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REVIEW OF THRESHOLDS AND RECOMMENDATIONS FOR REVISED EXPOSURE LIMITS FOR LASER AND OPTICAL RADIATION FOR THERMALLY INDUCED RETINAL INJURY

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ABSTRACT

Exposure limits (ELs) for laser and optical broadband radiation that are derived to protect the retina from adverse thermally induced effects vary as a function of wavelength, exposure duration and retinal irradiance diameter (spot size) expressed as the angular subtense α. A review of ex-vivo injury threshold data shows that in the nanosecond regime, the microcavitation-induced damage mechanism results in retinal injury thresholds below thermal denaturation-induced thresholds. This appears to be the reason that the injury thresholds for retinal spot sizes of about 80 µm (α = 6 mrad) and pulse durations of about 5 ns in the green wavelength range are very close to current ELs, calling for a reduction of the EL in the nanosecond regime. The ELs, expressed in terms of retinal radiant exposure or radiance dose, currently exhibit a $1/\alpha$ dependence up to a retinal spot size of 100 mrad, referred to as α_{max}. For $\alpha \geq \alpha_{max}$, the EL is a constant retinal radiant exposure (no α dependence) for any given exposure duration. Recent ex-vivo, computer model and non-human primate in-vivo threshold data provide a more complete assessment of the retinal irradiance diameter dependence for a wide range of exposure durations. The transition of the $1/\alpha$ dependence to a constant retinal radiant exposure (or constant radiance dose) is not a constant α_{max} but varies as a function of the exposure duration. The value of α_{max} of 100 mrad reflects the spot size dependence of the injury thresholds only for longer duration exposures. The injury threshold data suggest that α_{max} could increase as a function of the exposure duration, starting in the range of 5 mrad in the µs regime, which would increase the EL for pulsed exposure and extended sources by up to a factor of 20, while still assuring an appropriate reduction factor between the injury threshold and the exposure limit.

Keywords: laser; optics; non-ionizing radiation; radiation damage

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INTRODUCTION

Exposure limits (ELs) for laser and incoherent broadband optical radiation are defined on the international level by ICNIRP (ICNIRP 1996, 1997, 2000). Other optical radiation standards and regulations either adopt the ICNIRP limits (IEC 2004, 2006, 2008, EU 2006) or, if nationally defined, are usually well harmonized with the ICNIRP set of ELs (ANSI 2007). In some documents, the exposure limits are referred to as maximum permissible exposure, MPE.

The laser and broadband ELs for thermally-induced retinal damage depend on the angular subtense of the apparent source α, expressed in milliradians (mrad) or radians (rad). For circular sources, the angular subtense α is proportional to the retinal irradiance diameter *D*. The issue of determining the apparent source size α for different irradiance profiles is discussed elsewhere (Henderson and Schulmeister 2004, Schulmeister et al. 2008b) and therefore is not addressed here. The basic dependence of the retinal injury threshold on the retinal area irradiated is discussed in terms of the retinal irradiance diameter (or retinal spot size) *D*. An apparent source which produces a larger than minimal retinal spot size is referred to as “extended source”. Most collimated laser beams produce a minimal retinal spot on the retina and therefore are referred to as “small source” or “point source”. This is the most hazardous types of sources, for a given exposure duration, the least amount of energy into the eye is required to produce a threshold lesion or injury. This “point source” image is the “default” condition for collimated laser beams and applies to all zero-order beams and generally to beams with good beam quality. For special laser beams, such as line lasers, lower quality laser beams, diffuse reflections or the introduction of light into the eye by Maxwellian view, a retinal spot size larger than the minimal retinal irradiance diameter is possible. On the other hand, sources that emit incoherent broadband radiation, at distances where they can present a retinal hazard, are always extended sources. Due to physical limitations, incoherent broadband sources very rarely represent a thermal retinal hazard. Only intense flashes and high power discharge lamps such as high power Xenon arc lamps (that were used for medical retinal photocoagulation before lasers) and the sun viewed with a telescope can induce thermal damage of the retina. Hence, laser injury thresholds and laser exposure limits are emphasized in this assessment; however, the discussion also fully pertains to optical broadband radiation.

