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Light: An Extrinsic Factor Influencing Animal-based Research

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Light is an environmental factor that is extrinsic to animals themselves and that exerts a profound influence on the regulation of circadian, neurohormonal, metabolic, and neurobehavioral systems of all animals, including research animals. These widespread biologic effects of light are mediated by distinct photoreceptors—rods and cones that comprise the conventional visual system and melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) of the nonvisual system that interact with the rods and cones. The rods and cones of the visual system, along with the ipRGCs of the nonvisual system, are species distinct in terms of opsins and opsin concentrations and interact with one another to provide vision and regulate circadian rhythms of neurohormonal and neurobehavioral responses to light. Here, we review a brief history of lighting technologies, the nature of light and circadian rhythms, our present understanding of mammalian photoreception, and current industry practices and standards. We also consider the implications of light for vivarium measurement, production, and technological application and provide simple recommendations on artificial lighting for use by regulatory authorities, lighting manufacturers, designers, engineers, researchers, and research animal care staff that ensure best practices for optimizing animal health and well-being and, ultimately, improving scientific outcomes.

Abbreviations and Acronyms: bLAD, blue-enriched LED light at daytime; Clock, circadian locomotor output kaput; CCT, correlated color temperature; CWF, cool white fluorescent; IGN, intergeniculate nucleus; ipRGC, intrinsically photosensitive retinal ganglion cell; HIOMT, hydroxyindole-*O*-methyltransferase; K, Kelvin temperature; LAN, light at night; LED, light-emitting diode; LGN, lateral geniculate nucleus; PLR, pupillary light reflex; POT, primary optic tract; RHT, retinohypothalamic tract; SCN, suprachiasmatic nuclei; SPD, spectral power distribution.

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Introduction

Light is a fundamental extrinsic factor in animal-based research that like noise, vibration, and temperature requires serious consideration in the design and operation of animal facilities and the conduct of research using animals. The influence of light on circadian neurohormonal, neurobehavioral, and physiologic parameters is well established.[14,74,93-102,130,137,138,160,181,196,238,247,284,300,301,349,370,371,381,394,434] Over the past 30 y, experimental evidence has revealed that almost all life on our planet varies in a species-specific manner with regard to how it is affected by photic energy.[50,51,162,163] While light supports vision that allows us to see and move about in the world around us, it also functions below the level of consciousness, regulating a wide range of behavioral and physiologic responses that alternate with a near 24-h rhythm (Figure 1) throughout each day (i.e., circadian rhythm).[52] Minor changes in light intensity,[45] spectral quality,[46] and duration[47] at specific times of day can disrupt the circadian regulation of these neuroendocrine and neurobehavioral responses required for optimal animal health and well-being. In addition to the most obvious circadian rhythms of locomotor activity and sleep, hormones (including melatonin, corticosterone, and insulin), core body temperature, metabolism, immune function, and many other metabolic, physiological, and behavioral processes, have circadian rhythms that are entrained by the environmental light–dark cycle.[104,107,151,212,315,339,340,401,417,420,426] Incorrect measurement and reporting of light, as well as improper lighting protocols, in animal research facilities may present a source of unrecognized animal distress and a confounding variable in scientific investigations. This may, in turn, undermine the 3Rs of refining research animal models and reducing the number of animals used in research,[80,336] while also compromising reproducibility, transparency, and accountability in research studies.[77]

Light is the most influential and potent regulator of the circadian clock system, and by synchronizing circadian rhythmicity, it integrates almost all neurohormonal and neurobehavioral systems that incorporate a multitude of biologic processes under retinal control (Figure 2A and 2B).[7,48,126,136,164,175,177,178,197,217-219,278,360,362,365] Research animals exposed to artificial light emitted by a number of lighting technologies at an inappropriate light intensity, wavelength, or duration at a given time of day are at risk for circadian disruption.[37-41,44-52,57,59,78,79,90,91,94-102,137-140,149,162,163,167,182,183,216,224,250,280] Unfortunately, the current eighth edition of the *Guide for the Care and Use of Laboratory Animals*[187] (the *Guide*) is antiquated as it provides limited guidance on the management of light and lighting protocols. While the *Guide* cautions that inappropriate lighting and lighting protocols may result in blindness or undue stress, the emphasis is primarily limited to rodents and, more specifically, Sprague–Dawley rats based on information available to 1985 and associated with the primary optic tract (POT) and related phototoxic retinopathy investigations.[33,74] Light's influence is only briefly mentioned as related to husbandry, pigmentation, body temperature, hormone status, age, species, sex, stock or strain of the research

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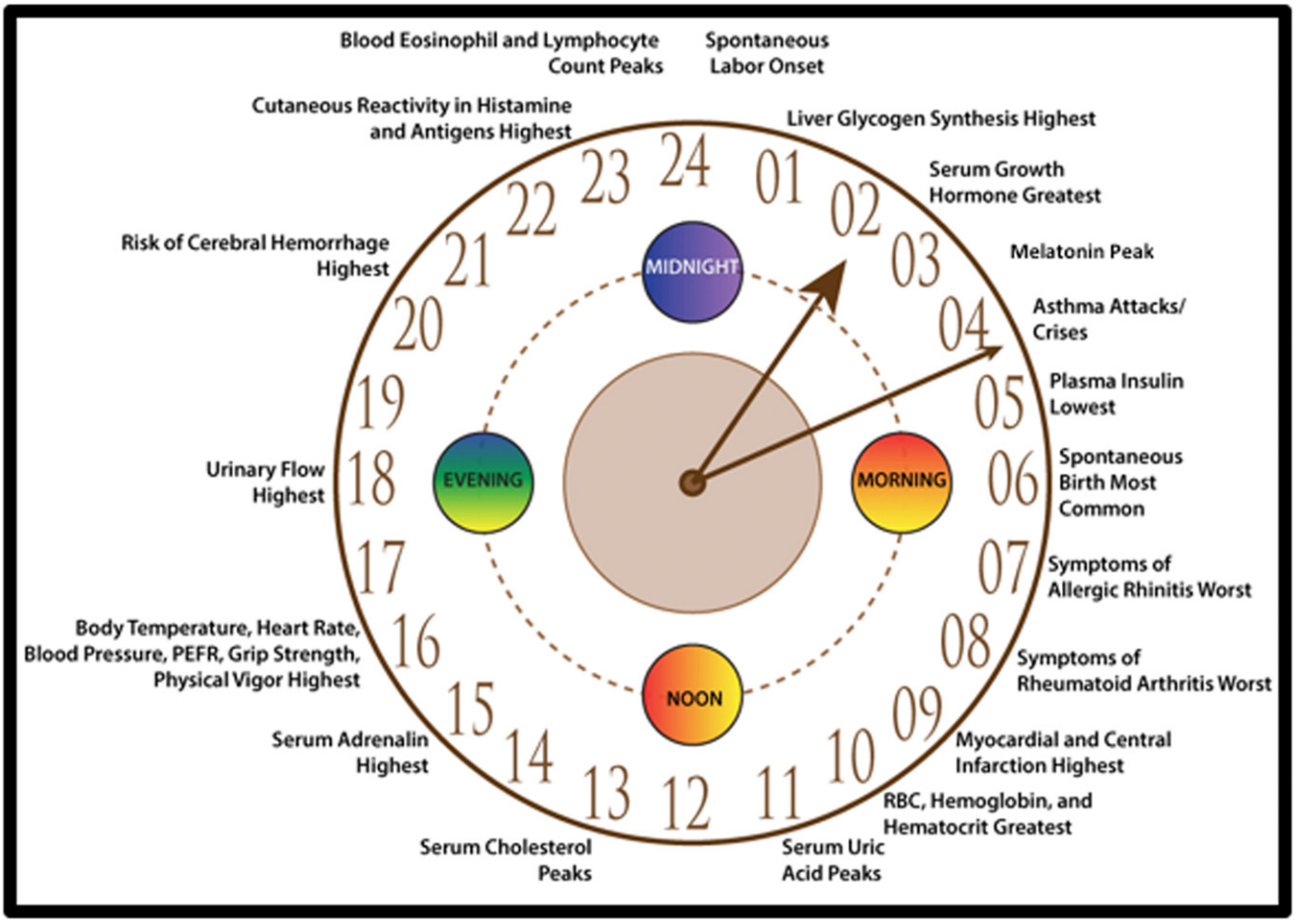

Figure 1. Circadian rhythms have a cycle of about 24 h per day. This figure is presented with permission from the American Association for Laboratory Animal Science.

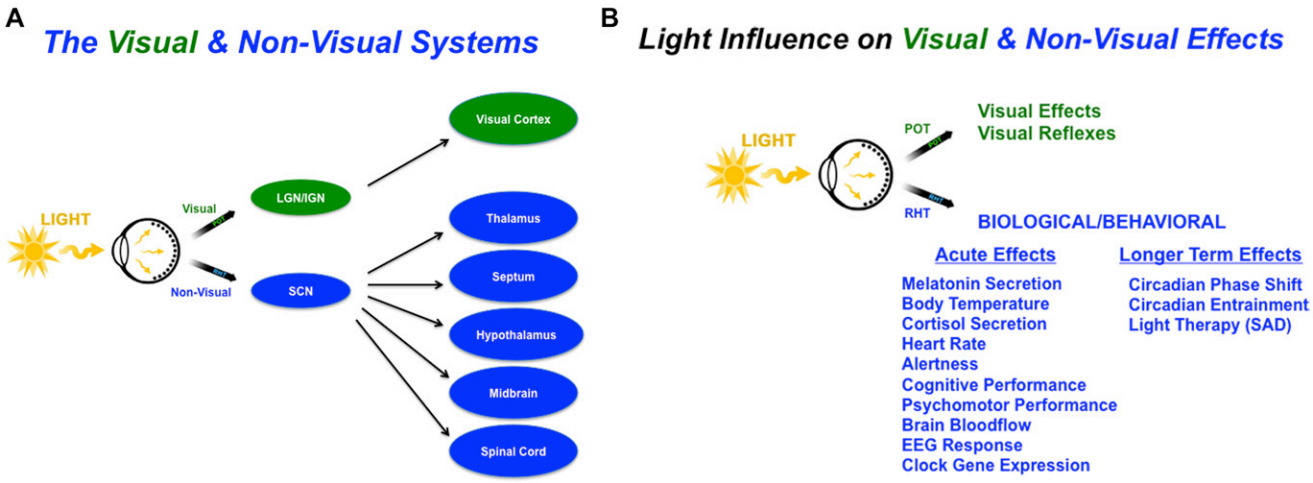

Figure 2. (A) This simplified diagram is a schematic of the neuroanatomy responsible for mediating the sensory capacity of the visual (primary optic tract [POT]) and nonvisual (retinohypothalamic tract [RHT]) regulation of circadian, neuroendocrine, and neurobehavioral functions. LGN = lateral geniculate nucleus; IGN = intergeniculate nucleus; SAD = seasonal affective disorder; SCN = suprachiasmatic nuclei. (B) This is a schematic of the neuroanatomy responsible for mediating sensory capacity of the visual (POT) and nonvisual (RHT) regulation of circadian, biological, and neurobehavioral acute and long-term effects in greater detail.

animals, reproductive activity, eating, cage position, and low-light levels.[18,45,67,116,154,155,198,282,283,319,329,345,346,349,371] Furthermore, the *Guide*[187] barely acknowledges the nonvisual circadian system as it pertains to rodents and lighting technologies in use today, for example, the rapidly emerging light-emitting diode (LED) technology. The *Guide*[187] provides no information on the influence of daytime exposure to LED lighting on the biology of either humans or research animals.

As stated in the *Guide*,[187] the traditional objectives of animal facility lighting pertaining to both animal research personnel and animals used in research were codified by the lighting industry's Illuminating Engineering Society (IES)[182,183] and

Commission Internationale de l'Eclairage (International Commission on Illumination [CIE]),[78,79] both established in the early 20th century. The objectives state that lighting must 1) be optimal for visual performance; 2) permit aesthetic appreciation of space and the environment; 3) be visually comfortable; and 4) conserve energy. For the most part, the first 3 objectives are reasonably easy to achieve using any of the technologies currently available. Regarding the fourth objective, the current solid-state LED technology is, arguably, the most versatile, energy-efficient, and cost-effective option as compared with all other lighting technologies.

Another resource often used by animal research facilities, particularly for NIH-funded projects is the U.S. National Institutes of Health Design Requirements Manual,[273] which specifically states that it follows the specifications established by the IES. The manual, however, focuses primarily on construction-related specifications that also apply to the U.S. Department of Energy with regard to community lighting concerns.[394] The general requirements are human specific and deal with uniformity of lighting, including glare, shadows, unbalanced brightness in the workplace, and vertical surface illumination with light levels determined based on comfort and the visual task involved. The intensity of lighting for humans for offices, research animal housing, and support areas ranges from 270 to 540 lx (110 to 220 $\mu W/cm^2$). Light uniformity is based on human perception of intensity and is measured in lux (lx; illuminance) as a ratio of how light is evenly distributed on the ground compared with the light source above. The closer this ratio is to 1 the more evenly distributed the light is perceived. Measures of lux, appropriate for human daytime vision, are not appropriate for quantifying light stimuli that regulate circadian, neuroendocrine, or neurobehavioral physiology in humans or animals.[49,50,292] Measures of irradiance (in $\mu W/cm^2$) take into account both photopic (daytime) and scotopic (nighttime) light stimuli and reflect the more accurate reporting commonly used by the lighting industry.[78,79,183] Both measures are presented here for ease of understanding; standard photoradiometers measure both illuminance (lx) and irradiance ($\mu W/cm^2$). Minimum average light levels (with uniformity ratio of 3:1 or lower) are set as follows, measured in illuminance (irradiance): animal facilities housing rodents, 270 to 810 lx (110 to 331 $\mu W/cm^2$); animal facilities housing nonhuman primates (NHPs), 540 to 810 lx (220 to 331 $\mu W/cm^2$); facilities housing aquatic species, 540 to 800 lx (220 to 331 $\mu W/cm^2$); animal surgery rooms, 2,200 lx (898 $\mu W/cm^2$); procedure rooms, 1,075 lx (439 $\mu W/cm^2$); cage wash areas, 430 to 540 lx (176 to 220 $\mu W/cm^2$); feed and bedding storage areas: 160 to 270 lx (64 to 110 $\mu W/cm^2$); and facility corridors, 160 to 270 lx (64 to 110 $\mu W/cm^2$). Little information is provided regarding fluorescent lighting technology or species-specific lighting (wavelength, intensity, duration requirements); LED lighting technology is only briefly addressed.

