Of mice and women: Light as a circadian stimulus in breast cancer research

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Bullough, J.D., M.S. Rea, and M.G. Figueiro. 2006. Of mice and women: Light as a circadian stimulus in breast cancer research. *Cancer Causes and Control* 17(4):375-383.

DOI: 10.1007/s10552-005-0574-1

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(revised 3 November 2005)

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Abbreviated title: Of Mice and Women

Financial support: Preparation of this manuscript was supported by the Lighting Research Center and by the National Institute of Environmental Health Sciences grant ES11659.

*The title is a variation on the title of John Steinbeck's classic novel, *Of Mice and Men*.

Abstract

Objective: Nocturnal rodents are frequently used as models in human breast cancer research, but these species have very different visual and circadian systems and, therefore, very different responses to optical radiation or informally, light. Because of the impact of light on the circadian system and because recent evidence suggests that cancer risk might be related to circadian disruption, it is becoming increasingly clear that optical radiation must be properly characterized for both nocturnal rodents and diurnal humans to make significant progress in unraveling links between circadian disruption and breast cancer. In this paper, we propose a quantitative framework for comparing radiometric and photometric quantities in human and rodent studies.

Methods: We reviewed published research on light as a circadian stimulus for humans and rodents. Both suppression of nocturnal melatonin and phase shifting were examined as outcome measures for the circadian system.

Results: The data were used to develop quantitative comparisons regarding the absolute and spectral sensitivity for the circadian systems of humans and nocturnal rodents.

Conclusions: Two models of circadian phototransduction, for mouse and humans, have been published providing spectral sensitivities for these two species. Despite some methodological variations among the studies reviewed, the circadian systems of nocturnal rodents are approximately 10,000 times more sensitive to optical radiation than that of humans. Circadian effectiveness of different sources for both humans and nocturnal rodents are offered together with a scale relating their absolute sensitivities. Instruments calibrated in terms of conventional photometric units (e.g., lux) will not accurately characterize the circadian stimulus for either humans or rodents.

Key words: melatonin suppression, phase shifting, breast cancer, animal studies, lighting

Introduction

The incidence of breast cancer has continuously increased in modern industrialized society [1, 2] and is the most frequently diagnosed malignant disease in women of all ethnic groups in the United States and Northern Europe.

Many lines of research have been directed toward an understanding of this phenomenon (e.g., [3-7]). Hrushesky was perhaps the first to show a link between breast cancer prognosis and circadian regulation. In the mid 1980s he showed that the effectiveness of cancer treatment varies according to when, in terms of circadian time, the treatment is applied [8]; subsequent work continues to suggest an important role of circadian rhythms for cancer growth [9].

In the 1980s, Stevens [10] proposed that the high incidence of breast cancer in industrialized society was related to exposure to too much light* at night, which in turn suppressed nocturnal melatonin, a hormone produced at night and under conditions of darkness. According to his hypothesis, known as the melatonin hypothesis [12], suppression of melatonin allows estrogen levels to rise and stimulate the turnover of breast epithelial stem cells, increasing the risk of cancer development. The melatonin hypothesis stimulated various lines of research, from animal models to epidemiological studies with humans. Using nocturnal rodents as laboratory models for understanding the effects of melatonin suppression on cancer growth, Blask, Dauchy and their colleagues have clearly shown that reduction in nocturnal melatonin levels will increase the growth rate of several types of cancer, including human breast cancer [13, 14]. Furthermore, epidemiological studies suggest a possible link between nightshift work (a

*Light, like time and mass, is a fundamental quantity, but unlike all other fundamental quantities, is defined in terms of a specific *visual* response in *humans* [11]. As such it is technically incorrect to refer to *light* when referring to other organisms, or in relation to nonvisual (e.g., circadian) responses in humans. The term *optical radiation* is preferred to describe the portion of the electromagnetic spectrum spanning ultraviolet, visible and infrared radation. However, given the wide use of the term *light* to describe optical radiation in the biological and medical research community, the two terms are used interchangeably, albeit technically incorrectly, throughout this paper.

surrogate for light at night exposure to suppress melatonin) and cancer risk [15-18] as well as an association between cancer risk and circulating levels of melatonin [19].

