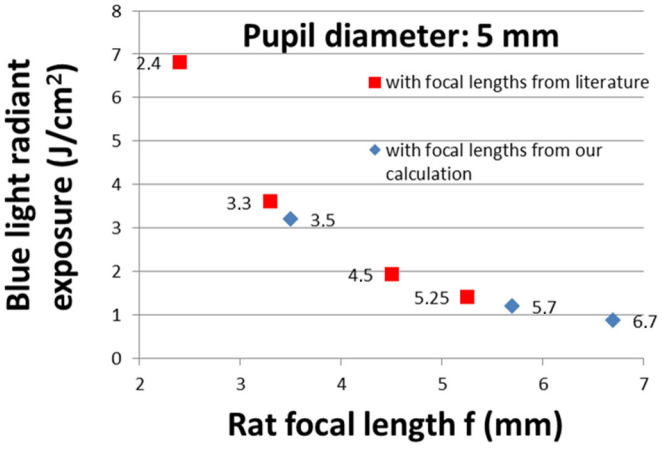

Fig. 6. Calculated values of radiant exposure for values of focal length in Tables 2 and 3 at a 5 mm rat pupil diameter for 20 000 s (≈5 h30 min) long exposure to an 8 W/m²/sr LED. Blue light exposure is the product of blue light irradiance by duration.

3.1.3 Effect of rat eye pupil size and focal length on exposure calculation

Equation (1) shows the relationship between source radiance *Ls* and retinal irradiance *Er*, for paraxial light. It must be noted that the ratio $\frac{Er}{Ls}$ is dependent on the ratio of squared pupil diameter d^2 and squared focal length f^2. What is the effect of possible values of $\frac{d^2}{f^2}$ on the calculation of $\frac{Er}{Ls}$? Figure 4 shows values of $\frac{Er}{Ls}$ ratio for values of rat focal length taken in Tables 2 and 3 in case of a 0.4 mm pupil diameter. Figure 5 shows values of the $\frac{Er}{Ls}$ ratio for values of rat focal length in Tables 2 and 3 and a 5 mm pupil diameter.

$$Er = \frac{\pi.Ls.t.d^2}{4f^2}[W.m^2], \quad (1)$$

where t is the eye transmission, d is the pupil diameter and f the eye focal length.

What is the consequence of possible variation of $\frac{Er}{Ls}$ on calculated radiant exposure? Figure 6 shows values of calculated exposure for 4 values of focal length at a 5 mm pupil size, in the case of a 20 000 s long exposure to a white LED used in former studies (Point and Lambrozo, 2017; Point, 2018) whose full radiance Le is 8 W/m²/sr and effective blue light radiance $L_b = 1$ W/m²/sr. The full spectrum and B (λ)-weighted spectrum of this LED is provided in Figure 7. Depending on the choice made for *d* and *f*, the calculated value of radiant exposure can be significantly above or below the currently accepted radiant exposure limit (2.2 J/cm²). If damages are observed after experiment on rat retina, depending on the choice of d and f used for exposure calculation, the experimenter will draw very different conclusions regarding the validity of the radiant exposure limit. As a consequence, it appears to be of primary importance, for every author using a rat model in studies on mechanisms of photic damage, to provide a discussion on the validity of the values of d and f chosen for calculation, to avoid assigning damage to wrong radiant exposure and drawing incorrect conclusions regarding the validity of the exposure limit value.