Unfortunately, this paucity of information translates to an inability of researchers and animal husbandry personnel regarding guidance on how to deal with light and lighting protocol concerns, what to measure, how and why to measure, and what factors to avoid, such as exposure to light at night (LAN). Since other authors have reviewed the many problems associated with LAN and lighting protocols in the vivarium,[122,132-136] the purpose of this overview is to propose a series of light measurement practices that can provide conservative guidance for facility management and research investigators.

In this overview, we discuss a brief historical perspective of 1) lighting technologies; 2) light and circadian rhythms; 3) our current understanding of the visual and nonvisual systems; 4) recent findings on the effects of extrinsic light exposure on research animals; 5) evolving light-measurement strategies (metrics), taking into account the complex nonvisual photoreceptive inputs for visual and nonvisual responses to light; and 6) simple recommendations for modifying research animal holding facilities and improving practices to enhance the control of lighting and light–dark cycles. These recommended improvements and practices are conservative, easy to achieve with minimal resources and planning, and consistent with the *Guide*,[187] *Animal Research: Reporting of In Vivo Experiments (ARRIVE) Guidelines*,[293] the *Concordat on Openness in Animal Research*,[80] the 3Rs,[336] and the recent NIH mandate regarding reproducibility, transparency, and accountability in research.[77] Use of these recommendations should reduce experimental variability, increase reproducibility, reduce the number of animals used, and enhance the health and well-being of research animals, thus improving scientific outcomes.

A brief history of lighting technology. For a complete review regarding the history of lighting technology, we suggest that the reader draw upon the information provided in several references we used for this review.[45,93,94,96,244,292] The earliest available evidence indicates that the controlled use of fire by our ancestor *Homo erectus* appeared to have occurred during the early stone age (Lower Paleolithic Era) nearly 1.4 million years ago. Fire was initially obtained opportunistically from natural occurrences (lighting strikes, meteor impacts, etc.) and transitioned to the use of animal dung and other slow-burning substances during wet and dry seasons and finally to kindled fire.[393] Oil lamps first appeared in 70,000 BC and were made from nonflammable materials like rocks and shells that were covered with moss drenched in animal fat or tallow. Subsequently, the Chinese and then the Romans burned olive oil, sesame oil, fish oil, beeswax, and whale oil. At that time, olive oil was almost nonexistent in northern Europe. Swiss chemist Aime Argand invented an oil lamp that had a cylindrical wick and a glass cylinder chimney that directed a draft over the flame. Oil was widely used until the kerosene lamp took over somewhere in the 17th century. One of the oldest light sources, which has not changed much through history, was a mass of wax with an embedded wick, and one of the most common materials used was beeswax. In the 18th century, spermaceti, the crystallized oil of sperm whales, was identified as a replacement for tallow. Spermaceti resulted in a brighter light, was produced in great quantities, and did not smell. Colza oil and rapeseed oil also provided smokeless light. In the 1850s, James Young refined paraffin wax by distilling coal. As late as the 19th century, illumination of large areas (streets, public places, factories, even rooms in houses) was not possible. The solution had been present in the ground for thousands of years and was overlooked for an additional 140 y after it was discovered. In 1790, William Murdoch, an employee of a factory in Soho, began experimenting with flammable gas. Coal gas, which he produced by distillation of coal, provided the brightest flame, as compared with all previous technologies. In 1807, Pall Mall in London was the first street to be gas lit; Paris followed in 1820. In 1816, Baltimore became the first city in the United States to have gas streetlights. The first experiments in electrical illumination were made by Sir Humphry Davy in the 19th century (1801 to 1816). He took a filament made from a platinum strip and connected it to a battery; as the filament heated, it began to emit light. In the 1870s, Sir Joseph Swann and Thomas Edison used a carbon filament in an improved vacuum to produce the first commercially usable light source. Filaments were later made from tungsten and enclosed in an atmosphere of noble gas.

One of the first recorded marine animal research facilities in the United States was the R/V Albatross I, commissioned in 1882. It employed both kerosene lamps and, later, incandescent lamps for lighting in its aquaria facilities. During 40 y of service, she surveyed Newfoundland Banks and the Bering Sea, visited archipelagos of the Pacific, and served in 2 wars. Her work continued the earlier investigations of Charles Darwin while he was at Cambridge's Christ's College (1828 to 1831) and his subsequent studies that were conducted in the daytime during his 5-y voyage on the HMS Beagle (1831 to 1836). Meanwhile, a contemporary but obscure Austrian monk and scientist, Father Gregor Mendel, unbeknownst to Darwin and the general scientific community, carried out inheritance experiments in peas and honeybees at the Augustinian St. Thomas Abbey in Brünn, also under sunlight, thus setting the stage for modern genetics by studying plants and animals.

As these events were transpiring, the modern age of the industrial revolution began to gain speed, reaching full throttle in the United States in the 1850s. The technological advancements made during this period changed lives, made vast fortunes, and positioned the United States for its rise to a global superpower. Key to this revolution, however, was the development and harnessing of electric power and, of course, the emergence of the incandescent light bulb. Over the years, the way we light our homes has changed from the warm glow of an open fireplace to candles, oil lamps, gas lamps, and then to electric lighting. Thomas Edison patented his incandescent light bulb in 1881 and then figured out how to implement a system for generating and delivering electricity to provide electric lights in our homes. The mass production and use of this remarkable new technology spread globally, and its use changed the industrialized world forever. However, this change meant that people were now exposed to considerably less natural, blue-enriched daylight due to the population becoming more industrialized and transitioning out of the agricultural fields to the home and workplace for increasingly longer periods of time. In addition, people were now exposed to more broad-spectrum LAN in the community, home, and workplace. This single difference in our exposure to light, a little more than 140 y ago, was one of the most profound environmental changes affecting us on our planet in millions of years of evolution. In addition to effects on humans, animals maintained under conditions of artificial lighting were also affected by this single environmental, extrinsic factor.

Peter Hewlett invented the first low-pressure mercury fluorescent light in 1901, but its color was very unappealing, and it was not popular. The broad-spectrum high-pressure fluorescent light was invented in 1927 by 3 German scientists, but General Electric created a more practical version like the lamp in use today; it was put into production in the late 1930s. The halogen light was invented a year after the incandescent light bulb, but it did not go into production until the mid-1950s.

Today's emerging technology, the light-emitting diode (LED), was based on the work of Henry Round, a British radio researcher in 1907. However, Nick Holonyak is generally considered to be the 'Father of the LED light.' In 1962, while at GE, he invented the first LED; it fluoresced red light because it used gallium arsenide phosphide as a substrate for the diode. In 1972 George Craford at Monsanto Company invented the first yellow LED, and Monsanto was the first company to mass-produce LEDs. But the remarkable work of 3 persistent Japanese investigators, Drs. Akasaki, Amano, and Nakamura, led to the creation of the blue light-emitting diodes in 1994, fundamentally changing the lighting industry as we know it today. These 3 scientists shared the 2014 Nobel Prize for their work. With the creation of the blue LED light, which had eluded scientists for nearly 20 y, the next generation of brighter, blue-enriched, cool white lamps, combining red, amber, and high-energy blue light were now available and formed the basis for all LED screens, including the 2010 development of 'tunable' strip lighting for research animal housing units.

In making general comparisons among traditional light sources, cool white fluorescent light, or cool white fluorescent (CWF) lamps, provide the same intensity or amount of visible light while using only 20% to 30% of the electricity used by incandescent and halogen lights, and they last 8 to 15 times longer. Although the upfront cost of the fluorescent light is higher, it can save over 5 times the purchase price in electricity costs over its lifetime. The fluorescent lamp is cooler than incandescent bulbs, generating less heat, due to a simple principle: electrons bound to mercury atoms are excited to states from which they radiate UV light (UV, 390 to 410 nm) as they return to lower energy levels; this UV light is converted to visible light as it strikes the fluorescent coating on the inner wall of the lamp. The fluorescent lamp radiates a markedly consistent spectral power distribution (SPD) as compared with all previous technologies. SPD describes the power per unit area per unit wavelength of an illumination. More generally, SPD describes the concentration of light as a function of wavelength. The drawbacks of fluorescent lighting (CWF) include the following: 1) disposal, fluorescent lights contain toxic mercury; 2) many governments have banned discarding these lamps as regular refuse; 3) the light bulb loses significant intensity over a short period of time; 4) ballasts (activating units within the luminaire) burn out within a short time frame; 5) ultrasonic noise, which particularly affected rodents; and 6), buzzing, slow-start, and dimming, which have been solved over time but are still considered by a part of the U.S. population as being 'not warm' or aesthetically appealing, as is the warm glow of a fireplace.

Currently, the most common lighting technology used in vivaria and offices around the world is white CWF lighting. LED light, and more specifically LED light enriched in the blue-appearing portion of the visible spectrum, is rapidly replacing both fluorescent and incandescent lighting systems globally. LED lighting can now be regulated (tunable) for intensity and wavelength to provide a 'warmth' range from warm white to cool white. LED light has a host of advantages over fluorescent, incandescent, and halogen lighting, including higher efficiency, lower heat production, and a significantly longer operating life (up to 42 y).[289] These advantages accrue because LEDs convert electricity directly to photons of light, rather than using a wasteful mixture of heat and light generated inside traditional bulbs or lamps. Inside an LED, electric current is applied to a sandwich of semiconductor materials that emit a specific wavelength of light depending on the chemical makeup of those materials. This feature allows control of the variable wavelength or color of the light, making it appear more 'warm' or 'cool' to the observer. Because 20% of the world's electricity is being used for lighting, calculations indicate that maximal use of LED lighting could reduce this usage to as little as 4%.[183,289] Therefore, all in all, based on its features of superior spectral control, solid state sturdiness, size, and weight, LED lighting offers some attractive long-term, inexpensive alternatives to conventional lighting. However, another important advantage of LED lighting as compared with all other high-intensity discharge technologies currently in use is that it emits little-to-no high-frequency vibration due to the solid-state nature of this technology.

Both of the LED and CWF T8 lamps (tubular, 1-in. diameter, 48-in. length) that we used in our animal research[39,40,94-102]