More recently, researchers have been investigating the impact of circadian disruption, rather than simply nocturnal melatonin suppression, on the development and growth of cancer [20]. This evidence suggests, for example, that disruption of the circadian system plays an important role in the development and growth of breast cancer [21-24]. Since light is the primary regulator of the circadian clock, irregular light-dark patterns are now being considered as "endocrine disruptors", resulting in an increased risk for certain types of cancer [21, 22]. In general then, all of these studies support the inference that circadian regulation impacts cancer development, growth and treatment, and that the absence of a robust light-dark pattern may increase the risk of breast cancer in women.

Given these increasingly important links between light, circadian regulation and breast cancer, it becomes extremely important to continue systematic experimental programs both with humans and with animal models. Although often recognized, there is a nagging, if quiet, concern about using nocturnal rodents as a model for breast cancer in diurnal humans made even more acute in this context because light is the primary regulator, or disruptor, of circadian rhythms. Blask, Dauchy and their colleagues have looked at tumor growth in rats under different lighting scenarios [13, 14], suggesting that relatively small doses of light at night can reduce melatonin and thereby increase the rate of cancer growth in these animal models. Extrapolations are then made from these animal data and epidemiological studies about the impact of light on human breast cancer development [25]. Yet, there have been no direct comparisons of optical radiation as a stimulus for the circadian systems of rodents and humans. No doubt this is a result of the many complications arising from quantitative comparisons of the different stimuli and the variety

of measured responses used by researchers to deduce circadian functions in these different species.

The purpose of this paper is to offer a quantitative comparison of optical radiation as it affects the circadian systems of nocturnal rodents and as it affects diurnal humans. In doing so, it is hoped that a firmer foundation can be established for bridging studies of human breast cancer with studies of circadian disruption in humans and in animal models.

Brief Comparative Review

In this section, several studies of the effects of light on human and rodent circadian systems are summarized (identified through searching MEDLINE). Since both animal and human studies vary considerably in experimental procedures and the outcome measures employed, it is very difficult to precisely compare stimuli across species. Indeed, precise comparisons are impossible. Generally, the uncertainties associated with the comparisons made in this paper are large, no better than an order of magnitude (i.e., a factor of 10). As shown subsequently, however, the differences in the amount of optical radiation needed for stimulating the circadian systems of humans and for nocturnal rodents are so large that the uncertainties associated with the comparisons become relatively small. As will be discussed, the circadian systems of nocturnal rodents are about 3 to 4 orders of magnitude more sensitive to optical radiation than that of humans.

The comparisons among species offered here would have been ideally based upon studies following a constant criterion *response* methodology, such as the threshold for circadian activation (melatonin suppression or phase shifting). The formal definition of light used to characterize the spectral response of human vision, for example, is primarily based upon a

constant criterion visual response methodology (i.e., flicker photometry) [11]. In contrast, studies using a constant *stimulus* methodology (e.g., recording responses to equal irradiances from different wavelengths) to deduce circadian function do not avoid the contributions from non-linear, post-receptor processes, usually confounding quantitative comparisons between studies, even within a single species. Although the influences of studies using a constant stimulus methodology were minimized, it was impossible to rely solely on studies using a constant criterion response methodology without excluding many of the published data on circadian-related responses to light. As a consequence of relying on some constant stimulus methodologies, precise comparisons among studies was compromised.

Many studies used broadband, "white" light as the stimulus without specification of its spectral power distribution or the geometries used to make the photometric or radiometric measurements. As will be discussed in more detail later, the relative effectiveness of "white" light sources for the circadian systems of nocturnal rodents or humans can vary by a factor of two or three, depending of their respective spectral power distributions. Depending also upon the location of the light measuring device, misrepresentation of retinal flux densities (illuminance or irradiance) can also vary by a factor of 20 or more. Studies that do not document the spectral power distribution or the geometric relationship between the source, measurement instrument and the corneas of the species under investigation significantly increase the uncertainties associated with specification of the circadian stimulus. Consequently, the precise circadian stimulus cannot be well specified in many studies, further exacerbating the problem of making quantitative comparisons between study results.