In this review, threshold retinal injury doses and exposure limits (EL) are presented both in terms of the total intraocular energy (TIE) expressed in millijoules (mJ) or microjoules (μJ) and in terms of retinal radiant exposure (mJ cm^{-2}). In exposure guidelines, ELs are generally expressed in terms of the corneal radiant exposure, where the exposure that is to be compared with the EL is to be averaged over a 7 mm aperture. The TIE measured at the cornea is simply the total energy incident upon the cornea that can be transmitted to the retina unrestricted by the pupillary aperture. Retinal injury thresholds are often report in terms of the TIE which is a directly measured quantity. By multiplication of the EL values with the area of a 7 mm diameter aperture, ELs can be expressed in terms of the TIE and directly compared with injury thresholds. Likewise retinal injury thresholds and ELs can also be expressed in terms of the retinal radiant exposure (i.e. the energy per unit area incident upon the retina). The retinal radiant exposure can be calculated by multiplying the TIE by the optical transmission of the outer ocular media (cornea, aqueous humor, lens, vitreous humor) and dividing by the irradiated retinal area. For simplicity and comparison purposes, the transmission of the outer ocular media is often assumed to

Table 1. Dependencies on α and retinal spot diameter D for the different spot size regimes.

		Dependence of EL when specified as	
Angular subtense α (α_{min} = 1.5 mrad, α_{max} = 100 mrad)	**Retinal diameter D**	**TIE or corneal radiant exposure**	**radiance or retinal radiant exposure**
$\alpha < \alpha_{min}$	D < 25.5 µm	D^0 (i.e. no dependence)	$1/D^2$ or $1/\alpha^2$
$\alpha_{min} < \alpha < \alpha_{max}$	25.5 µm < D < 1.7 mm	D^1 or α	$1/D$ or $1/\alpha$
$\alpha > \alpha_{max}$	D > 1.7 mm	D^2 or α^2	D^0 (i.e. no dependence)

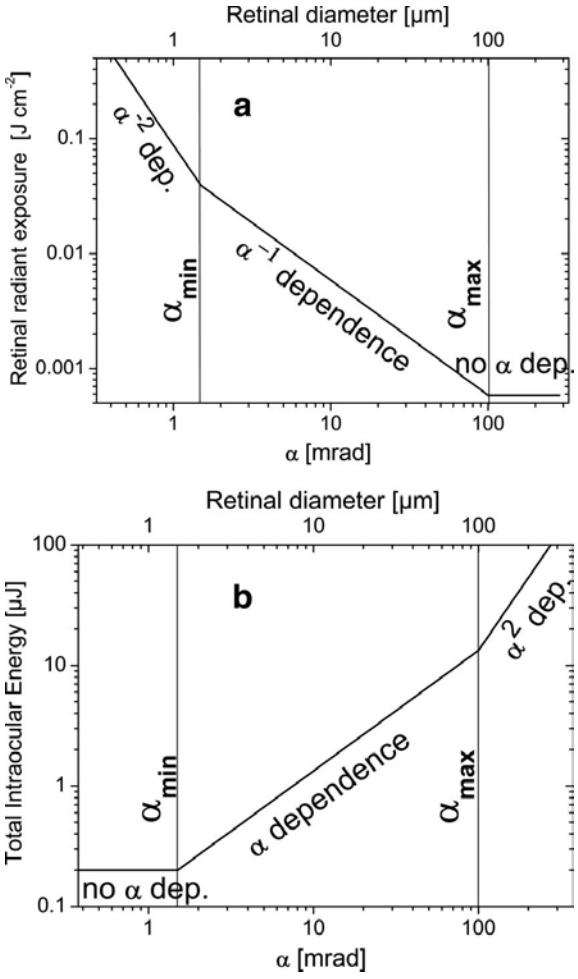

Fig. 1a and 1b. General retinal spot size dependence of the EL values. a) Specified as retinal radiant exposure (or radiance dose, as is the case for broadband incoherent ELs). b) Specified as TIE or corneal radiant exposure (as is the case for laser ELs). The actual values are derived from the laser EL for the example of pulse durations between 1 ns and 18 µs for visible wavelengths and assuming an ocular transmittance of 1 for the calculation of the retinal exposure values.

be 1.0. The retinal radiant exposure is proportional to the time integrated source radiance (Sliney and Wolbarsht 1980, Henderson and Schulmeister 2004). The broadband ELs are expressed in terms of the source radiance (W cm^{-2} sr^{-1}) or time integrated source radiance (mJ cm^{-2} sr^{-1}) (also referred to as radiance dose).