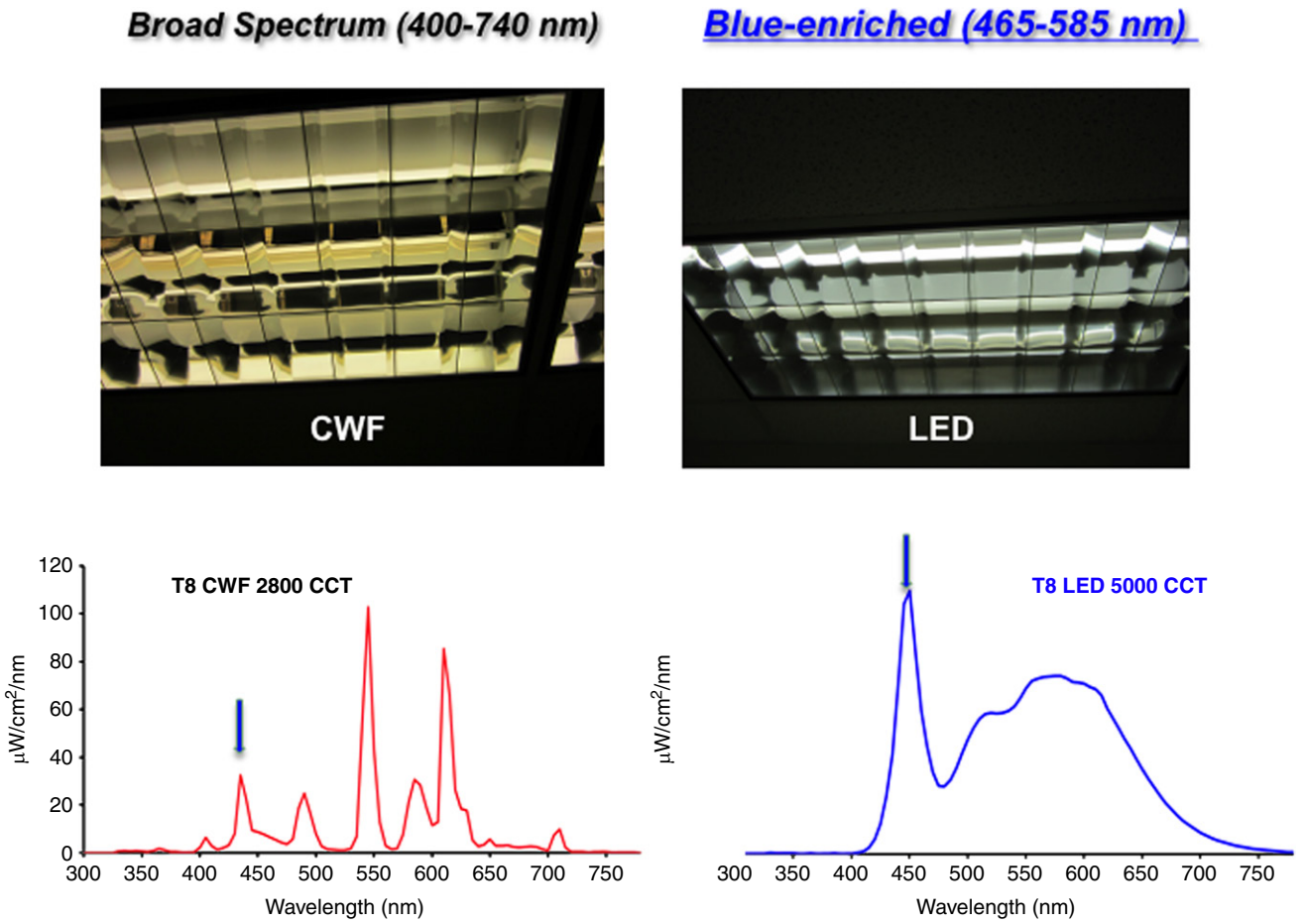

Figure 3. Photoimage of luminaires with standard T8 (1-in. diameter; 48-in. length) broad-spectrum cool white fluorescent (CWF; 2,800 CCT/K, left) and blue-enriched light emitting diode (LED; 5,000 correlated color temperature/Kelvin [CCT/K], right). Lamps are shown in upper panels, and their respective spectra are shown in lower panels in units of µW/cm^2/nm. Blue arrows indicate blue-enriched peaks for each light source.

fit easily into the standard, traditional CWF overhead 48-in. luminaire (fixture) (Figure 3; CWF, top left; LED, top right), eliminating the need to change out the ballast system (current regulator and stabilizer) and thereby avoiding a major expense. The major manufacturers in the lighting industry market that lamp to institutions considering a transition to the new technology. For the purposes of this article, one may think of color temperature (degrees Kelvin) as a measure of warmth of a light, as perceived by the human observer. In general, when employing this metric, the higher the Kelvin temperature (perceived brightness) and correlated color temperature (CCT; perceived blue-enriched or cool), the less warm and more cool the light emitted by a source. Many LED lamps today are significantly blue-enriched (450 to 485 nm) and have a CCT of 5,000 K (Figure 3, bottom right), as compared with 4,000 K for white fluorescent lamps. In general, both fluorescent and LED light sources can range in CCT from 2,200 to 6,500 K and even extend beyond this range. Traditionally, animal research facilities were illuminated with 'warmer' fluorescent lamps of 3,500 or 4,000 K CCT. In comparison, the new LED sources at 5,000 K appear 'cooler' even though the total luminous flux, or lumens, a measure of the total quantity of light, can be somewhat lower in the LEDs.[244]

Light and Circadian Rhythms

Most animal species on earth evolved under an important geophysical event, the daily and seasonal rising and setting of the sun. For thousands of generations, people and animals were exposed to the presence and absence of light on a daily basis due to the earth's rotation. All mammals have internal mechanisms that respond to alternating cycles of light and darkness and profoundly influence neuroendocrine systems throughout the 24-h day. Currently, we know that extrinsic light associated with light–dark cycles regulates virtually every major mammalian biological rhythm from birth to death.[50-52,93,136,137,300,417] These mechanisms also apply to research animals that are maintained in the artificial light/dark environments of vivaria around the world. The 4 basic biological rhythms are as follows: 1) circannual rhythms with a cycle of about 1 y, such as seasonal reproduction cycles, migrations, and hibernations; 2) infradian rhythms, with a cycle of less than a year, such as the female menstrual cycle; 3) ultradian rhythms, with a cycle of less than a day, such as heart rate and encephalogram patterns and eating cycles; and 4) circadian rhythms, with cycles of about 24 h. Circadian rhythms are the focus of this article, including rhythms of neuroendocrine hormones (i.e., melatonin) and the many other rhythms shown in Figure 1. The study of circadian rhythms encompasses the temporal organization and integration of circadian neurohormonal and neurobehavioral responses, collectively referred to as circadian physiology.[259] While written records of circadian physiology are available for only a few millennia, daily variations in physiologic processes in early humans were likely aligned with the 24-h daily photoperiod. The Egyptians developed sundials nearly 5,500 y ago, and the Chaldeans of Mesopotamia created the sophisticated

nondecimal time measurement system from which our system today is derived.[314]

The modern era of circadian rhythm study began with the work of the eminent German botanist Erwin Bünning in the 1930s, who first introduced the idea of internal clocks by studying the opening and closing of flowers.[58] Subsequently, the German physician and behavioral physiologist Jürgen Aschoff suggested that alterations in the light/dark cycle could disrupt an organism's internal 'Zeitgeber' or timekeeper, leading to adverse neurobehavioral outcomes. Aschoff's student, the British/American biologist Colin Pittendrigh at Princeton University showed in both *Drosophila* and rodents how circadian rhythms entrain to the light/dark cycle. In the 1960s Franz Halberg coined the terms 'Circadian' and 'Chronobiology.'[160] These 4 pioneers are considered the fathers of modern Chronobiology. The next great leap occurred in the early 1970s—the discovery of the suprachisamatic nuclei (SCN) or master biologic clock. These bilateral nuclei, located in the anteriobasal portion of the hypothalamus, sit along the midline above the optic chiasm in the floor of the third ventricular recess of the brain. For an outstanding historical review and detail of the circadian aspects of all this work, we highly recommend Roberto Refinetti's classic text, *Circadian Physiology*.[314] The 2017 Nobel Prize in Medicine or Physiology was awarded to Jeffrey C Hall, Michael W Rosbash, and Michael W Young, all students of Pittendrigh, for their discovery of the clock genes *Period* and *Timeless* in *Drosophila*.[161]

The advent of electrical lighting has influenced the nature of all the aforementioned biological rhythms and most significantly circadian rhythms.[86,87,163,289] This influence applies not only to humans and feral animals but also to animals in the controlled environment of the vivarium (Table 1). In efforts to improve research animal habitat and vivarium design, the consideration of both the visual and nonvisual effects of light will become increasingly important. For example, one might question the extent to which a specific architectural design replicates the biologic effects of natural sunlight, much like the emerging, blue-enriched LED technology,[93,94,101] or how lighting can be used to minimize the deleterious effects of LAN and enhance research animal health and well-being.

Current practices for measuring light in the vivarium. The lighting industry, biomedical research community, and research animal care groups are now beginning to address the concerns associated with light, lighting technologies, and lighting protocols.[93] However, making progress in this work first requires proper quantification of how light influences physiology and behavior. As a matter of course, light measurements fall into 2 categories: radiometry and photometry.[244,292] Radiometry incorporates the physical properties of light wavelength and energy. A radiometer quantifies radiant power over a defined bandwidth of electromagnetic energy. In contrast, photometry, a specialized branch of radiometry, accounts for the fact that biologic receptors are not equally sensitive to all light wavelengths. A photometer is a radiometer that uses filters to weight the detector response to various wavelengths according to the spectral sensitivity of vision in a species. The majority of commercially available photometers use a weighting function, the photopic luminous efficiency function (Vλ), which reflects the spectral sensitivity of the long- and middle-wavelength–sensitive cones.[55,57,243] Depending on the geometric properties of interest, luminous intensity (unit of measure, candela [cd; lumens/steradians {lm/sr}]), luminance (cd/m^2), or illuminance (lux [lx; lm/m^2]) can be determined from the output of these devices. During the 1980s through 2000, the vast majority of both human and animal research studies on circadian, neuroendocrine, and neurobehavioral responses to light quantified the stimuli in terms of photopic illuminance[240-244] because light meters that measured in lux were inexpensive and readily available. Two subsequent areas of investigation, however, have shown this practice is inadequate.

First, during the past 20 y, scientists have learned that although the photoreceptive capacity of the retina is dominated by rhodopsin-based rods and cones, a small subset of the retina's output neurons, the melanopsin-based retinal ganglion cells are also directly photosensitive (Figure 4).[34,168-170] Most aspects of animal physiology and behavior are influenced by retinal illumination, but they are distinct from the general aspects of vision for image formation[14,15,120,214,306,377] because they are not related to spatial patterns of light exposure and persist even in animals that are blind.[140,264,265,269,286,362,433]

Second, empirical observations have shown that circadian, behavioral, and physiological responses to extrinsic light have distinct spectral sensitivities (Figure 5). More than 12 analytic spectra studies based on selective wavelength comparisons in humans, NHPs, and rodents demonstrated that peak sensitivities in the short-wavelength portion of the visible spectrum (447 to 484 nm [blue-appearing])[34,48,49,242,387,433] clearly diverge from that predicted by $v\lambda$ (peak sensitivity, 555 nm).

Taken together, these findings indicate that established photometric light measures using the $v\lambda$ spectral weighting function (e.g., photopic lux) are inadequate for quantifying the light that regulates nonvisual physiology and behavior. An alternative method put forth by the Commission Internationale de l'Eclairge in 2018 is currently available, satisfying this unfilled need, which has important ramifications for the animal and biomedical research communities.[79] However, the lack of a fully accepted metric (i.e., an agreed-upon method for the measurement of light) complicates the comparison of research findings and the replication of experimental conditions.[244] Furthermore, this deficiency hinders the ability of the lighting industry and regulators to predict the influence of various lighting protocols on behavioral and physiologic systems. The fundamental obstacle in addressing this requirement has been the difficulty in determining a spectral weighting function (similar to $v\lambda$) for nonvisual responses.[244] Understanding the full scope of this challenge requires a review of our current knowledge of the visual system and, more importantly, of basic neurophysiology of intrinsically photosensitive retinal ganglion cells (ipRGCs) and their interactions with the classic rods and cones of the visual system.

The visual and nonvisual (circadian) systems. Over the past 30 y, scientific evidence has demonstrated that many aspects of animal physiology and behavior are influenced by retinal illumination (Table 1).[14,15,331] While some responses originating in the eye are related to vision (i.e., image formation), others are unrelated to spatial patterns of light exposure and can persist in some blind animals. These types of light responses are referred to as nonimage-forming or nonvisual responses and are related to the circadian system (Figure 4). Most of the significant advances in our understanding of these 2 systems indicate that they have similar ocular architecture and responses. As mentioned earlier, their most influential effect is the light-induced entrainment (circadian regulation or Zeitgeber [timekeeper] signals) of endogenous circadian clocks. Because circadian rhythmicity is a characteristic of almost every physiologic, metabolic, and behavioral system, this phenomenon brings a wide array of biologic processes under indirect retinal control. That said, the term nonvisual (circadian) response has come to encompass an

Table 1. Selected articles of light impact on animal biology and health

Species	Research areas/impacts	References
Homo sapiens	Bright light suppresses melatonin secretion	227
	Light and biologic rhythms	15
	Light, circadian regulation, adiposity, and aging	260, 318, 319, 348, 421, 422
	Photoreception and neurobehavioral regulation	52, 379
	Bright light reset the human circadian pacemaker	90,91
	Monochromatic light and plasma melatonin levels	47
	Light, melatonin, and breast cancer	175, 207
	Light estrogen receptors and breast cancer	311
	A novel retinal opsin: melanopsin	308
	Temperature	433
	Action spectrum of melatonin suppression	49
	Shift work, light at night (LAN), and breast cancer	103, 424
	Melatonin circadian re-entrainment with blue light	236
	LAN, poor sleep, glucose metabolism, and obesity	366
	Photopigment and melatonin suppression	388
	LAN and breast cancer	38, 39, 148
	Phototransduction and circadian clock	34
	Spectral responses and the circadian system	152
	Melanopsin-containing retinal ganglion cells	168-170
	Phase response curves and single bright exposure	203
	LAN and breast cancer	39, 252
	Distinct population of intrinsically photosensitive	92
	Melatonin receptors and sleep	114
	Light, neuroendocrine/neurobehavioral regulation	164, 416
	Measuring and using light	245
	Seasonal light circadian, entrainment, and health	342
	Light exposure devices and nighttime sleep disorder	398
	LEDs and physiology	147, 290
	Circadian disruption and fat overload	224
	Seasonal clock, ulcerative colitis, and Crohn disease	130
	Oxidative stress	324
	Recommendations for light exposure and sleep	57
	Light and glucocorticoid pulsatility	230, 340
	Excessive light exposure, DNA damage, and cancer	321
Gorilla gorilla	Light, glucocorticoid secretion, and fitness	31
Pongo pygmaeus		
Pan paniscus	Light, metabolism, and neurohormones	20, 254
Macaca mulatta	Light pupillary reflex	143, 306
	Ganglion cells and visual and nonvisual systems	92
	Light or melatonin shifts circadian rhythms	255
	Light, aging of circadian rhythms	444
Callithrix jacchus	Light circadian rhythms and blindness	363
Cebus capucinus	Light and hormonal regulation	191, 192
Hylobatidae hylobates		
Nomascus, Hoolock		
Symphalanges	Light and sleeping behavior	126, 316
Saimiri sciureus	Light and circadian rhythms of locomotor activity	390, 391
Cetacea	Light, circadian rhythms	237, 396
	Light, melatonin, and cortisol	287, 288, 374, 375
Chiroptera	Light and clock genes	441
Artiodactyla	Light, field conditions, and behavior	115, 187, 240, 291, 331, 377, 428
Bos taurus	Melatonin isolation	221
	Impact on neuroendocrine and neurobehavior	233, 408, 409
	Light, circadian regulation	64