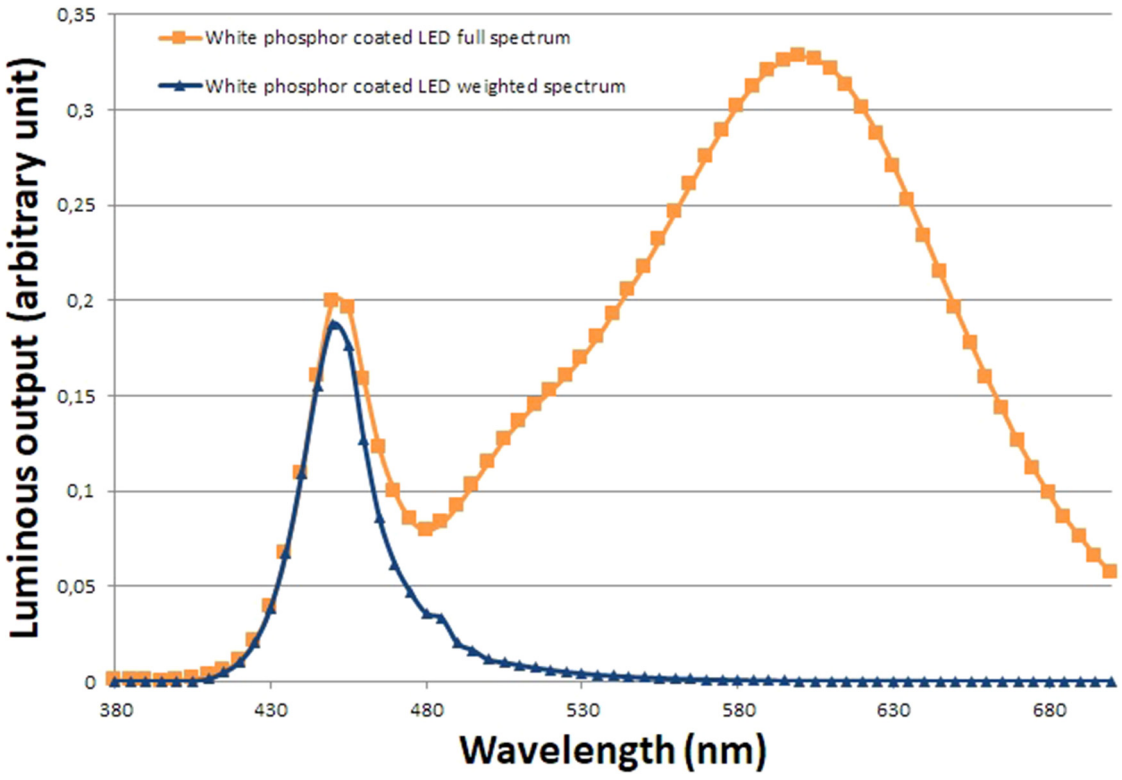

Fig. 7. Full spectrum and B-weighted spectrum of LED Xanlite evolution 5 W used in Point and Lambrozo (2017) and Point (2018).

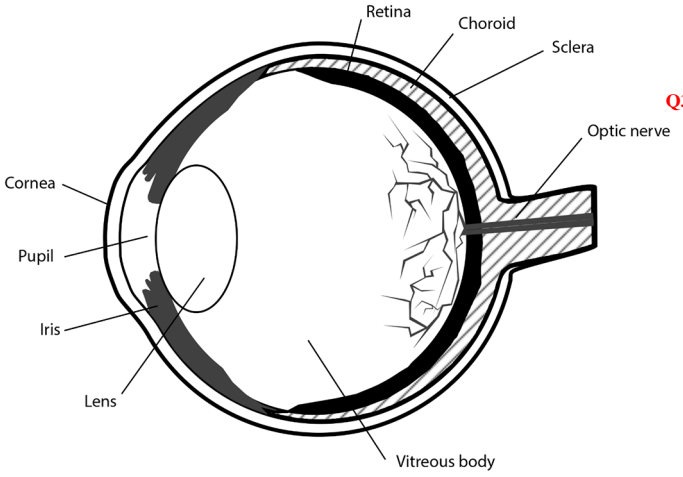

Fig. 8. Human eye schematic view.

3.2 Are fundamental biometric differences between rodent eye model and human eye model correctly taken into account?

A human eye is a 24 mm diameter ball with a small anterior biconvex lens, whose shape can be changed by contraction of ciliary muscles, what permits accommodation (Fig. 8). Natural maximal myosis allows for a 2 mm pupil size (under bright light), while natural maximal mydriasis allows for an 8 mm pupil size (in the dark) (Spector, 1990). In 1984, Sliney drew attention to significant biometric differences between species, that can affect the calculation of retinal irradiance (Sliney, 1984). Table 4 shows, for a given radiance, the ratio between human retinal irradiance (calculated with a 17 mm focal length and 3 mm pupil size as used by ICNIRP for expressing radiant exposure from radiance dose, ICNIRP, 2013) and rat retinal

Table 4. Relation between rat retinal irradiance and human retinal irradiance for a given radiance, depending on values chosen for d and f for rat model. For human: $d = 3$ mm; $f = 17$ mm.