A retinal injury threshold determined experimentally in vivo or ex vivo for a given set of exposure conditions is usually reported as the ED_{50} as determined by probit statistics (Sliney et al. 2002). The ED_{50} is that dose which results in a 50% probability of observing a response or "lesion" at some time after exposure (typically 1 – 48 hours). The underlying probability distribution of the dose-response curve is assumed to be normally distributed with the log of the dose. The slope of dose-response curve defined as ED_{84}/ED_{50} or ED_{50}/ED_{16} is typically 1.2-1.4 for in-vivo (see for instance Lund et al. 2007) and 1.05 -1.2 for ex-vivo (Schulmeister et al. 2008a) thresholds.

The regimes and spot size dependencies of the retinal thermal EL are summarized in table 1, where the retinal diameter D on the human retina is calculated by multiplying the angular subtense of the source α by the air equivalent distance between the retina and the relevant principle plane of the standard human eye which is the effective focal length of the human eye or 17 mm. The two equivalent ways to plot the spot

size dependence of both the ELs as well as damage threshold data are shown in Fig 1a and 1b. A linear dependence on α (or D) in "corneal space" (i.e. the space where the laser ELs are defined) will become a $1/D$ dependence when the data is plotted as retinal radiant exposure or radiance dose. For values of α larger than α_{max} the spot size dependence in terms of TIE ("corneal space")[§] is proportional to D^2 which will be transformed to a D^0 dependence (i.e. no dependence on D) when the data is plotted as retinal radiant exposure or radiance dose. It is instructive to plot the data in terms of both the TIE and the retinal radiant exposure to assess the spot-size dependence of the damage threshold.

There are three distinct spot size dependence regimes, and we discuss these regimes starting with large retinal spot sizes. For $\alpha > \alpha_{max}$, there is no spot size dependence when the ELs are plotted as retinal radiant exposure (or as radiance dose). This can be understood on the basis of radial cooling (Schulmeister et al. 2008a). Radial heat flow from the exposed retinal area to the un-exposed surrounding cools the irradiated area. This cooling "wave" proceeds from the edge of the exposed area to its center as described by the laws of thermal diffusion. The width of the ring that is affected by cooling, starting from the edges, increases as the square root of time. In the large spot regime, i.e. $\alpha > \alpha_{max}$, the retinal irradiance profile is so large that the cooling effect does *not reach* the center of the irradiated spot during the pulse duration. Consequently, the temperature that is reached in the center of the spot at the end of the pulse does not depend on the diameter of the spot. In that regime, the maximum temperature of the center of the spot depends on the radiant exposure only, and not on the size of the laser spot. In the second regime, for spot sizes $\alpha_{min} < \alpha < \alpha_{max}$, the cooling effect *does reach* the center of the irradiated spot during the pulse duration and the ELs depend on the spot size α. The spot size dependence of the ELs is related to the time it takes to reach the center of the spot: smaller spots are cooled from an earlier point in time onwards than larger spots. This results, for a given retinal radiant exposure, in lower temperature rises for smaller spots as compared to larger spots. Therefore, in terms of retinal radiant exposure (or time integrated radiance), smaller spots feature higher EL than larger spots. Finally, in the third regime of spot sizes less than 25 µm (equivalent to α_{min} = 1.5 mrad for 17 mm eye length), the EL in terms of retinal radiant exposure exhibits a square dependence on the nominal laser spot diameter, which is equivalent to no spot size dependence when stated as TIE or corneal irradiance. That is, in terms of TIE, for retinal spot sizes smaller than α_{min}, the EL for a spot size of α_{min} applies. This is based on the assumption that, due to scattering and aberrations in the eye, the minimum achievable spot diameter in the eye is 25 µm.

The value of α_{max} = 100 mrad of the ELs is based on very limited and early experimental spot size dependence threshold studies, the basic one was conducted with a rabbit model (Jacobson 1962). Recently, more complete sets of data related to thermally induced damage of the retina became available (Lund et al. 2007, Schulmeister et al. 2008a) that provide for a more complete understanding of the spot size dependence for different pulse durations that pertain to exposure of both laser and broadband radiation, as discussed in this review.