(*continued*)

Table 1. (Continued)

Species	Research areas/impacts	References
Equus ferus	Chronobiology and the horse	270, 271
	Light impact on circadian rhythms and health	271
Elephas maximus	Light and immunoglobulin regulation	186, 303
Ursus arctos	Light, food entrainment, and circadian rhythms	112, 195, 411
Ursus maritimus	Light and circadian rhythmicity	194, 412
Phascolarctos cinereus	Light and hormone secretion	2, 239
Sus domesticus	Light intensity, circadian rhythms, and health	156, 185
Sus scrofa domesticus	Lighting and locomotor activity	36, 381
Capra hircus	Light and reproduction	68
	Light and gene expression	228
	Light cycles and health	296
Ovis aries (sheep)	Melatonin analysis	10, 11
	Photoperiodism and seasonal breeding	36, 427
	Light cycle impact on reproduction and health	282
Bradypus variegatus	Light and blood pressure	113
Choloepus hoffmanni	Light and locomotor activity	179
Canis lupus	Circadian-mediated metabolism	68, 69
Canis familiaris	Light and circadian profiles	297, 298
Hyaenidae	Light and feeding patterns	88
Felidae	Light and reproduction	56
Felis catus	Varying photoperiods and neurohormone concentrations	225
Marmota monax	Light, circadian rhythms, hibernation arousal, and mating	439
Mustelidae	Light cycles, feeding, hormone circadian rhythms	42, 373, 374, 445
Procyon lotor	Light and seasonal reproduction	17, 280
Microcebus murinus	Light and reproduction	223
Mesocricetus auratus	Adrenocortical cytogenesis	322, 323
	Hypothalamic activity of luteinizing hormone and follicle-stimulating hormone releasing hormones	37
	Light and the parasympathetic system	25
	Photoperiod and adiposity	30
	LAN and depression-like behavior	28
	LAN and immune suppression	29
	Different light spectra and pineal melatonin	44, 305
	Light irradiance, wavelength, and reproduction	46
	Light synchronization of ovulation	3
	Photoperiod and reproduction	67
	Light and melatonin suppression	294, 295
	Photoreceptors and circadian rhythm entrainment	380
	Light and circadian phase shifting	360
	Photoperiods, circadian rhythms, and depression	35
Rattus	Constant light and pituitary function	217
	Light and body temperature entrainment	258
	Light and pineal gland serotonin levels	206
	Light and corticosterone controls	344, 345
	Retinal photopigment that mediates pineal response	62
	Hormonal influence in phototoxic retinopathy	283
	Light and phototoxic retinopathy	33
	Pinealectomy and melatonin suppression	226
	Photoperiodic control of reproduction	277
	Ambient light intensity and melatonin rhythm	213, 248
	Light and phototoxic retinopathy	74
	Light in summer and winter	182
	Diurnal susceptibility to phototoxic retinopathy	116
	Cyclic light threshold and phototoxic retinopathy	350
	Light illumination in animal quarters	45

(*continued*)

Table 1. (Continued)

Species	Research areas/impacts	References
	Preference for low light intensities	346,347
	Phototoxic retinopathy	27
	Phototransduction in ganglion cells	34
	Light impact on heart rate	18
	Animal facility LAN and human cancer growth	95,96
	LAN, Warburg effect, and breast cancer	40
	Melatonin suppression of breast cancer	37-41, 96, 102, 164
	Daytime blue light exposure and prostate cancer	98
	Degenerative retinal lesions	431
	Daytime LED light and enhanced animal health	1, 97, 101, 423
	Facility lighting and circadian regulation	164, 192
	Melatonin inhibition of multiple diseases	324, 325
	Light and circadian clocks	146, 328, 329
	Light and tissue growth	369
	Light, melatonin, and brain trauma recovery	389, 390
Mus	Low light intensity preference	413
	Light influence on organ weights	337, 338
	Light, clock gene expression, and behavior	1, 7, 12
	Light and behavioral paradigms	118, 330
	Light and genetic control of melatonin synthesis	119
	Melatonin variation in different mouse strains	153, 403
	Photoreception in the retinally degenerate mouse	140
	Nutrient preference	19
	LAN and anxiety	43
	Melatonin and metabolism	202, 235
	Phototransduction by retinal ganglion cells	34, 417
	Melanopsin and rod–cone photoreceptive systems	170, 171
	Diminished pupillary response	243
	Light and circadian wheel-running behavior	132
	Fatty acid oxidation	144
	Diurnal variation and inflammation	253
	Light, rod–cones, and sleep modulation	6
	Light and aging	166, 184, 351, 387
	Light and sleep	167
	Light and tumor development	219
	Aberrant light impairs mood and cognitive behavior	220
	Light, melanopsin measurement	262, 263
	Light and feeding behavior	180, 353
	Modulation of memory performance by light	385
	Light and the laboratory mouse	293
	Facility LAN alters scientific outcomes	102, 122
	LAN and metabolic changes	131
	LAN and body weight increases	135, 173
	LAN and depression	132, 134
	Daytime LED light promotes health and well-being	94
	Light and metabolic dysregulation	261
	Light and circadian clocks	16, 65
	Light and circadian clock gene mutations	368
	Light intensity and gonadal and spleen growth	407, 418
	Light and cyclic cellular protein expression	419
Octodon degus	Photoperiods and seasonal affective disorders	16
Suncus etruscus	Recommended light levels for healthy maintenance	9, 145
Aves	Artificial photoperiods and circadian rhythms	76
	Photoperiod and circadian rhythm	147
	Circadian clock in an arctic animal	240, 332

(*continued*)

Table 1. (Continued)

Species	Research areas/impacts	References
	Circadian rhythms and environmental photoperiods	158
	Light and molt rhythms	159
	Moonlight feeding behavior	72
	Light, circadian rhythms, and energy	60
	Artificial light and behavior	111, 160, 348
	Light and circadian rhythms	437
	Photoperiods and gut health	89
	Light and circadian variation in indole content	445
	Moonlight and behavior	73
	Light, circadian rhythms, and temperature	370
	Light and melatonin rhythms	436
Gallus gallus	Dim-light, melatonin, metabolism	2
	Food consumption and growth	60
	LED light and health	234
	Monochromatic light and immune response	429
Reptillia	Light, melatonin circadian rhythms	127
	Designing environments, photoperiods, and health	106
	Light and pineal melatonin secretion	265
	Moonlight and behavior	72
	Photoperiods and healthful development	127
	Moonlight and activity	414
Rana	Isolation of melatonin	222
Amphibia	Light, temperature, and body mass	53
	Breeding behavior	22
	Light, circadian rhythms, and health	410
	LAN and circadian disruption	136, 410
Nauphoeta cinerea	Photoperiod-dependent and pheromone suppression	209
Carassius auratus	Light and mRNA expression patterns	400, 401
Danio rerio	Sleep and regulation	442, 443
	Light-induced gene transcription	415
	Light, gene expression, and sleep	362
	Lighting conditions and gene expression rhythms	109, 204
	Light-entrainable circadian pacemakers	266
	Light, spatial distribution, and swimming behavior	352
	Responses to ambient illumination	354
Hymenoptera	Light and fitness	238
	Light and circadian regulation	315
Leucophaea maderae	Light, circadian oscillations, and homeostasis	302
Photuris pyralis	LAN and courtship behavior	128
Homoptera	LAN and population dynamics	339
Drosophila melanogaster	Circadian systems	301
	Molecular genetics, circadian cycling, and behavior	24
	Visual system mutations and circadian rhythms	117
	Light, per gene and circadian cycling	150, 162, 386
	Lighting protocols and fitness	210
	Light and lifespan	229
	Light and entrainment of the circadian clock	272, 273, 299, 300
	Light regulation of circadian clocks	138, 139, 208
	Light and circadian rhythms	302, 432
	Circadian rhythms and feedback loops	334
	Light and eclosion rhythms	356, 357
Ixodes scapularis	Circadian gene dysregulation and host feeding pattern	205
Onchidium reevesii	Light, circadian rhythms, and memory	157, 430
Platyhelminthes	Light and circadian rhythms	172, 190

(*continued*)

Table 1. (Continued)

Species	Research areas/impacts	References
Porifera	Light and behavior	123, 129
Spongillida	Light and circadian behavior	267, 439, 441
Conus mollusca	Circadian rhythms	279
Conicus	Circadian immunologic responses	438
Strongylocentrotus intermedius	Circadian rhythms and spawning behavior	123, 438, 440
Cephalochordates	Light, evolution, and photosensitivity	211
Caenorhabditis elegans	Light and locomotor activity	4,61
Hymenolepis diminuta	Light and other rhythms	171, 189
Schistosoma mansoni	Light and gene expression	313, 314
Eylais extendens	Periods of light and hatching larvae	435
Enterobacter aerogenes	Circadian clock and light	292

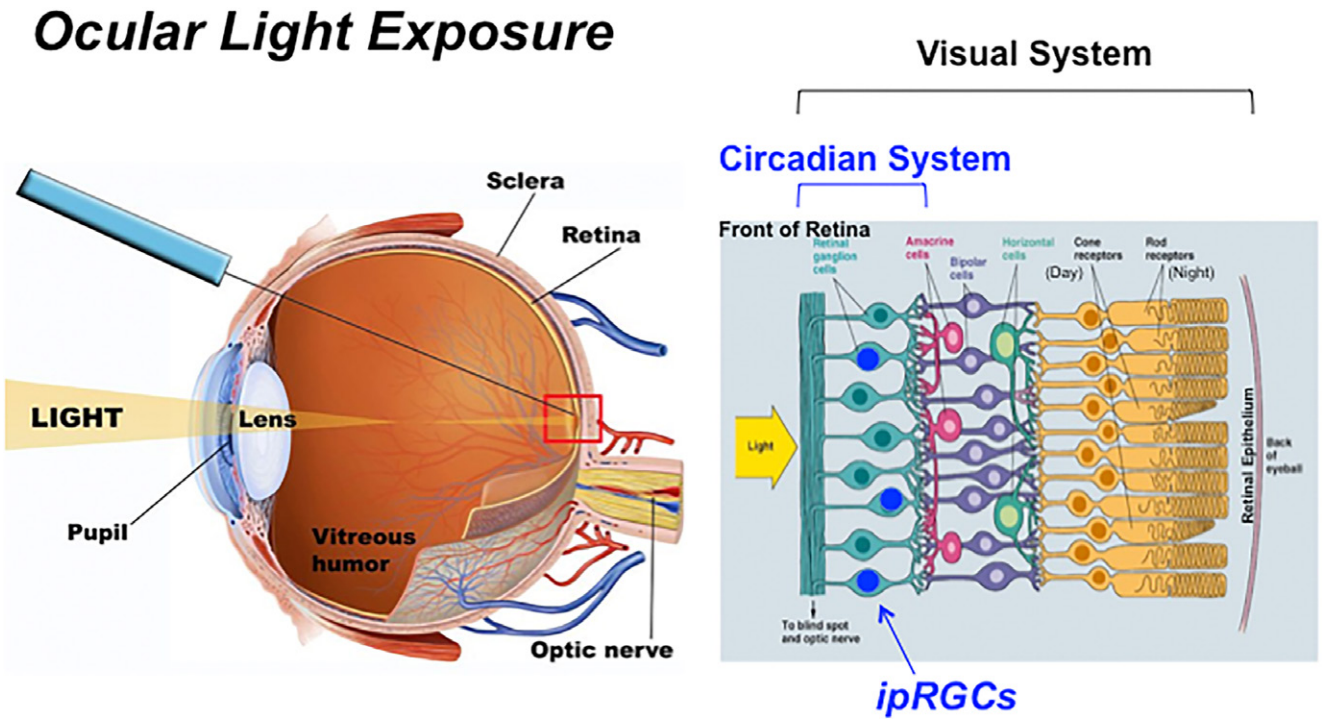

Figure 4. The human retina and eye. The ocular structure of most species has similar characteristics in both sexes. The retina is a layered structure; light passes through the lens and inner retinal layers (retinal ganglion cells, amacrine cells, bipolar cells, and horizontal cells) to reach the light-sensitive photoreceptors in the outer retina (rods and cones). The retina contains 2 classes of visual photoreceptors: rods, which mediate low-light (scotopic) vision, and cones, which mediate bright-light (photopic) vision and provide color vision. Most mammals have 3 cone opsins, short-wavelength (SWS), middle-wavelength (MWS), and long-wavelength (LWS)–sensitive opsins, except for mice, which have only 2 opsins (SWS and MWS). These opsins are coexpressed in 95% of cones. In addition to rods and cones, a subset of ganglion cells containing the pigment melanopsin (referred to as melanopsin-containing intrinsically photosensitive retinal ganglion cells [ipRGC]) capture light in the blue-appearing portion of the visible spectrum and mediate many nonvisual (circadian) responses to light. This figure is presented with permission from the American Association for Laboratory Animal Science.