	Rat focal length		
Rat pupil size	0.4 mm (extreme contraction under bright light)	2 mm (normal contraction under dim light)	5 mm (atropinized eye)
2.4 mm	$E_{rat} = 0.9.Er_{human}$	$E_{rat} = 22.Er_{human}$	$E_{rat} = 139.Er_{human}$
5.25 mm	$E_{rat} = 0.2.Er_{human}$	$E_{rat} = 5.Er_{human}$	$E_{rat} = 29.Er_{human}$

irradiance (calculated with some previously shown values of focal length and pupil size, as found in literature). A factor of several orders of magnitude can be seen for retinal irradiance between rat and human models, when calculated as a function of *d* and *f*. Here again, it is of primary importance that this fundamental biometric difference is taken into account before attempting to extrapolate to human results obtained by the rat model, and before arguing for a reduction of exposure limit value for humans on the basis of these results.

4 Conclusion

The main interest of using rats to study the effects of blue light from LEDs is their low price, easy management, and low ethical questionability. However, literature does not show a clear consensus regarding the eye biometry of rat model. This lack of consensus undermines the validity of exposure calculations, unless the choice of the values can be justified. If the choice of a focal length or pupil size cannot be justified, by consensus or by biological measurement of the tested sample, calculation of radiant exposure should be made utilizing the most extreme plausible values, to express the uncertainty of the calculated radiant exposure and avoid drawing incorrect conclusions. Otherwise, to increase the validity of their results and extrapolate on behalf of humans, experiments should be made on animal models with *d*/*f* ratio that is as close as possible to the d/f ratio of human.

Acknowledgement. Authors wish to sincerely thank Alex Dudman for English editing.

Conflicts of interest. The authors declare the following interests: Sébastien Point and Maïlys Beroud are employed by Cooper Sécurité SAS (electrical lighting manufacturer).

References

Bawa G, Tkatchenko TV, Avrutsky I, Tkatchenko AV. 2013. Variational analysis of the mouse and rat eye optical parameters. *Biomed. Opt. Express* 4(11): 2585–2595.

Block MT. 1969. A note on the refraction and image formation of the rat's eye. *Vis. Res.* 9(6): 705–711.

Campbell MC, Hughes A. 1981. An analytic, gradient index schematic lens and eye for the rat which predicts aberrations for finite pupils. *Vis. Res.* 21(7): 1129–1148.

CENELEC. 2015. *Luminaires – Part 1: General requirements and tests*. EN 60598–1.

Chaudhuri A, Hallett PE, Parker JA. 1983. Aspheric curvatures, refractive indices and chromatic aberration for the rat eye. *Vis. Res.* 23(12): 1351–1363.

Gorgels T, Van Norren D. 1992. Spectral transmittance of the rat lens. *Vis. Res.* 32(8): 1509–1512.

Ham WT, Mueller HA, Sliney D. 1976. Retinal sensitivity to damage from short wavelength light. *Nature* 260(5547): 153–155.

Hughes A. 1979. A schematic eye for the rat. *Vis. Res.* 19(5): 569–588.

ICNIRP Guidelines. 2013. On limits of exposure to incoherent visible and infrared radiation. *Health Phys*. 105(1): 74–96.

IEC 62471. 2006. *Photobiological safety of lamps and lamp systems*.

Jaadane I *et al*. 2015. Retinal damage induced by commercial light emitting diodes (LEDs). *Free Radic. Biol. Med*. 84: 373–384.

Jaadane I *et al*. 2017. Effects of white light-emitting diode (LED) exposure on retinal pigment epithelium in vivo. *J. Cell Mol. Med*. 21(12): 3453–3466.

Krigel A *et al*. 2016. Light-induced retinal damage using different light sources, protocols and rat strains reveals LED phototoxicity. *Neuroscience* 339: 296–307.