[§] It is noted that for laser ELs (which are specified as corneal radiant exposure), to specify a measurement field of view equal to α_{max} and to limit the EL to the value that it assumes for $\alpha = \alpha_{max}$ is equivalent to an α^2 dependence and an open field of view (see for instance Henderson and Schulmeister 2004).

ANALYSIS OF THRESHOLD DATA

Spot size threshold data for µs and ns pulses

The dependence of the thermal retinal laser ELs on retinal spot size has been questioned for some time, particularly for pulse durations in the microsecond to nanosecond range. For exposure conditions shorter than a few microseconds there is negligible heat flow during the pulse, and the thresholds expressed in terms of the retinal radiant exposure are not expected to depend on the retinal spot size. That is, for a given exposure duration and a range of retinal spot sizes, the threshold retinal radiant exposure should be constant. If the thresholds were expressed in terms of the TIE, a D^2 or α^2 dependence should be exhibited. This expected dependence was confirmed by a study for nanosecond and microsecond pulse durations (Zuclich et al. 2000) where experimental ED-50 damage thresholds, when expressed as retinal radiant exposure, exhibit little or no spot size dependence for spot sizes above about 80 µm (Fig. 2). The thresholds for spot sizes smaller than about 80 µm for the 5 ns data and at a less well defined breakpoint for the 3 µs data do not follow the expected dependence and this "small spot – spot size behavior" is currently not fully understood (see discussion by Schulmeister et al. 2008a). In Fig. 2, the EL is also shown and it is pointed out that the non-human primate (NHP) damage threshold for the macular region for the retinal spot size of 80 µm and a pulse duration of 5 ns is almost equal to the EL.

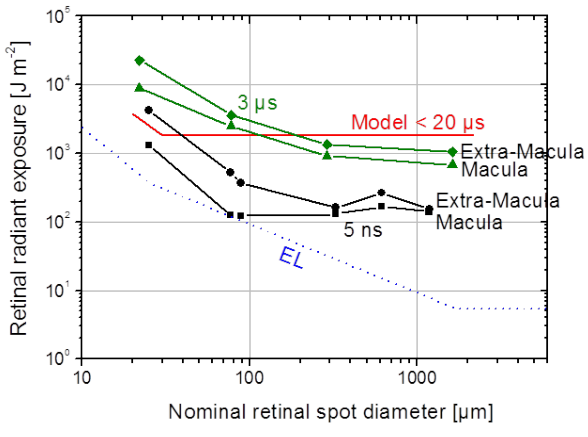

Fig. 2. Experimental 24 h threshold values for 3 µs (590 nm) and 5 ns pulses (532 nm) from Zuclich et al. 2000, computer model data from Schulmeister et al. 2008 and the exposure limit (EL), plotted as retinal radiant exposure. No correction was made for transmission loss in the ocular media in both the experimental data as well as the exposure limit.

Ex-vivo bovine and computer model data

Ex-vivo damage thresholds of bovine explant retinas expressed as retinal radiant exposure are shown in Fig. 3 for a wavelength of 532 nm, together with results of a computer model (Schulmeister et al. 2008a). Data are provided for the pulse duration range of 10 µs to 2 s and a spot size diameter range of 23 µm to 2 mm (for 10 µs pulse duration only computer model data are available). The ex-vivo samples are obtained from fresh bovine eyes and the uppermost, exposed tissue is the RPE layer of the retina. The thresholds for damage are based on cell death of individual RPE cells approximately 15 minutes after exposure. The computer model is based on an Arrhenius integral damage criterion of the RPE layer.

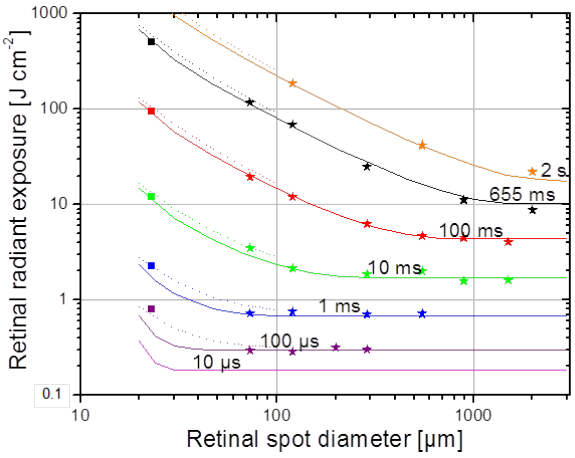

Fig. 3. Damage threshold values for bovine ex-vivo samples plotted as retinal radial exposure adopted from Schulmeister et al.2008a. Square symbols indicate a Gaussian beam profile (small spot size), star symbols represent top-hat (TH) profiles. The lines are the result of a computer model (full for TH, dotted for Gaussian).