ever-expanding list of more acute effects of light that ensure a normal physiologic state. For example, light constricts the pupil, abrogates pineal melatonin production, increases heart rate and core body temperature, stimulates neurohormone production, and acts to increase subjective and objective measures of alertness and psychomotor reaction time, mood, and learning.[255,293,298,305,383] Appreciation of this basic biology has led to numerous therapeutic applications in both humans and animals, including treatment for depression, seasonal affective disorder, and circadian disruption associated with jetlag, shift work, space flight, and problems with cognition and fatigue.[250,314,370,374,397,417]

In brief, light enters the eye and passes through the lens to excite the retina. Photic signals are transmitted via the POT to the thalamus and then to the visual cortex providing vision (Figure 4). A parallel but separate pathway extends from the retina and optic chiasm to a nonvisual part of the brain in the anteriobasal hypothalamus and the SCN (the master biological clock). This paired nuclear group is located above the optic chiasm and near the supraoptic recess of the third ventricle, allowing it to readily receive light/dark information from the retina. There is a short projection from the SCN to the paraventricular nucleus and a long descending multisynaptic pathway to the upper thoracic level of the spine. The retinohypothalamic tract (RHT) pathway then leaves the central nervous system through the superior cervical ganglion, and postganglionic autonomic nerve fibers climb up the vasculature to innervate the pineal gland.[288,302] The pineal gland synthesizes and secretes a variety of compounds,

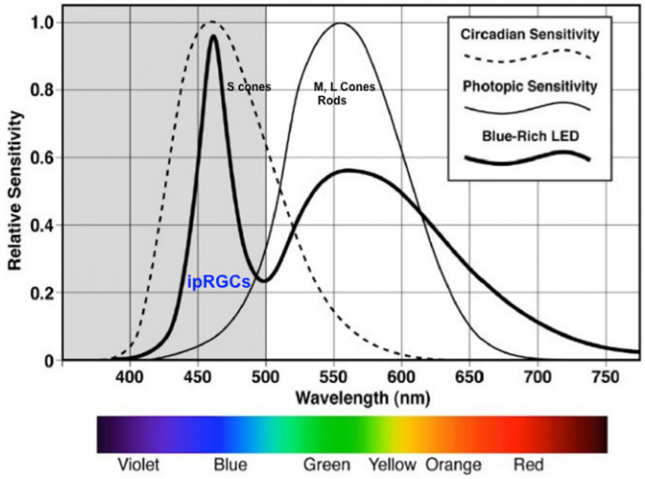

Figure 5. This graph illustrates the relative wavelength sensitivity of the photopic visual system. The photopic, or daytime, system uses Cones that are capable of color vision and are responsible for high spatial acuity. The 3 types of cones are referred to as the short-, medium-, and long-wavelength–sensitive cones (S-, M-, and L-cones). The scotopic (dark phase) system primarily uses rods, which mediate vision at low light levels. Rods do not mediate color vision and have low spatial acuity. At dawn and dusk, light levels are low, and both rods and cones are operational; this is arbitrarily referred to as the mesopic system. Rods and M- and L-cones have peak sensitivities of 555 nm, whereas the peak sensitivity of mammalian circadian, neuroendocrine, and neurobehavioral responses regulated by the ipRGC blue-rich LED system ranges between 446 and 484 nm. If you have normal color vision, and you can see the spectrum at the base of the slide, your 3-cone system is working with peak sensitivity at 555 nm; this is known in the neural literature as the 'standard observer.'

but the most widely studied is the circadian nighttime neurohormone, the 5-methoxyindole melatonin (MLT). Systemic MLT levels are high at night and low during the daytime. This light–dark-dependent entrainment of the SCN regulates circadian rhythms of metabolism and physiology in all mammals. Its long, multisynaptic pathway provides 2 forms of information through our nervous system: vision and biological time.[50] In this manner, light influences both the POT regulation of both visual effects and visual reflexes of mammals and RHT regulation of acute and long-term biological and behavioral effects (Figure 2A and 2B).

Light must pass through the inner layer of the inner retina layer to reach the light-sensitive photoreceptors of the outer retina (Figure 4). The retinal photoreceptor layer of the eye contains rod and cone photoreceptors that, respectively, mediate scotopic (low light) and photopic (bright light) vision via the POT. In most mammals, including nocturnal rodent species (the most widely used for animal research), the retina is rod dominated, with approximately 6.4 million rods that account for about 97% of photoreceptors.[105,140,217] Conversely, the retina contains only about 200,000 cones, which account for less than 3% of the photoreceptors.[292] In contrast to the primate retina, the mouse retina does not have a fovea centralis, or central region, that contains the highest cone density and lacks rods and other neurons. The densities of rods and cones peak in the area centralis, a broad central region with fewer receptors than the fovea but more than the peripheral parts of the eye, decrease peripherally around the retina. Peak rod density in mice is about 100,000/mm^2, whereas peak cone density is approximately 16,000/mm^2; the peak cone density is comparable to that of humans, NHPs, and cats.[217]

The photoreceptor outer segment contains light-sensitive visual pigments, which are transmembrane proteins comprising an opsin protein bound to a light-sensitive vitamin A–based chromophore, 11-cis retinal.[176] Absorption of light photons leads to isomerization of the 11-cis retinal to an all-trans state, resulting in a conformational change in the opsin that triggers activation of the G-protein transducin. Once activated, transducin subsequently leads to activation of phosphodiesterase that, in turn, hydrolyzes cGMP, a serine/threonine-specific protein kinase, into GMP. This step results in the closure of cyclic nucleotide–gated ion channels and hyperpolarization of the photoreceptor cells. Photoreceptor cells are depolarized during the dark phase and constitutively release glutamate, effectively reducing their output signal.[13,124,213]

The retinas of rodents, particularly mice, contain 3 visual pigments: a rod opsin with a peak sensitivity (λ_{max}) at 498 nm and cone opsins that are sensitive to middle-wavelength (λ_{max}, 508 nm) and UV (λ_{max}, approximately 360 nm) light.[54,110,192,193] Due to this UV-sensitive pigment, mice show a greater sensitivity to UV light than humans.[192,193,365,399] In addition, unlike humans and some other mammals, mice lack a long-wavelength opsin and thus are less sensitive to longer wavelength light. A common misconception is that mice cannot perceive red-appearing light in the visible spectrum.[100,292] For example, humans are 12 times more sensitive to a red-light stimulus of 600 nm than are mice.[292] This characteristic, however, does not mean that mice cannot detect such light via both the visual and nonvisual systems. When such light is of sufficient intensity and duration, both of the photosensitive systems that regulate the circadian rhythms of metabolism and physiology in mice are quite capable of responding to long-wavelength light.[100,284,285,292]

The nonvisual (circadian) system, which consists of the RHT emanating from the ipRGC of the retina, controls circadian rhythms of metabolism and physiology via light and light–dark cycles. This system was not discovered until 2003 (Figure 4).[34,170] These unique ganglion cells achieve their intrinsic photosensitivity through the expression of the opsin photopigment melanopsin, which absorbs light primarily in the blue-appearing portion of the visible spectrum (564 to 582 nm).[306-308,310] Melanopsin-containing ipRGCs comprise only a small portion of the overall ganglion cell population (1 to 5% depending on the species and estimation methodology), but they project to all major portions of the brain via the RHT, including those with nonvisual (circadian) responses.[57,120,121,152,165] At least 5 subsets of ipRGCs have been identified in primates (4 in the case of nonprimates).[34] Their density is species dependent and described to date only in humans and specific NHPs and rodents.[34,169,170,243,244,416]

The response of ipRGCs to light is an irradiance-dependent increase in photic activation, with downstream responses that are activated by much lower levels of illumination than classic rods and cones.[170] In the field of photobiology, an action spectrum is one of the principal tools for identifying how melanopsin initiates a light-induced response that ultimately translates to circadian regulation. Photopigments like melanopsin have their own action spectrum (Figure 5), or pattern of wavelength sensitivity that varies from species to species.[49,50] Specific ablation of ipRGCs only abolishes nonimage-forming responses, thus identifying this cell class as the principal conduit of photic input to circadian and other systemic responses to light.[57,120,152] Indeed, ipRGCs can detect light when isolated from the retina proper, thus explaining why the photosensitivity of these cells survives the loss of functional rods and cones[34,138,152,195,241,433] and why the spectral sensitivity of nonimage-forming responses is different from that of rod- or cone-based vision.[6,34,90,91,137,241,433] In all mammals, light provides the principal cue for entraining

the circadian system.[14,15] The photoreceptors mediating this process are exclusively ocular, and enucleation eliminates all responses to light.[138,276] However, circadian photoreception, phase-shifting, and suppression of pineal melatonin responses to light are sustained even in the absence of rods and cones and when animals are visually blind.[285] Indeed, all mammals sustain circadian entrainment, suppression of melatonin, and preservation of neuroendocrine and neurobehavioral responses to light via the nonvisual melanopsin-containing ipRGC cells,[307,308] which are directly photosensitive and project via the RHT to the anterior basal portion of the hypothalamus. The hypothalamus is the site of the SCN, which comprise the master circadian oscillator in mammals.[247,425] The SCN projects over a polysynaptic pathway to the pineal gland, thereby driving a series of molecular events that lead to the production of pineal melatonin (*N*-acetyl-5-methoxytryptamine) primarily at night.[10,114,205,261,263] The daily rhythmic melatonin signal contributes to the temporal coordination of normal behavioral and physiologic functions including sleep-wake,[68,246,266,361,443] cognitive performance,[134,141,295,382] reproductive cycles,[68,276,281,317,321] immune functions,[29,63,71,82,228,248,249,341,403] gene expression,[30,66,85,188,256,395,405] hormone levels,[104,188,190,199,211,231,232,274,310,319,348,358,363,381,391,392,403] temperature regulation,[50,53,114,201,234,257,369,376] electrolyte balance,[107] glucose metabolism,[212,230,335,396,414] neural protein synthesis,[23,354,355] and redox states,[323-326,383] and melatonin has remarkable anticancer and antioxidant properties.[142,323-326] Although ipRGC can mediate nonvisual responses to light in the absence of rods and cones, functional rods and cones contribute to these responses under normal circumstances. However, if rods, cones, and melanopsin-containing ipRGCs are lost, then all responses to light are abolished.[34,292] These responses to light include circadian entrainment and pupillary light responses,[143,304] pineal melatonin suppression,[268,269,275] adaptation of visual pathways to light,[245,292] acute disruption of activity,[149] sleep,[5,91,246,298,299] mood and cognition,[219,384] and other important responses that influence animal health and well-being (Table 1).

The pupillary light reflex (PLR), a melanopsin-ipRGC–driven response controls the amount of light reaching the retina by a simple, well-characterized pathway that links a sensory signal and light irradiance to the motor output of pupillary constriction.[143,244,305,331] Data from both animals and humans show that rods, cones, and ipRGCs all participate in the PLR and that their contributions are variable depending on light intensity and spectral content; however, the ipRGCs are spectrally distinct photoreceptors and their 'firing rate' is sensitive to even a few photons of light, which drives the PLR and ultimately most physiological and behavioral responses to light.[59,143,269,305] This feature is particularly relevant during the vivarium dark phase. At the initiation of the lights-off period, when prior retinal irradiance (from light phase ocular exposure) has exceeded the threshold of melanopsin activation, PLR persists for many seconds into the dark phase. In the presence of LAN in the animal room, both PLR and ipRGC activation may continue. During the light phase, this activation is critical for normal circadian regulation of neuroendocrine and neurobehavior parameters associated with animal health and well-being. However, animals exposed to light during the dark phase are at high risk of circadian disruption of the central (i.e., SCN) and peripheral clock systems and subsequently to disruptions of physiologic and behavioral circadian rhythms. While some laboratories[108-112,122,276] have proposed that the nighttime 'dim-light' exposure of one strain of mouse is approximately 5 lx (2.0 µW/cm^2), our lab has demonstrated that in several strains of both rats[37-41,96-101] and mice,[94,102] exposure to broad-spectrum CWF LAN of as little as 0.2 lx (0.08 µW/cm^2) for a period of as brief as 2 h during dark phase is sufficient to disrupt circadian patterns of neuroendocrine and neurobehavioral responses. We discuss this phenomenon more completely in the subsequent section on extrinsic LAN.

Additional considerations for vertebrates. Extrinsic light exposure influences SCN regulation of the hypothalamic–pituitary–gonadal axis[205] and significantly influences metabolism and physiology, resulting in greater uptake of fatty acids by both normal and neoplastic tissue, reduced lean-to-muscle mass,[172] impaired organ function, and more comorbidities.[63,149] Exposure to light at the wrong time of day (such as LAN) elevates serum fatty acids,[26,34,35,94-101] body mass, and body fat.[70,94,135,424,425] Exposing mice to LAN reduces energy expenditure and promotes carbohydrate over fat metabolism, thus increasing body fat mass.[40] Administration of physiologic levels of exogenous melatonin to mice and rats exposed to dim LAN attenuates disruption of circadian rhythms of metabolism in adipose tissue.[40,425]

Light modulates glucocorticoid-associated control of an array of biologic functions, including those maintaining homeostasis and physiologic functions.[162,163,378] These functions include the regulation of corticosteroid levels in hamsters,[190,339] mice, and rats.[133,229,310] Exposure to LAN also affects various physiologic processes that include inflammatory responses, wound healing, blood pressure, growth and development, blood glucose levels, muscle and bone physiology, and mentation.[216,397]

With regard to reproduction, exposure to LAN in the vivarium affects the ovaries of a variety of species from fish to mammals. Oscillating clock genes in the ovaries are regulated in a defined fashion by light–dark cycles; misalignment of the circadian clock can alter or inhibit reproduction.[3,7,67,68,123,222,292,398] Reproduction in research species that are seasonal breeders depends on seasonal patterns of light–dark exposure and melatonin production.[325] Indeed, reproduction in photoperiodic animals is compromised by aberrant lighting during the daily dark phase and is highly improved when animal facilities are completely LAN decontaminated to ensure normal nocturnal melatonin signaling.