Lashley KS. 1932. The mechanism of vision. V. The structure and image-forming power of the rat's eye. *J. Comparat. Psychol.* 13 (2): 173–200.

Lozano DC, Twa MD. 2013. Development of a rat schematic eye from in vivo biometry and the correction of lateral magnification in SD-OCT imaging. *Invest. Ophthalmol. Vis. Sci*. 54(9): 6446–6455.

Massof RW, Chang FW. 1972. A revision of the rat schematic eye. *Vis. Res.* 12(5): 793–796.

Point S. 2018. Blue Light Hazard: Are exposure limit values protective enough for newborn infants? *Radioprotection* 53(3): 219–224.

Point S, Lambrozo J. 2017. Some evidences that white LEDs are toxic for human at domestic radiance? *Radioprotection* 52(4): 297–299.

Remtulla S, Hallett PE. 1985. A schematic eye for the mouse and comparisons with the rat. *Vis. Res*. 25(1): 21–32.

Shang YM *et al*. 2013. White Light-Emitting Diodes (LEDs) at domestic lighting levels and retinal injury in a rat model. *Environ. Health Perspect*. 122(3): 269–276.

Shang YM *et al*. 2017. Light-emitting-diode induced retinal damage and its wavelength dependency in vivo. *Int. J. Ophtalmol*. 10(2): 191–202.

Sliney D. 1984. Quantifying retinal irradiance levels in light damage experiments. *Curr. Eye Res.* 3(1): 175–179.

Spector RH. 1990. The pupils (Chapter 58). In: *Clinical Methods: The History, Physical, and Laboratory Examinations*. (3rd edition). Boston: Butterworths.

TSE. 2016. *Self-ballasted LED-lamps for general lighting services by voltage > 50 V – Safety specifications*. EN 62560/A1.

Van Norren D, Schellekens P. 1990. Blue light hazard in rat. *Vis. Res.* 30(10): 1517–1520.

Van Norren D, Gorgels TG. 2011. The action spectrum of photochemical damage to the retina: A review of monochromatic threshold data. *Photochem. Photobiol*. 87: 747–753.

Youssef PN *et al*. 2011. Retinal light toxicity. *Eye* 25(1): 1–14.

Annexe A. Detail of eye image focal length (f) calculation.

$f = n_4/Vo$

$Vo = Vc + Vcr - H'coHcr.Vc.Vcr$

$Vc = Vcaf + Vcpf - e_1.(Vcaf.Vcpf).n_1$

$Vcaf = (n_1 - n_0)/R_1$

$Vcpf = (n_2 - n_1)/R_2$

$Vcr = Vcraf + Vcrpf - e_{3.}(Vcraf.Vcrpf).n_3$

$Vcraf = (n_3 - n_2)/R_3$

$Vcrpf = (n_4 - n_3)/R_4$

$H'coHcr = -P_2H'co + e_2 - P_3Hcr$

$P_2H'co = -e_2.f'c/f'caf$

$f'c = n_2/Vc$

$f'caf = n_1/Vcaf$

$P_3Hcr = e_3.fcr/f'crpf$

$fcr = -n_3/Vcr$

$f'crpf = n_4/Vcrpf$

P_2 Vertices of corneal anterior face

P_3 Vertices of crystalline anterior face

Hcr Object principal point of crystalline lens

H'co Image principal point of cornea

Vo Vergence of the entire eye

Vc Vergence of the entire cornea

Vcr Vergence of the entire crystalline lens (homogenous model)

Vcaf Vergence of the corneal anterior face

Vcpf Vergence of the corneal posterior face

Vcraf Vergence of the crystalline lens anterior face

Vcrpf Vergence of the crystalline posterior face

f'c Image focal length of the cornea

f'caf Image focal length of the corneal anterior face

fcr Object focal length of crystalline lens

f'crpf Image focal length of crystalline lens posterior face

Cite this article as: Point S, Beroud M. 2019. Blue light hazard: does rat retina make relevant model for discussing exposure limit values applicable to humans? *Radioprotection* 54(2): 141–147