In addition to these methodological issues, fundamental differences exist between nocturnal rodents and humans. The duration of light exposure needed to elicit a criterion

circadian response (e.g., nocturnal melatonin suppression) differs markedly between nocturnal rodents and humans. Perhaps because of their generally smaller size, the time course of melatonin suppression is much faster in rodents than in humans [26-29]. Melatonin suppression occurs within 15 to 20 minutes in rodents, whereas suppression of human nocturnal melatonin can take as long as 60 minutes to reach asymptotic values. Other fundamental differences are the phototransduction mechanisms in nocturnal rodents and humans. Bullough *et al.* [30] showed that the *murine* circadian system was additive in response to light. That is, a single circadian luminous efficiency function could be used as a stimulus rectifying variable to weight the spectral power distribution of any real or imagined source. In contrast, the human circadian system, through spectral opponent mechanisms in the retina also leading to color vision, appears to be subadditive [31]. A non-linear model of human circadian phototransduction has been developed [32] to weight the spectral power distributions of different sources, instead of a single circadian luminous efficiency function.

In order to begin to disentangle these complicated issues related to specification of the stimulus and methodologies, as well as fundamental species-specific temporal and spectral dynamics of the circadian systems, we separately examine studies using broadband and nearly monochromatic illumination, using two primary outcome measures: (1) melatonin suppression, or (2) phase shifting of hormone, temperature or activity rhythms.

Melatonin Suppression

Broadband illumination - rodents. There are clear differences between nocturnal and diurnal rodents in terms of the threshold light doses needed for melatonin suppression [26]. Nocturnal rodents such as Syrian hamsters [33], Sprague-Dawley and Long-Evans rats [34, 35],

cotton rats [36] and Buffalo rats [13] have measurable suppression of nocturnal melatonin to irradiances of around 0.1 μW/cm². In comparison, diurnal species such as Richardson's ground squirrel [37], 13-lined ground squirrel [38], Mexican ground squirrel [39] and Eastern chipmunks [40], require much higher irradiances, on the order of 1000 μW/cm², to suppress nocturnal melatonin.

Broadband illumination - humans. Humans are also diurnal mammals and, similar to the diurnal rodents that have been studied, typically require high intensities of white light to suppress melatonin within about 60 minutes, on the order of 100-1000 μW/cm² [27-29, 31, 41-43].

Nearly monochromatic illumination - rodents. Studies of the spectral sensitivity of the nocturnal melatonin suppression response in various rodent species have been made. In rats [44] and in Syrian hamsters [45], the wavelengths corresponding to peak sensitivity in these rodents for melatonin suppression are around 460-540 nm. Cardinali *et al.* [44] found an irradiance of 65 μW/cm² at 530 nm resulted in nearly 80% melatonin suppression in rats, but did not test any other irradiances. Brainard *et al.* [45] tested light near wavelengths of 355, 468, 532, 597 and 660 nm in Syrian hamsters. Light at both 468 and 532 nm, having an irradiance of less than 0.1 μW/cm², produced measurable suppression of melatonin in these animals. In golden hamsters, Nelson and Takahashi [46] found the threshold for melatonin suppression for light delivered onto the eyes of animals was less than 0.005 μW/cm² at 503 nm with a saturated response at 0.05 μW/cm². Lucas *et al.* [47] found reliable suppression of melatonin in domestic mice from 0.03 μW/cm² at 509 nm. Sensitivity to ultraviolet radiation in nocturnal rodents has also been demonstrated with respect to nocturnal melatonin suppression [48-50].

Nearly monochromatic illumination - humans. Brainard *et al.* [51] and Thapan *et al.* [52] measured nocturnal melatonin suppression to light of varying wavelengths in human subjects

with dilated pupils. Pupil dilation increases pupil area (and thus, the amount of light reaching the retina) approximately tenfold relative to natural pupils. Both groups of researchers found the wavelength of maximum sensitivity to be around 460 nm. Brainard *et al.* [51] found an irradiance of 3 μW/cm² measured at the cornea presented for 90 minutes to suppress melatonin reliably, with about ten times this amount to achieve saturation. Correcting for pupil area, this would be approximately equivalent to 30 μW/cm² for humans with normally-constricted pupils. Thapan *et al.* [52] used exposure durations of 30 minutes and at 456 nm (the closest wavelength to 460 nm used by these researchers), an irradiance of about 6 μW/cm² at the cornea reliably suppressed melatonin and about 60 μW/cm² achieved maximal suppression. The differences between irradiances needed to affect the human circadian system equally in the Brainard *et al.* [51] and Thapan *et al.* [52] studies appear to be largely attributable to the differences in exposure durations, albeit not proportional, in these studies.