Thoughts regarding invertebrates. Extrinsic light conditions are also a major concern when housing and maintaining invertebrates for research, given that biologic rhythms in these animals, including unicellular organisms, share nearly identical complexity with mammals.[32,428] Indeed, clock genes were first identified in fruit flies (*Drosophila melanogaster*), work that was awarded the 2017 Nobel Prize in Physiology or Medicine.[161,333,433] Fruit flies remain an important model for the study of genetics, development, and disease.[32,207] Although constant bright light in animal facilities can adversely affect fecundity, longevity, and development in fruit flies,[209,357] little information is available regarding the effect of daytime light (including LED light) on the physiology and metabolism of fruit flies.[2,94,98,101,406] Irregular lighting conditions may also negatively impact less commonly studied invertebrates. Exposure to LAN attenuates immune responses in crickets,[128] reduces clutch sizes in ants,[237] and dramatically reduces the likelihood of successful mating in moths, fireflies, and aphids.[128,338,398] No information is currently available regarding the use of daytime LED. Nonetheless, these studies underscore the importance of inappropriate lighting, particularly LAN, on circadian rhythms of metabolism and physiology that are highly conserved across species. The use of stable species-appropriate light–dark cycles should always be incorporated into invertebrate housing.

Extrinsic light at night exposure in the vivarium. Human and animal exposure to LAN is one of the most common events in the community, home, workplace, and vivarium.[125,360,387] Approximately 95% of animals used in research are rodents,[122] but the deleterious effects of exposure to LAN on health and well-being apply to all humans and animals. Although rodents have poor visual acuity, they are highly sensitive to light intensity,[21] responding to levels as low as 0.2 lx (0.08 µW/cm^2) or less.[96,99] Exposure of Syrian hamsters to even low levels (15 lx; 6.12 µW/cm^2) of red-appearing 'safety' lights[100] or 0.05 lx (0.02 µW/cm^2) of green-appearing light[365] is enough to disrupt normal nighttime melatonin rhythms, leading to disruptions in other metabolic and physiologic rhythms. Melanopsin-ipRGCs, which regulate circadian rhythms of metabolism and physiology in both normal and neoplastic tissues, are highly sensitive to LAN and can be activated by less than 1 lx (0.41 µW/cm^2) of light.[147,148] Clearly, extrinsic LAN in the vivarium, which can originate from light leaking around doors and hallway lights, observation windows, room circuits and electronics, and racks,[106] disrupts circadian rhythms and triggers a host of metabolic and physiologic effects through 3 key mechanisms: 1) altered expression of clock genes; 2) melatonin suppression; and 3) sympathetic stimulation.[201,218,359,360] Clock genes, which include brain and muscle ARNT-like protein 1 (*Bmal1*), circadian locomotor output cycles kaput, cryptochrome (*Cry*) 1 and 2, and period (*Per* 1 to 3), all of which are regulated by light and light–dark cycles, work together to control cellular functions and maintain homeostasis.[7,355,358,364,367,378] Disruption of these clock genes by LAN alters feedback loops from the normal 24-h cycle and results in misalignment of circadian rhythms, metabolism, and physiology.[258] Dark-phase exposure to dim LAN for as little as 15 min elevates baseline expression of clock genes and phase shifts the SCN activity in mammals.[259,358,367] Chronic exposure to 5 lx (2.04 µW/cm^2) LAN altered circadian expression of *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2* in mice[253] and Siberian hamsters.[28] One further thought for consideration involves the natural setting of feral animals. Light at night in the natural setting from a bright super moon and starlight have been reported to provide combined intensities of less than 0.3 photopic lx, although 0.1 lx is a more realistic value for moonlight.[244,292] For best practices, in the case of the 'controlled environment' of the research animal vivarium setting, we recommend LAN intensity values of less than 0.1 lx, or better yet, no LAN contamination whatsoever, and provide details on how to achieve this situation relatively easily and in a cost-effective manner.[96]

Lists of melatonin-receptor–mediated and –independent physiologic functions are extensive.[63,324,325] Alterations in normal melatonin rhythms disrupt endocrine pathways of reproductive, adrenal, and thyroid hormone axes.[38,391,419] Nocturnal suppression of melatonin by light is species-specific and occurs in an intensity-, wavelength-, and duration-dependent manner.[47-52]

Most mammals have robust circadian nocturnal melatonin rhythms and pineal melatonin production (Table 1);[320] this characteristic, however, is not necessarily the case for all strains of mice.[118,119,201] Radioimmunoassay has revealed robust circadian dark-phase melatonin peaks in C3H, CBA[94,153,201,292,402,406], and Fox*n1* nude mice and rats,[102,201,292] but such peaks were not detected in other inbred strains of mice including C57BL/6, BALB/c, and AKR.[153,201,404] This finding has been countered by investigators who sampled more frequently and thus detected brief and very low level (>10 pg/pineal gland) nighttime peaks in these 3 strains of mice but with no evidence of a circadian rhythm.[82,201,402] Mutations in enzymes catalyzing the synthesis of melatonin, such as *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase,[200,201,205,334,402] may help to explain the variability of melatonin production in various inbred mouse strains. Nonetheless, these mice all maintain robust circadian rhythmicity of other neuroendocrine and neurobehavioral parameters associated with normal light–dark cycles. Indeed, the SCN generates circadian rhythmicity in autonomic nervous system signaling that is entrained to the light–dark cycle independent of the melatonin rhythm,[122] and rodents are 100 times more sensitive to light than humans.[50] Changes in lighting parameters can lead to alterations in sympathetic control that in turn disrupt physiologic processes, including cell cycle control.[25] These effects may help to explain in part why some mouse and rat strains are particularly susceptible to various metabolic diseases and cancers.[228]

A large amount of data documents the effects of LAN on cancer in both humans and rodents. The risk of several cancers is significantly higher in industrialized societies that experience circadian disruption due to nighttime light pollution.[125] Levels of LAN correlate strongly with the development of breast,[37-41,95,96,98,206] prostate, and colorectal cancers.[327,342,343] For more than 30 y, our team has focused its attention on LAN suppression of the pineal nighttime circadian melatonin signal and its effects on normal and neoplastic tissue metabolism and physiology in research animals.[37-42,94-102] Overwhelming evidence to date from our studies and others[81,174,251] demonstrates that circulating levels of melatonin suppress rodent and human tumor proliferative activity in vivo. This suppression occurs via guanine nucleotide-binding protein receptor–coupled MT_1 melatonin receptor–mediated blockade of linoleic acid metabolism to the mitogen 13-hydroxyoctadecadienoic acid via 15-lipoxygenase 1 and aerobic glycolysis (Warburg effect), leading to suppression of the mitogen-activated extracellular signal-regulated kinase p44/p46 (ERK1/2), insulin-like growth factor 1, and serine/threonine kinase signaling pathways. Experimental findings clearly show that exposure to LAN and disruption/suppression of the normal nighttime circadian melatonin signal markedly augments rodent and human tumor linoleic acid metabolism and the Warburg effect to stimulate tumor growth progression.[37-41,94-102,174,215,251]

Melatonin also can reduce estrogen receptor-α mRNA expression or transcriptional activity and aromatase action.[41,262,320,326] In addition, melatonin can inhibit invasion and metastasis by elevating the expression of adhesion proteins E-cadherin and β1-integrin and reducing that of matrix metalloproteinases.[41,252] This potent neurohormone also counteracts tumor immune invasion by promoting IL2, IL12, and IFNλ production in T cells and monocytes, thus further amplifying oncostatic responses.[63] All beneficial effects of melatonin on cancer initiation, metabolism, progression, and immune cell response are attenuated in animals that are exposed to LAN.[320] Whether due to general LAN disruption of circadian rhythms, abrogated circadian nighttime melatonin production, or a combination of the 2, LAN increases cancer risk in humans and animals. As a result of our work and that of others, the International Agency for Research on Cancer (IARC) in 2010 classified night shift work involving circadian disruption, a proxy for LAN exposure, as a probable Class II Carcinogen.[423]

Lighting Technology

The lighting technology that is used in vivaria can have major effects on research animal health and well-being.[8,94-102]

Currently, broad-spectrum CWF lighting is the conventional type of lighting being used worldwide in the home, community, workplace, and vivaria.[182,183] The average rated lifespan (ARL; or B50) indicates when approximately 50% of the lights will fail in terms of usage in hours. The ARL for CWF lighting is between 8,000 and 10,000 h, whereas older technologies have shorter ARLs (e.g., 2,000 to 4,000 h for halogen lighting and 450 to 750 h for incandescent lighting (450 to 750 h), with values depending on temperature (indoor or outdoor; temperatures above or below approximately 23 °C). The temporal period of decay, as measured in terms of degradation of light source intensity (lx; $\mu W/cm^2$) over time, follows a similar trend, with CWF lighting decay periods that are much longer than those of either halogen or incandescent lighting technologies. This trend also applies to increases in light source vibration and ultrasound over time in the aging process of these lighting technologies.[78,79,163,173,183] However, although CWF light has many advantages over older technologies, such as incandescent and halogen lighting, it also has several drawbacks, including disposal issues (CWF light contains toxic mercury, the disposal of which in regular garbage has been banned by many governments around the world), rapid loss of intensity, higher noise and vibration, and rapid burn out (2 to 3 y), depending on usage, temperature, and ballast type. Many of the problems with slow light onset, buzzing, and dimming have been corrected, but the general population considers CWF light as not warm or appealing, as is the glow of a fireplace.[182,183] The last matter can be addressed by using CWF lamps with lower CCT characteristics (i.e., 2,500 K and lower). The CCT is a perceived visible color characteristic of the light source; generally speaking, light with a higher CCT (above 5,000 K) tends to appear more bluish or white appearing (cool) to the observer, compared with light of a lower CCT (below 1,500 to 2,500 K), which appears more reddish or yellow-white (warm).[183]

Worldwide, vivaria are rapidly converting from conventional lighting technologies, such as incandescent and CWF, to LED technology.[86,87,93,173] The LED lighting that is most commonly adopted during this transition is enriched in the blue-appearing portion of the visible spectrum, because this option reflects most closely the full spectrum of natural sunlight to which all life has been exposed during evolution over thousands of generations.[50] LED lighting currently comprises approximately 30% of the light technology used globally by industrialized nations and is estimated to grow to 80% in usage by 2030.[289] As compared with incandescent and CWF technologies, LED technology is cost-effective, energy-efficient, produces minimal heat and virtually no noise or vibration, has sustained spectral quality, lasts up to 40 y without replacement, and may also be tunable (i.e., it can also be regulated for both intensity and spectral quality (wavelength) to provide a wide range of CCT and intensities suitable for personnel. LED lights convert electricity directly to photons of light, as compared with the wasteful mixture of heat and light generated by traditional bulbs and lamps (incandescent, CWF) or those that use high-intensity discharge technology that typically involves electricity-gas discharge using tungsten electrodes and noble gases (mercury vapor, metal halide, sodium vapor, xenon vapor).[289]

As mentioned above, an important feature of LED lighting technology attributable to its solid-state technology is that it emits little-to-no high-frequency vibration or noise (including ultrasonic), as compared with older lighting technologies. In addition, all of the world's leading manufacturers of LEDs, which are comparable in size to standard CWF lamps, produce a wide range of lamps that easily fit and function in standard luminaires, so ballasts need not be replaced. Taken together with the remarkable long-term cost and energy savings, these features make it easy to understand why institutions around the world are rapidly transitioning to LED technology. Indeed, in the animal research field, a number of vendors are rapidly producing and marketing LED-lighted animal housing units to meet demand.

While some information regarding the use of LED technology at night is available for the community, home, and workplace,[78,80] little information is available regarding its daytime use, particularly in animal research settings. Furthermore, companies may send LED products to market without prior investigations of their effects on animal health and well-being or experimental outcomes. The little work that has been conducted to date by groups such as the U.S. Department of Energy and the Environmental Protection Agency has focused primarily on the adverse effects of nighttime LED lighting on humans in the community setting as relevant to visual glare, sleep disorders, or disruption of various circadian biologic rhythms.[86,87,289] The antiquated *Guide*[187] unfortunately does not directly include the emerging new LED technology when addressing the topic of lighting technology. One suggestion in this regard may well be to transition to a type of 'living' or interactive *Guide,* whereby the most up-to-date scientifically supported information pertaining to all facets of animal care and use, including extrinsic factors such as light, is immediately accessible for the animal research community. Organizations, such as the CIE,[78,79] AMA,[86,87] IES,[183] NIH,[273] as well as those associated with the *Concordat*[80] and the ARRIVE guidelines,[293] have been using this type of electronic online technology for many years with great success and acceptance.