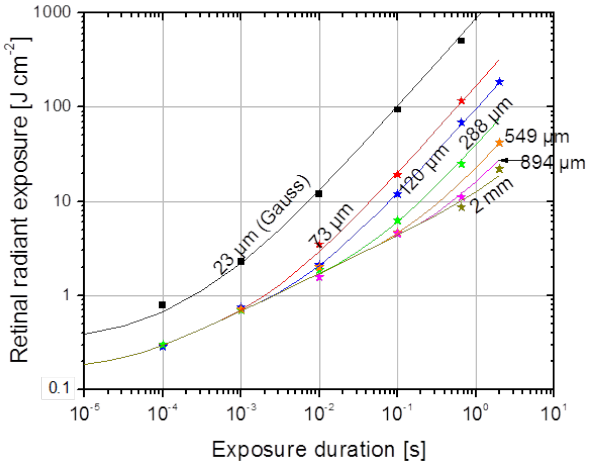

Fig. 4. Threshold data shown in Fig. 3 plotted as function of pulse duration for a range of retinal spot size diameters, adopted from Schulmeister et al. (2008a). Square symbols indicate a Gaussian beam profile (small spot size), star symbols represent top-hat profiles. Lines are the result of the computer model.

The slope S (ED_{84}/ED_{50}) of the ex-plant thresholds is close to 1 (typically around 1.1, but never larger than 1.2), indicating both little variability within different eyes as well as a small uncertainty. This set of thresholds provides the most complete coverage in terms of spot size dependence for all relevant pulse durations for thermally induced retinal damage that is currently available and could not realistically be obtained for non-human primates: 4911 exposures are the basis of the 33 thresholds shown in Fig. 3.

Two regions can be clearly distinguished in Fig. 3, one where the logarithmic slopes of the curves (threshold as function of spot diameter D) are close to -1, i.e. an approximate $1/D$ dependence, and another where the thresholds do not depend on the diameter D, i.e. D^0. These two regions are separated by an inflection in the curve, which can be characterized by a point when straight lines (in logarithmic coordinates) are fitted to the left and to the right part of the curves. It is noted that the threshold data for the smallest spot sizes tend to lie higher than a $1/D$ dependence would predict. This is explained with the effect of a minimal visible lesion (MVL) diameter which in the computer model is set to be 20 µm. The model parameter "MVL" has the meaning that the damaged spot for the calculation of the threshold has to have a diameter equal to the MVL – smaller damaged areas are not considered to be a lesion. If the MVL would tend towards zero, the curves for 0.1 ms and shorter would be straight horizontal lines. This effect of the MVL "bending" the threshold curves upward amplifies the $1/D$ effect for pulse durations of about 1 ms, and is the dominating effect that leads to deviation from a straight horizontal line for smaller pulse durations. The position of the inflection point depends on the pulse duration: for pulse durations less than 10 µs the inflection point is located at about 25 µm and increases to 2 mm for a pulse duration of 2 s.

The threshold data shown in Fig. 3 can also be plotted as function of pulse duration for a given spot size (Fig. 4). The dependence of the threshold as function of pulse duration for pulse durations longer than approximately 1 ms can be fitted well with a straight line in log-space and equals $t^{0.9}$ for small spots and $t^{0.41}$ for large spots.