Phase Shifting

Broadband illumination - rodents. Sharma *et al.* [53] measured circadian phase shifts (advances and delays) of locomotor activity in nocturnal field mice exposed to various irradiances from diffused daylight. Irradiances as low as approximately 0.05 μW/cm² were sufficient to obtain measurable phase shifts, relative to darkness. The response saturated at an irradiance of about 500 μW/cm².

Broadband illumination - humans. Boivin *et al.* [54] measured phase shifts of core body temperature in humans exposed to five hours of illumination from fluorescent lamps of varying levels. Irradiances of 50-100 μW/cm² were sufficient to produce reliably measurable phase advances of the body temperature rhythm, with a cube-root relationship between irradiance and

length of the phase shift up to irradiances of 1000-2000 μW/cm². Zeitzer *et al.* [41] measured phase shifts to 6.5 hour pulses of light and found a half-maximal response around an irradiance of 30-50 μW/cm².

Nearly monochromatic illumination - rodents. Most studies of spectral sensitivity in various nocturnal rodent species including mice [30, 55-57], rats [58], and golden hamsters [59, 60] have found peak sensitivity around 480-530 nm, similar to the results of melatonin suppression studies. Sensitivity to ultraviolet radiation for phase shifting is also a characteristic of many nocturnal rodent species [30, 50, 61].

For nearly monochromatic wavelength stimuli in this spectral region, McGuire *et al.* [58] found that light at 530 nm was able to entrain the body temperature rhythm of rats at an irradiance of 0.1 μW/cm². Geetha and Subbaraj [57] exposed nocturnal field mice to 5 μW/cm² of light at 549 nm and measured large phase delays and advances from this irradiance. Provencio and Foster [55] measured large phase shifts in mice from 0.5 μW/cm² at 516 nm. Yoshimura and Ebihara [56] found that less than 0.04 μW/cm² from 515-nm light elicited measurable phase shifts in mice. Freedman *et al.* [62] measured approximately 1-h phase shifts in domestic mice exposed to 0.1 μW/cm² at 509 nm. In golden hamsters, Takahashi *et al.* [59] found that light at 515 nm began to result in measurable phase shifts at an irradiance of approximately 4 μW/cm². Using a carefully controlled stimulus presented onto the eyes of golden hamsters, Nelson and Takahashi [46] found the threshold for circadian phase shifting was approximately 0.005 μW/cm² at 503 nm, and the maximum response was obtained at about 50 μW/cm².

Nearly monochromatic illumination - humans. In humans, the spectral sensitivity for phase shifting [63-65] has been demonstrated to be maximal for wavelengths between 440 and 500 nm, similar to the region of maximal sensitivity for nocturnal melatonin suppression. Wright

and Lack [63] and Wright *et al.* [64] measured phase delays and advances, respectively, to 65 μW/cm² of light at 470 and 497 nm and found these stimuli to elicit large shifts. Warman *et al.* [66] utilized a 28 μW/cm² pulse of light distributed at 436 and 456 nm and found this stimulus resulted in measurable phase shifts. Revell *et al.* [67] used 25 μW/cm² from light at 470 nm and found this stimulus to result in reliable phase shifts. Lockley *et al.* [65] used light at 460 nm at an irradiance of 12 μW/cm² and also measured reliable phase shifts.

Differences Between Rodents and Humans

The evidence clearly points to differences in the absolute and spectral sensitivities to optical radiation between nocturnal rodent and human circadian systems. This presents a serious problem for characterizing the circadian stimulus for both humans and animals because there are no widely used instruments for measuring "circadian light" in any species (an instrument for measuring the photometric stimulus for the human circadian system has recently been described [68]), and because spectroradiometric equipment is rarely used in circadian studies. Moreover, these findings underscore the significant errors in interpretation that can occur when comparing circadian light across species (e.g., [25]). In this section an attempt is made to reduce the uncertainty in the discussion of circadian light, both in terms of characterizing circadian light for a given species and for making more meaningful comparisons of circadian light across species.

As noted earlier, two representative models of circadian phototransduction, one for diurnal humans [32] and one for nocturnal mice [30] can be used to estimate the relative effectiveness of light sources for circadian regulation in these species. A criterion nocturnal melatonin suppression of 35% was used in the Rea *et al.* [32] model to estimate the relative effectiveness of various sources of light in humans. In mice, because circadian phototransduction

appears to exhibit additivity [30], selection of a criterion phase shift is unnecessary because all sources will have the same rank order in terms of effectiveness for circadian phase shifting, so long as the criterion response is above threshold and below saturation.