For many years now, our team has studied the influence of blue-enriched LED light during the day (lights-on) phase (bLAD) on animal health and well-being in the vivarium setting.[147] Recent IACUC-approved studies from our laboratory revealed that rodents exposed to bLAD, as compared with CWF lighting, and maintained on static rack systems in a standard LD 12:12 photoperiod, exhibited 6- to 7-fold higher circadian dark phase melatonin blood levels, resulting in a marked positive enhancement of the circadian regulation of neuroendocrine, metabolic, and physiologic parameters associated with animal health and well-being.[93,97,98,101] Subsequent studies corroborated these findings in mice and Sprague–Dawley rats[1,406] that were maintained on individually ventilated caging (IVC) systems. This work provided the first experimental data on how the use of bLAD technology affects animal physiology in the vivarium setting. With these data in mind, we suggest a few easily achievable approaches for animal research communities.

Recommendations for the Animal Research Community

Consistently monitor and report light measurements. Computer-directed lighting sensor equipment is currently available on the open market to monitor and record animal room lighting intensities during light and dark phases. Unfortunately, in many cases, these sensors have wide ranges of sensitivity, particularly during dark-phase measurements, fail frequently or become inaccurate over time, or furnish inaccurate light–dark cycle information to a central computer source.[131] In some cases, due to a breakdown in the light control or sensing service, computer-generated light–dark cycles can be inadvertently altered for weeks without notification of personnel, compromising both animal health and well-being and research outcomes.

This error is typically that lights that remain on during the expected dark phase, rather than lights that stay off during the expected light phase (a situation that would be noticed by personnel). In this regard, we recommend that alarms associated with such computer-directed lighting sensor systems be programmed to alert animal care personnel (via office or home computer or cell phone) immediately when deviations in animal room lighting protocol concerns occur; in addition, these alarm systems should be monitored regularly. Lighting deviations are chronotoxic in that they adversely affect normal circadian rhythms of behavioral, physiologic, and metabolic functions.[35-41,96,98,102,103,148,251,320,326,327,342,343] Any deviations should be corrected immediately, as the correct protocols are relatively easy to implement.

We also encourage personnel to directly and regularly monitor, record, and report light-phase illuminance (lx) or irradiance ($\mu W/cm^2$) levels in the macroenvironment (animal room) and microenvironment (within a cage at eye level) as completely as possible. A variety of low-cost radiometer–photometers are currently available for both older (i.e., CWF) and newer (i.e., LED) lighting technologies that can collect this information after appropriate calibration. Such reporting would allow all stakeholders to meet the basic recommendations of the current *Guide*[187] and the ARRIVE guidelines.[292] We further strongly recommend that investigators report the time of day that animal handling and experiments are conducted (including surgeries, tissue harvests, and treatment regimens) relative to the animal's light on-off schedule because time of day significantly affects circadian rhythms of animal metabolism and physiology and experimental outcomes.[9,37-41,94-102,406]

Reduce variation in vivarium light. The 2 principal elements in light-controlled regulation of animal behavior and physiology are physical-biologic stimulus processing and sensory-neural processing.[164,312] The physical-biologic processing elements are the light source physics, the animal's conscious and reflex behavior in relation to the light source, and the transduction of light to the retina. Factors influencing this physiology include the wavelength sensitivity of the retinal photoreceptors, photoreceptor distribution, photoreceptor adaptation state, and the ability of the CNS to temporally integrate photic stimuli.

Light source geometry relative to the eye is important in understanding the elements of ocular physiology that influence circadian regulation. One measurement technique that has been characterized for architectural lighting[108] and recommended by the *Guide*[187] is to simply place a light meter at 1 m above the floor of an empty animal room, aim it directly at the light source, and measure light illuminances with the lights on and off. However, the data derived from this approach do not accurately capture the corneal illuminance experienced by animals. Clearly, conscious and reflex behaviors such as head movement, eye motion, eye blink, source avoidance, and eye closure are important considerations.[143,179,244,292,305] On the microenvironmental level, cage type (i.e., polycarbonate or polysulfone), color, wall thicknesses, and location on the rack should all be considered. Nesting materials and enrichment devices can also influence circadian rhythms in neuroendocrine and neurobehavioral parameters in rats and mice.[1,77,81,83,358,359] Cage location on a rack can markedly influence light intensities. For example, light intensities are typically greater near the top of the rack[345] but may vary by as much as 80-fold on the same rack and differ by more than 10-fold when measured in the front, middle, or rear of the cage at a given location.[2,94,96,99,406] Cage placement on the rack also affects exposure, as top-tier cages receive 3 to 19 times more light than those at the bottom of the rack.[75,154]

Based on our current knowledge (Table 1), we recommend that ambient microenvironmental lighting intensities during light phase range between approximately 500 lx (204 $\mu W/cm^2$) and 800 lx (327 $\mu W/cm^2$) for humans; for domesticated and research animals, we recommend a lower range on the order of 100 to 400 lx (41 to 163 $\mu W/cm^2$). In the case of rodent species, light-phase ocular light intensities in the microenvironment (within-cage) should not exceed approximately 75 lx (31 $\mu W/cm^2$; average intensity, back-to-front of interior cage environment)[96,97,100,102,424,425] and should be lower when feasible.[163,164,244,292] In addition, the lighting technology should provide diffuse daytime lighting that is more blue-appearing (in the visible spectrum), with the objective of healthful exposure of both the visual (rod, cone) and nonvisual (melanopsin-ipRGC) photoreceptor systems to known thresholds of different biologic responses to light, including entrainment of the circadian clock, pupillary constriction, regulation of hormones such as melatonin and corticosterone, and modulation of sleep and cognition. In contrast, the *Guide* indicates that caution should be exercised with regard to increasing daytime illumination in animal rooms for purposes of housing, handling and maintenance and recommends lighting intensities between 130 and 325 lx at cage level in the room.[187]

A comment is warranted here regarding the effects of CWF or LED light on data collected in research animals. Light-phase exposure to LED light that is enriched in the blue-appearing portion of the visible spectrum (cooler, 5,000 K) clearly amplifies the dark-phase circadian melatonin signal, extending the signal for 2 to 4 h into the light phase,[93,97] as compared with broad-spectrum CWF light (warmer, 4,000 K). This extension has the opposite effect of CWF LAN and results in greater suppression of rodent and human tumor metabolism and growth by melatonin and enhancement of circadian rhythms of neurohormonal and neurophysiological factors.[40,41,95,96,99,101,102,163,174] Furthermore, others have suggested that either CWF or LED light enhanced in the violet portion of the visible spectrum (390 to 350 nm) at higher intensities (above 100 lx; above 45 $\mu W/cm^2$) (referred to as 'violet-pumped') may be most appropriate for vivaria because it appears 'white-like' to both humans and mice during light phase.[244,292] The effects of these violet/blue enhanced CWF and LED lighting technologies on animals and animal-based research models have not yet been reported. However, work underway by our laboratory and others will help to address these questions.

Nesting materials and enrichment devices can form physical barriers between animals and light sources and can thereby alter animal physiology and metabolism.[424,425] This situation sets the stage for significant interanimal variability and for potential changes in retinal morphology[154] that may confound toxicity studies.[245,309] In deference to competing considerations, particularly in regard to small research animal caging, one solution may be to reduce the number and/or size of enrichment devices that are placed in rodent cages or use enrichment devices such as cotton squares rather than light-blocking colored 'enrichment' items.[425] For some studies, particularly those that are circadian dependent, removal of all enrichment devices is also an option if justification is provided and IACUC approval is secured. At a minimum, the type and vendor information of such items should be reported in publications, particularly for rodents to support research reproducibility, transparency, and accountability.[77]

Options for minimizing light variation in cages include using a similar location for all cages on a given study, rotating cage

position on the rack to control for cage position on the rack, or using specially designed photobiologic light cabinets that deliver consistent lighting to all cages. Some investigators use small spaces or cubicles and place lamps in corners, which may result in more consistent illumination. In most cases and during specific investigations, cage racks can be placed appropriately under luminaires to deliver similar external light intensities to different units. In addition, cage material, bedding, and enrichment devices modulate the amount of light available to the animals.[425] Therefore, we recommend the following for the use of small animals such as rodents: 1) minimize the number and type of enrichment devices per cage; 2) be cognizant of and report the type of enrichment devices used; 3) be consistent during and between studies with regard to type/number of enrichment devices used; 4) maintain equivalent lighting for control and experimental animals; and 5) monitor and report macroenvironmental (room) and microenvironmental (within cage) lighting intensity illuminance and irradiance measures (at eye level) to promote experimental reproducibility, accountability, transparency, animal health and well-being, and valid scientific outcomes.[77,94,100,101,425] For short-term studies, some investigators may remove all enrichment devices, with IACUC approval. Recent studies have shown that the spectral transmittance of light passing through standard rodent cages (polycarbonate or polysulfone) of different tints significantly influences circadian metabolism and physiology in commonly used rodent strains.[97,98] Further elucidation of the specific ocular and neural elements mediating these biologic effects of light in mammals, particularly in determining the interdependence and variability, remains an emerging science.[97,138,244,292]

Cage rack technology (i.e., static, IVC, and emerging biocontainment technology) may be important when using either CWF or LED lighting during the light phase.[2,94,406] Whereas animals maintained on static or IVC systems are exposed to either diffuse, broad-spectrum CWF or LED lighting from overhead luminaire systems (i.e., tubular, or 'T' designated lamps), animals that are housed in these new types of biocontainment units are exposed to LED strip lighting that varies in its location due to differences among manufacturers. Animal ocular light exposure is linear across the cage unit and not as diffuse as with tubular lamp lighting, and light photons excite the visual rod-cone and melanopsin-ipRGC systems differently.[244,292] How this situation translates to potential circadian rhythm alterations in neurobehavioral and neurophysiological parameters has only been recently addressed.[1,94,97,98,406] These studies revealed that most strains of rats[97,98,101] and mice[94] maintained on either static or IVC caging[406] in translucent polycarbonate cages and exposed to bLAD had significantly higher plasma melatonin levels and lower body growth rates, food and water intake, and plasma circadian markers than did animals exposed to CWF light. However, one strain of rats (Sprague–Dawley) housed in a newly manufactured and marketed LED-lighted biocontainment system had elevated circadian nighttime melatonin blood levels and changes in some blood analytes.[1] Nevertheless, these studies[1,406] clearly showed that CWF or LED bulb type and technology can influence circadian rhythms. Nonetheless, LED light in general also has broad effects on the circadian regulation of neuroendocrine, metabolic, and neurobehavioral parameters. Despite variations in the type of light exposure and spectral quality due to the various aforementioned parameters, all should be standardized in experimental design and fully reported in research publications.

Another consideration regarding the rapidly emerging tunable LED technology is the use of gradual changes in light-phase and dark-phase onsets, simulating dawn and dusk.[122,244,292] In other words, at the onset of the light phase, light sources can be gradually increased in intensity from 0 to 400 lx (room measures) and in spectral quality from longer wavelength (red-yellow) to shorter wavelength (blue-enriched) over a brief period (e.g., 3 to 5 min). Conversely, at the onset of the dark phase, animal room lighting can be adjusted in reverse fashion to decrease intensity (from 400 to 0 lx, room intensity) and increase wavelength (blue-enriched to red-yellow–enriched to total darkness [0 lx]), thus mimicking the natural transition from day to night. Some rodent studies have shown that these gradual photoperiod transitions may reduce stress and positively influence animal health and well-being.[30,31,132,134,135] Based on the studies discussed above, implementation of gradual photoperiod transitions at light onset and offset should be considered.

Eliminate vivarium LAN pollution. The *Guide*[188] recommends the elimination or limitation of light exposure during the dark phase and the use of a time-controlled lighting system to guarantee regular cycling, with light cycles set at intensities described above. Despite these recommendations, vivarium lighting is often adjusted to meet the needs of animal care and research personnel. Brighter room lights are often used during cage changing or room cleaning to aid in visualization; dimmer intensities may be used during the remainder of the light phase when personnel are not present. These photic disturbances, including entering and exiting rooms from a lighted corridor during the dark phase and using observation windows, even when covered with red safety filters, alter animal ocular light exposure; the degree to which this occurs also depends on cage and rack location in the LAN-contaminated animal room.[99]

For many years, our Tulane Center for Circadian Biology team has studied the influence of light, particularly LAN, on human and animal metabolism and physiology. Although the role of light in vision is widely recognized, our studies have focused on the nonvisual effects of light, including entrainment of circadian rhythms and regulation of neurohormones and neurobehavior. More specifically, our NIH- and AALAS Grants for Laboratory Animal Science-supported studies provided the experimental evidence that supports epidemiologic findings[38-40,95,96,99] in the night shift work population regarding the association between LAN and risk of invasive breast cancer.[103,341-343,372] As mentioned earlier, night-shift work, which involves LAN exposure and circadian disruption, is currently classified as a Class IIA probable human carcinogen by the International Agency for Research on Cancer of the World Health Organization.[423]

In view of these considerations, we recommend the elimination of all LAN in animal housing rooms during the dark phase. As discussed above, LAN-induced suppression of endogenous melatonin production may promote various disease processes, including carcinogenesis and metabolic disorders.[38-40,95,96,99,102] LAN contamination in animal facilities is a common problem, even in modern facilities; however, simple remedies are available for many common sources of LAN contamination. To ensure maintenance of complete darkness, animal holding rooms should be inspected for sources of light pollution, and room entrances during the dark phase should be controlled to prevent light intrusion. A variety of cost-effective data loggers and alarm systems can be used to monitor animal facility light intensities and detect unwanted light and inappropriate entry during the dark phase. Although one set of recommendations may not be optimal for all animal uses, important considerations to ensure complete darkness during dark phase include the following: 1) removing unnecessary lighted equipment; 2) covering light sources in animal rooms, including electronic indicator

lights, ventilated tower screens, and circuits; 3) eliminating animal observation windows on doors or completely covering them with blackout shielding; 4) installing door frames shoes, seals, and sweeps with vinyl gaskets and anodized aluminum encasements; and 5) installing light-tight, black-out curtains. These modifications can be remarkably effective. When possible, entry into the main animal holding quarters from an unlighted LAN-decontaminated internal room, as compared with the outside lighted corridor, should also be considered.[96,99]