NHP 100 ms threshold data

Lund et al. (2007) reported retinal damage thresholds as a function of retinal spot size for 100 ms duration exposures from an Argon laser operating at 514 nm in a nonhuman primate (NHP) animal (rhesus monkey – macaca mulatta) model (Figs. 5a and 5b). The beam profile incident at the retina was Gaussian for the smaller spots and top hat for the larger spots. In Figs. 5a and 5b, the diameter is not the actual diameter at the NHP retina (which is not known) but rather a nominal value which would apply for a perfect optical system. The value of the nominal retinal laser spot diameter is derived from the measured far field divergence of the laser beam which is equal to the angular subtense of the retinal image for an eye which is accommodated to

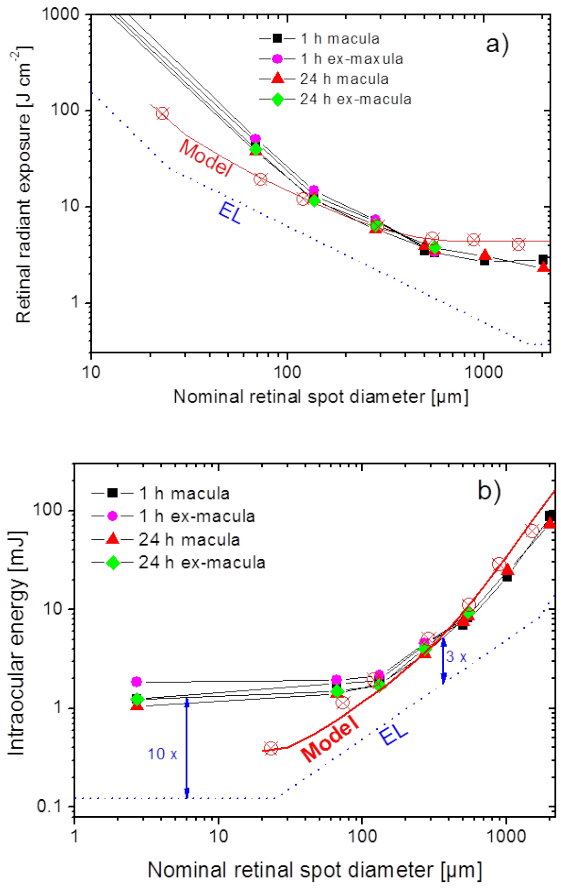

Fig. 5a and 5b. Rhesus monkey threshold data (see legend), bovine *in vitro* threshold data (crossed circles), model data (full line) and the EL values (dashed line). The data is plotted (not corrected for transmission losses for the NHP data) as retinal radiant exposure in a) and as TIE in b).

infinity (relaxed). This nominal value is to be differentiated from the actual retinal spot diameter which might be larger due to, for instance, scattering. The laser beam diameter at the cornea was 2.5 - 3 mm to minimize the influence of aberrations of the eye. In a subsequent study, Lund extended the 100 ms spotsize dependence curve to include retinal diameters of 1 and 2 mm using a Nd:YAG laser at 532 nm[**]. The NHP data (1 hour and 24 hour endpoint, macula and extra-macula) are shown in Figs. 5a and 5b together with damage threshold data of the bovine ex-vivo model as well as the computer model of the previous subsection.

[**] Lund DJ private communication 2009

Microcavitation in-vitro data

Porcine ex-vivo threshold experiments by Schuele et al. (2005) distinguished between thermally induced damage and cell death where bubble formation around the melanosomes (microcavitation) could be detected. They employed a range of pulse durations and showed that for pulse durations of less than about 50 µs, the damage mechanism at threshold level changed from a thermal one (that can well be modeled by the Arrhenius integral) to a damage mechanism which is based on the formation of micro-cavities (referred to as 'bubbles') around the melanosomes in the RPE which are heavily absorbing and can reach relatively high temperatures (Fig. 6). A similar study, conducted by Lee, Alt et al. (2007), indicated that bubble induced damage thresholds are lower than thermally induced damage for pulse durations less than 10 µs. Bubble-induced in-vitro threshold values shown in Fig. 6 are from several studies (Kelly 1997, Payne et al. 1999, Schuele et al. 2005).