Table 1 compares several light sources to common incandescent illumination for circadian stimulation in both species. These data are expressed in terms of relative illuminance (light levels) and irradiance (radiant flux density) for the following reason. Values based on relative illuminance are given because light measurements in rodent studies often employ conventional photometric equipment (e.g., measuring lux, or footcandles), even though the photopic luminous efficiency function for converting radiant to luminous flux (V_λ) is only strictly applicable to humans. Illuminance measurements can be difficult to interpret for nocturnal rodents, however, when a light source contains significant ultraviolet radiation (which by definition produces little to no luminous flux). Values based on relative irradiance may better describe the actual effectiveness of sources based on equivalent radiant power when ultraviolet radiation is a significant part of the spectral power distribution (e.g., daylight) and for this reason *both* illuminance and irradiance values are presented.

[Table 1 approximately here]

Consider the following example to illustrate how Table 1 might be used. Assume that a circadian biologist wanted to compare results from three studies, one that employed incandescent illumination another used a 7500 K (daylight simulating) fluorescent lamp and the third employed natural daylight (D65) to shift the phase of wheel running in mouse. Commercially available illuminance meters were used in both studies to measure the light stimulus. The light

levels measured at the base of the cages were 20 lux for all three light sources. The hypothetical results showed that the daylight light source had the greatest effect on phase shifting, followed by the fluorescent lamp and lastly by the incandescent lamp, all of which were measured as having the same illuminance level. Using Table 1, the circadian biologist noted that the daylight source had nearly twice the circadian effectiveness as the incandescent lamp for the same illuminance and that the fluorescent lamp was about 58% more effective than the incandescent lamp as a circadian light source for mouse. To achieve the same criterion phase shift for the three light sources, the circadian biologist would plan to have the following illuminance levels for the three light sources: incandescent, 20 lux; 7500 K fluorescent, 13 lux; and daylight (D65), 10 lux. Similar comparisons could also be made using radiometric units in the right-hand portion of Table 1.

Comparisons can also be made using Table 1 of the relative effectiveness of different general light sources for humans and for mouse, as might be considered when nocturnal rodents serve as models for human breast cancer. In general, differences in the rank orders of the relative effectiveness of commercially available light sources for stimulating the circadian systems of humans and mice are not pronounced, with the exception of the nearly monochromatic blue LED and the blacklight blue (ultraviolet) lamp. For these two special sources, significant errors in estimating their relative effectiveness could occur without this table. In general, these relatively large potential errors are a consequence of the fact that the circadian systems of both humans and mouse are tuned to shorter wavelengths than the photopic luminous efficiency function (V_λ). Despite the differences in spectral sensitivities, however, the relative values in Table 1 are, in fact, small compared to the difference in absolute sensitivities of the respective circadian systems of humans and mice.

Table 2, based on this review of circadian responses to light, shows a very large difference in the absolute sensitivities of the circadian systems of nocturnal rodents and humans. The ratio for the thresholds for melatonin suppression and for circadian phase shifting in nocturnal rodents and in humans is approximately 10,000:1 for white light and for narrow-band colored light presented near the respective peaks of their spectral sensitivities. It should be noted that diurnal rodents are similarly sensitive to light as humans, but these species are rarely used as models for human breast cancer. It should also be recalled that most nocturnal rodents have sensitivity in the ultraviolet region [50] and, unlike natural light sources, nearly all electric light sources generate very limited amounts of ultraviolet radiation.

[Table 2 approximately here]

Given that most of the rodent studies measured irradiance on the cage floor where the animals were housed, and most of the studies of the human circadian system measured (vertical) irradiances at the subjects' eyes, the differences between rodents and humans may even be greater than indicated in Table 2 which are all based upon illuminance measurements on a horizontal plane. Vertical illuminances at human eye level tend to be about 1/5 the magnitude of the horizontal illuminances on work surfaces reported and recommended for buildings [69,75]. Thus it is not unrealistic to suppose that there can be an absolute sensitivity ratio even greater than 10,000:1 between species, as it relates to their respective living environments. Again, the measurement geometries are quite important for accurately characterizing circadian light exposure.

Conclusions

The incidence of breast cancer in women continues to rise in modern industrialized society, despite a great deal of research aimed at reversing this trend. Why?