Finally, some animal species, including mice and rats, have generally been regarded as being insensitive to red light.[122] Although partially true with regard to the visual system, numerous studies that include irradiance response curves to long-wavelength light (>600 nm) demonstrate sensitivity to red light if the intensity and duration are high enough.[49,93,100,292] Limiting dark-phase exposure of animals to dim (not bright) red safety light (under 35 lx or 14 µW/cm^2) for less than 15 min during the dark phase (including red safety flashlights) can be an effective approach to maintaining circadian organization in research animals.[100] However, all red-appearing lights do not emit solely in the red spectrum and may not exclude all shorter wavelength light. We recommend using a photometer to confirm emitted wavelengths before use. As a result of this misunderstanding of photobiology, some facilities have used reverse lighting in animal facilities (lights off during the work day and on at night. This approach reverses animal circadian rhythm cycles, and red light or sodium light (589 to 590 nm) during the work day allows personnel to see but is on the margins of rodent circadian sensitivity.[292] The known visual pigments of the mouse retina are around 12 times less sensitive than those of humans to a 600-nm red light and around 8 times less sensitive to a 589-nm sodium light. As such, the level of nocturnal light required for humans to work in a mouse room for a sustained period of time would certainly produce biologic responses in mice. With this situation in mind, we recommend only limited use of these light sources (below 35 lx [14 µW/cm^2]) for less than 15 min) during the dark phase.[100] Reverse light cycles can work well for both research animals and personnel with regard to maintaining normal workday routines without compromising animal health and well-being or experimental results.[39-41,102,131-135,274-276] As described in these and other reports, both humans[246] and research animals, including rodents,[244,292] reverse their circadian rhythms of metabolism and physiology accordingly to the reverse light cycles. Changes in circadian rhythms of neurohormonal and neurobehavioral responses may begin to occur within 24 to 48 h.

Use and apply the new metric for measuring and providing vivarium light. Historically, the lack of a fully established and consistent method of properly measuring light in the research animal setting confounded the proper replication of experimental conditions and comparisons across investigations that hindered scientific progress. This has now changed, as will be discussed subsequently. As we have shown, the scientific literature contains numerous studies of circadian, neuroendocrine, and neurobehavioral responses to calibrated light exposure. That said, many studies fail to provide basic information pertaining to animal facility light levels, light spectral quality, or even lighting protocols other than the fact that they conform to local regulations. Almost always, such regulations are based solely on light intensity levels applicable to working conditions for staff rather than considerations for animal physiology and behavior.[273,292] More specifically, the physical properties of light and other portions of the electromagnetic spectrum (X-rays, UV, infrared, radio waves) are not differentiated, except with regard to the ability of light to support human vision,[244,292] and almost all light quantification currently assumes a human (standard) observer, as defined by the CIE.[79] Light may vary in not only total energy but also in its distribution across wavelengths. Because humans are not equally sensitive to all wavelengths, summing energy across a spectrum cannot predict brightness. Therefore, a spectral efficiency function ($V\lambda$, or photic sensitivity function) is used and defined based on human perceived brightness, which peaks at 555 nm and is far from the portion of the spectrum to which most animals are most sensitive. Indeed, some animal species can use UV radiation, which falls outside of the technical definition of light, for vision. Thus, the current anthropomorphic metrics are not suitable for quantitative guidelines for light exposure of animals.

When investigators provide light measurements, they generally report values in terms of lux (lx), which indicate the amount of light falling on a surface that stimulates the mammalian eye during the daytime (i.e., the perceived brightness to the human visual system).[244,292] The lux measurement unit is based on the daytime (photopic) sensitivity curve and has a peak sensitivity of about 555 nm, characteristic of the red and green (middle wavelength) M-cones of the human retina. As such, the lux unit is not relevant for most animal species, including rodents, because it does not adequately reflect nighttime (scotopic) responses that occur when rods provide the primary responses to light, nor does it include the contribution of the important nonvisual melanopsin-ipRGC system responses. Radiometric units based on unweighted power measurements (µW/cm^2) are more relevant for animals and are preferred in circadian biology.[83,84,244,292] In the context most familiar with biologic researchers (i.e., lux values), we recommend that the use of the new photometric units equivalent α-opic lux, where α is defined as the receptor opsin λ_{max} in nm.[79] The α-opic irradiance matrix weighting functions used for this metric are not defined by the spectral sensitivity of any single visual response (as is the case for $V\lambda$) but rather are based on the light sensitive receptors responsible for detecting light (and thus including all responses to light). The complement of retinal photoreceptors and their photopigments are largely retained across all mammals. Therefore, the photopigment complement of most animal species and each photopigment channel can be evaluated independently by defining α (S-cone: Cyanopic, λ_{max} = 419 nm; ipRGC-melanopsin: λ_{max} = 480 nm; Rod: Rhodopic, λ_{max} = 496 nm; M-cone: Chloropic λ_{max} = 531 nm; L-cone: Erythropic = 558 nm). The α-opic lux values are always identical to the photopic lux for a theoretical equal-energy radiator, based on a 32-y-old standard observer. One limitation of the α-opic measurement system is that although it is readily translatable across almost all species,[244] it is currently not readily scalable to all nonmammalian vertebrates. For instance, some fish species have over 10 photopigment classes. Nonetheless, α-opic irradiances can be calculated for subsets of these photopigment classes and for photopigment classes that have not yet been identified. This greater complexity of the nonmammalian photobiology underlies our decision to focus this review primarily on humans and research mammals.

As mentioned above, the primary reason for using illuminance measures of lux in animal studies is that lux meters are inexpensive and readily available, and lux is the primary output of the commercially available light meters. Historically, consensus of opinion holds that expecting all vivaria and researchers to adopt such strict guidelines is unrealistic and that reporting lux is better than reporting nothing.[244,292] Recent guidelines on the use of light in scientific investigations recommend that SPD of all light sources, or the amount of power that a light source contains

at each wavelength in the visible spectrum (400 to 740 nm)[79] should always be reported to support reproducibility.[77]

In February 2023, a workshop entitled third International Workshop on Circadian and Neurophysiological Photometry was held in Manchester, UK, to address the problem of light measurement in animal research. This workshop resulted in a consensus view of an expert working group that included expertise spanning mammalian photobiology, neurobiology, and animal husbandry and welfare. A specific aim of the workshop was to formulate a consensus agreement on appropriate metrics for quantifying light for nonhuman mammals and using these metrics to improve animal welfare and repeatability in animal research. The conclusion reached was that the best available approach to quantify light for research animals is a species-specific α-opic metrology that can be used for both animal husbandry and experimentation. A manuscript that is currently being prepared for submission to an open-access journal will provide guidance on using this metric for multiple rodent species and other mammals used in research.

Before this recent workshop, a rodent irradiance toolbox was developed to allow calculation of α-opic lux units based on the photopigments of the rodent retina.[292] This toolbox is freely available online.[277] Researchers can use any one of a range of properly calibrated low-cost spectroradiometers to accurately measure SPDs that can then be used as raw data for the rodent toolbox. The rodent irradiance toolbox enables calculations of α-opic lux units based on the photopigments of the rodent retina and provides effective irradiance calculations for rod, cone, and melanopsin photoreceptors that drive visual, circadian, neuroendocrine, and neurobehavioral responses.

With this in mind, our advice is that investigators record the light environment in the most complete form possible, namely corneal SPDs. Although the mathematical procedure for measuring α-opic lux values is fairly straightforward, simple-to-use light meters that employ these units are not currently available. As mentioned above, the rodent irradiance toolbox that was developed for this purpose allows calculation of lux-derived units based on the photopigments of the rodent retina.[292] The toolbox automatically calculates these quantities from information provided by the user. These quantities can also be calculated manually by using relevant spectral sensitivity functions that are provided in the reference portion of the worksheet. Researchers can also use any of a variety of properly calibrated low-cost spectroradiometers for accurate light irradiance measurements to create the raw data file for the rodent toolbox.[277] Spectroradiometers (capable of measuring the spectral output of the light source), as used in our studies (FieldSpec, ASD, Boulder, CO), are somewhat more expensive.

As an example, in our previous studies,[38-41,96-102,164] CWF and LED lamps were installed in overhead T8 assemblies in light-proof rooms and the spectral characteristics of each light source were measured separately using a spectroradiometer with a cosine receptor attachment (FieldSpec, ASD). Light source measurements through cages were carried out with a spectroradiometer with a minimum wavelength between 325 to 780 nm (most employ a minimum of 380 nm), generating a raw data file in an Excel spreadsheet. To calculate the effective rodent rod, cone, and melanopsin photoreceptor illuminances, the light sources were entered into a toolbox worksheet. The SPDs for these experiments were imported into the worksheet in 1-nm increments between 325 and 782 nm. The toolbox lists the rodent spectral range as extending to 298 nm, which is beyond the range of the spectroradiometer used in our studies. According to Toolbox instructions, values between 298 and 325 nm were manually changed to 0. The 5 basic steps for using the rodent toolbox are summarized as follows based on the online website: 1) beginning with the right side in the blue box, select the title; 2) select the mode: 1 nm, 3 nm, 5 nm, or approximate; 3) input the light source information from the dropdown box; 4) input units, amount, and additional light source parameters; and, 5) on the right side, input raw data file from the Excel spreadsheet.

The current rodent toolbox calculates radiometric and photometric values (Photon flux [cm^2/s], irradiance [$\mu W/cm^2$], photopic illuminances [lux; $\nu(\lambda)$], and rodent retinal photopigment weighted illuminances [α-opic lux]) for small, medium, and long cones (just small and medium in mice), and the melanopsin-ipRGCs, where photon flux represents the number of light photons per second per unit area of the retina. For a more complete definition of all terminology employed in this section, readers are directed to the CIE website.[79] Melanopic lux (mLux) represents the final component of the new metric. This value is the basis for all other calculations for visible light that quantify the impact of the biological (melanopic) effect of lighting on animals. It is associated with the response of the nonvisual ipRGC system, rather than the cones and rods, as is the case for traditional lux; therefore, the new metric term 'mLux.' The rodent toolbox provides several straightforward examples that include user-measured SPDs, comparison of light source, and simple light conversions that include calculation of mLux values. The ideal tool for measuring α-opic irradiances will occur with the development of an inexpensive, widely available light meter that returns the relevant metrics without requiring the user to manually perform these calculations. While such devices could be produced by combining a spectrophotometer with the appropriate data processing system, manufacturers have not yet developed this technology. However, the recent development of portable multichannel light sensor technologies provides a means to this end. Such devices could directly and accurately provide species-specific measurements with a minimal error rate. Until that time, we strongly encourage the use of this toolbox to report vivarium light measures that influence animal health and well-being and support reproducibility, transparency, and accountability,[77] particularly if the goal is to provide a comprehensive description of light as it affects circadian, neuroendocrine, and neurobehavioral systems.

Conclusions

Light is an extrinsic factor that much like noise, vibration, temperature, humidity, and air and water quality profoundly influences animal physiology, behavior, health, and well-being. Consistent light exposure beneficially modulates intrinsic factors that include circadian rhythms, genetics, aging, and immune and endocrine status. Whether emitted by the emerging LED or conventional light technologies, light regulates our circadian systems in an intensity-, duration-, and wavelength-dependent manner.

Biomedical research and engineering rely on accurate measurement and reporting. Our increasing understanding of the visual and nonvisual systems and their role in regulating physiology and behavior have revealed that the current methods of light measurement and reporting are inadequate. Exactly how these methods should be updated is a question that remains and will no doubt be revisited as our understanding of both systems evolves. The current state of the science, nonetheless, has now reached a point that compels us to take important steps forward in this process. To this end, our team participated in the aforementioned expert working group in Manchester, England, on the effects of light on rodent physiology and behavior. While

the aim of this international meeting was to develop simple lighting guidelines for housing and testing research animals, particularly rodents, based on scientific consensus with regard to published data, the results of this important meeting will soon be available.

Understanding the influence of light on animal physiology, metabolism, and behavior must take into account the functions of both the visual and nonvisual (circadian) systems, including their differing sensitivities to light intensity, wavelength, duration, how they interact, differences in lighting technologies, as well as a multitude of species-specific differences in responses to light. We hope that this overview of the influence of light on circadian rhythms, current industry standards for appropriate light measurement in the vivarium, the visual and nonvisual systems, simple recommendations for improving control of vivarium light/dark cycles, and appropriate recording and reporting light measurements has helped to clear up some of the currently misunderstood aspects of light as an extrinsic factor influencing animal research. The consistency and quality of lighting technology used to control photoperiods during research animal experiments are of paramount importance in maintaining normal animal biologic rhythms of metabolism physiology and behavior in positively influencing scientific outcomes. We, therefore, encourage the animal research community to be cognizant of the critical impact of light as an extrinsic factor, lighting technologies, and lighting protocols on the research animals that we use and care for, as well as on our own daily lives.

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