Other threshold data

Other published laser threshold data were reviewed and no other NHP threshold data

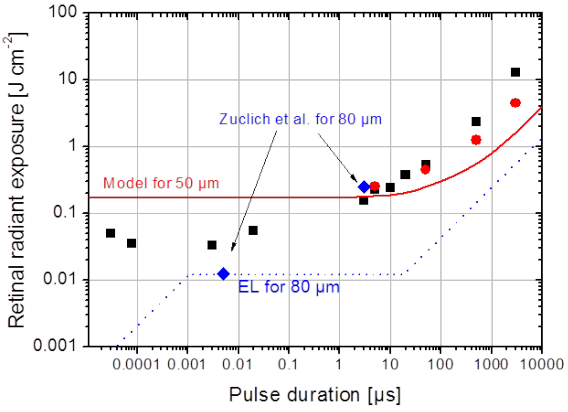

Fig. 6. In vitro bubble induced damage thresholds from various sources (squares) compared with thermally induced RPE cell damage in a porcine model (circle), NHP data by Zuclich et al. (2000) for a retinal spot size of 80 µm (diamonds) and thermal model data.

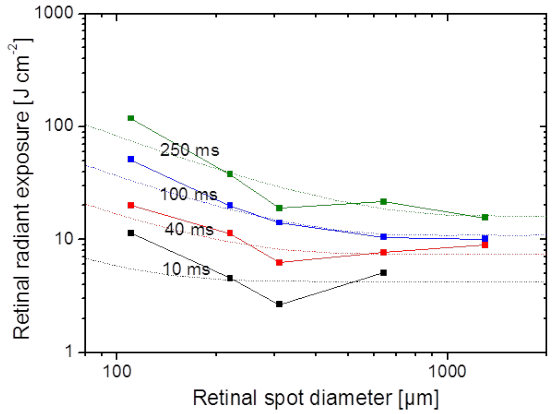

Fig. 7. Spot size dependence threshold data obtained with a Xenon arc lamp by Allen et al. (1967), shown together with computer model data by Schulmeister et al. (2008a), adjusted with a constant factor of 2.5 as compared to the data shown in the previous sections.

could be identified where the spot size dependence in terms of the inflection point between 1/*D* threshold dependence and no-spot-size dependence for the retinal radiant exposure can be evaluated, because the retinal spot sizes do not achieve large enough diameters. However, data is available for the 1/*D* threshold dependence region (Beatrice and Frisch 1973, Ham et al. 1970) for pulse durations of 250 ms and 1 s. Threshold data is published also for short pulses and these exhibit no spot size dependence when plotted as retinal radiant exposure, including 2 ms pulse duration data (Allen et al. 1967) as well as microsecond and nanosecond data (Zuclich et al. 2000). The only NHP retinal threshold data which covers a large enough spot size range in the millisecond range is for Xenon arc lamp exposure (Allen et al 1967), and these data do very clearly show the predicted breakpoint with 1/*D* dependence to the left of the breakpoint and no spot size dependence of the retinal radiant exposure thresholds for spot sizes larger than the breakpoint (see Fig. 7). The computer model and ex-vivo model thresholds of Schulmeister et al. (2008a) for 532 nm are a factor of between 2 and 3 lower than the Xenon arc lamp data, which can be explained by the spectral distribution of the Xenon lamp that also contained red and infrared components with higher thresholds than in the green, as well as by the endpoint of 5 min for the Xenon data. However, the relative spot size dependence, including a breakpoint in the 100 ms Xenon lamp data is predicted very well.

Spot size dependence threshold data for the near infrared for the NHP model are very limited (Ham et al. 1979). Thermal computer models and bovine ex-vivo thresholds[††] show that the general spot size dependence observed in the visible wavelength range also holds in the infrared (Fig. 8) and that the model data is also supported by the available NHP data (shown with star symbols in Fig. 8).

DISCUSSION

General spot size dependence

The computer model as well as the 532 nm bovine ex-vivo model data of Schulmeister et al. (2008a) fits well with the 514 nm and 532 nm NHP spot size dependence study with a pulse duration of 100 ms of Lund et al. (2007), indicating that the damage mechanism for 1 h and 24 h endpoint NHP thresholds is also based on thermally induced damage of the RPE in the pulse duration range under discussion and for the green wavelength range. For very large spots, the NHP thresholds are somewhat below the ex-vivo thresholds, however, both sets of data exhibit the same inflection point between the two regions of spot size dependence. The following discussion will be based on the spot size dependence of the bovine ex-vivo data, since it is the most complete set of data. When expressed as retinal radiant exposure values, the location of the inflection point between the 1/*D* threshold dependence and the constant threshold region for larger spots is not

[††] Schulmeister K, Rahat U, Jean M, Fekete B, to be submitted.