It seems increasingly clear that circadian disruption affects the etiology of breast cancer in women. Since light is the primary regulator of circadian function in humans, indeed in all species, a more formal approach should be taken in *all* studies of light, circadian disruption and breast cancer. Hopefully this review underscores that point, particularly because nocturnal animals are commonly used as laboratory models for diurnal human breast cancer development and growth. Compared to humans, the circadian systems of these animals are remarkably different in both their spectral and absolute sensitivities to light. These differences may have completely obscured insights into the roles that light and the circadian system play in breast cancer.

If we are to seriously approach the study of human breast cancer through our growing insight into circadian regulation, then it is important that we develop a much more detailed and quantitative understanding of optical radiation as it impacts their respective circadian systems. A simple way to bridge human and animal studies of breast cancer is outlined in this review. Beyond the points made here, however, we should begin to rethink our entire approach to the study of breast cancer, circadian disruption and light. In particular, we need to better quantify and understand the role that electric and natural light *now* plays in modern societies with respect to its potential impact on breast cancer in women. The entire light-dark cycle experienced by young girls and women is very different in our modern societies than it was a century ago. The light-dark cycle is muted by the indoor built environment and electric light has significantly extended the light portion of the cycle. In laboratory animals, the relatively sharp, 12-hour-on,

12-hour-off transition between darkness and quite high light levels contrasts markedly with the natural lighted environment of many of these nocturnal rodents. Without a quantitative understanding of these evolutionary new light-dark cycles it will be difficult to design appropriate epidemiological as well as laboratory animal studies to unravel the health implications of modern lighting. Indeed, it might be safely said that, unconsciously, we are now either ignoring or misrepresenting the facts about the role that light and darkness might play in determining whether a woman will or will not get breast cancer, or whether perhaps she could can use light and darkness to enhance the effectiveness of treatment [8, 9] if the disease is contracted. This review, hopefully, provides a solid framework for us to more seriously and consciously begin to demonstrate whether light does or does not play a role in the increasing incidence of breast cancer in modern industrialized society.

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Table 1. *Comparison of relative (to incandescent) effectiveness of various light sources for circadian responses.*

Source	**Relative effectiveness on an equal (photopic) illuminance basis**		**Relative effectiveness on an equal irradiance basis**	
	Human	**Mouse**	**Human**	**Mouse**
*Incandescent**	1.00	1.00	1.00	1.00
3000K fluorescent†	0.74	1.00	1.07	1.46
7500K fluorescent†	1.57	1.58	1.91	1.93
Metal halide‡	0.92	0.96	1.41	1.47
High pressure sodium‡	0.43	0.61	0.78	1.09
Clear mercury†	0.40	0.62	0.76	1.18
White LED†	1.15	1.48	1.42	1.82
Blue LED†	27.9	10.2	7.29	2.66
*Daylight (D65)**	1.90	1.96	1.91	1.79
Blacklight blue (ultraviolet) †	320	2578	3.95	1.72

*Commission Internationale de l'Éclairage standard illuminant.
†Measured by authors
‡Estimated based on data from Rea [69].

Table 2. *Approximate illuminance and irradiance values (for nominally white light) for eliciting visual and circadian responses in humans and nocturnal rodents.*

Approximate (photopic) illuminance (lux) or irradiance (μW/cm²)	**Physical description***	**Human response**	**Nocturnal rodent response**
10^{4}	Paper under daylight		
10^{3}			
10^{2}	Paper in office	Circadian threshold[†]	Damaging[§]
10			
1		Photopic threshold[‡]	
10^{-1}			Photopic threshold[‖]
10^{-2}	Paper under moonlight	Mesopic threshold[‡]	Circadian threshold[#]
10^{-3}			Mesopic threshold[‖]
10^{-4}	Paper under starlight		
10^{-5}			
10^{-6}		Scotopic threshold*	
10^{-7}			
10^{-8}			Scotopic threshold**

*Based on Sekuler and Blake [70].
[†]Based on McIntyre *et al.* [28, 29] and Zeitzer *et al.* [41].
[‡]Based on He *et al.* [71].
[§]Based on Rapp and Williams [72] and Webb *et al.* [35].
[‖]Based on Wang *et al.* [73].
[#]Based on Reiter [26] and Webb *et al.* [35].
**Based on Lyubarksy *et al.* [74].