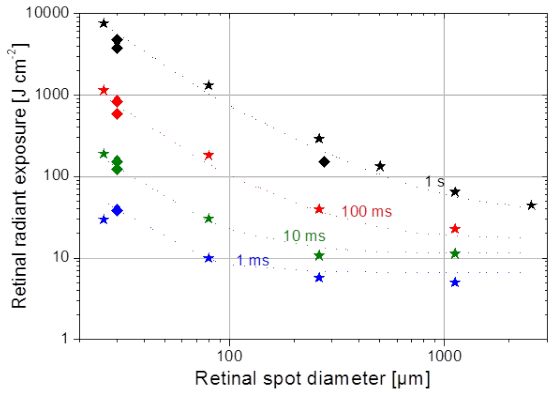

Fig. 8. NHP in-vivo damage threshold values for 1064 nm (squares, Ham 1979), as well as ex-vivo bovine (stars) and computer model thresholds (lines) for 1090 nm (Schulmeister et al. to be submitted).

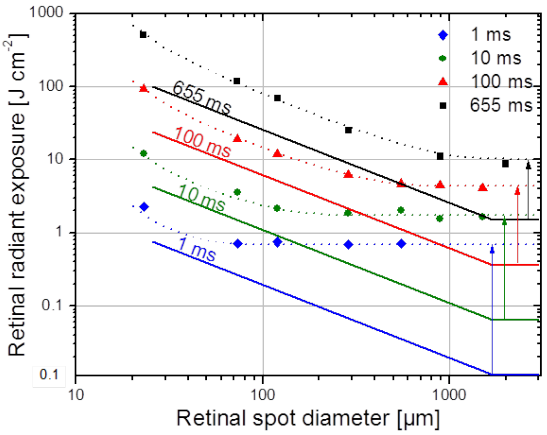

Fig. 9. EL values (dashed lines, not adjusted for transmission losses) with α_{max} fixed at 100 mrad compared to ex-vivo bovine and computer model damage thresholds from Schulmeister et al. 2008a.

constant, as implied by the current ELs, but shifts to smaller diameters for shorter pulses. The inflection point is in the region of 1.7 mm (100 mrad for the human eye) only for pulse durations longer than about 1 s. The pulse duration dependence of the inflection point can be explained based on thermal diffusion. As noted in the introduction, the ELs when expressed in terms of retinal radiant exposure (or radiance dose) show no spot size dependence when the spot is so large that its center it is not affected by radial cooling during the pulse duration (which is also approximately the time it takes to induce the threshold radiant exposure). The critical spot size (equivalent to α_{max}), where the cooling wave "almost" reaches the center of the spot at the end of the pulse, depends, however, on the pulse duration: for short pulses the spot does not need to be large so that the cooling wave does not reach the center of the spot, while for longer pulse durations, the spot has to be correspondingly larger for the center not to be affected. The lateral extent of radial cooling depends on the pulse duration in the usual way the thermal diffusion distance depends on time, namely with a square root dependence. This square root dependence is well reflected in the pulse duration dependence of the inflection point.

For spot sizes that are larger than the inflection point, the spot size dependence of the laser and incoherent broadband ELs does not reflect the spot size dependence of the damage thresholds, which is α^2 or a constant value ("α^0 dependence") when expressing the thresholds as corneal radiant exposure or radiance dose, respectively. Due to the decrease of the radiance dose ELs with increasing α (while the damage threshold levels remain constant for spot sizes beyond the inflection point), the factor between the damage threshold and the EL increases for spot sizes that are larger than the inflection point, leading to large factors for short pulses and large spot sizes, as is shown in Fig. 9. The data show that the reduction factors (i.e. the threshold injury dose divided by the exposure limit) are higher than usually considered necessary for large retinal spot sizes and exposure durations in the microsecond to millisecond range and a considerable increase of the EL for short pulses and extended retinal irradiance patterns is possible while keeping the necessary level of reduction factor. This could be accomplished by introducing a pulse duration dependent factor α_{max}, as is presented in the conclusions.

Small-spot spot size dependence

For spot sizes above 80 µm, the ex-vivo bovine and computer model agree well with the NHP data for 100 ms and 514 nm (Fig. 5a and 5b). However, for spot diameters less than 80 µm, there is striking deviation of both the computer model and the ex-vivo bovine model thresholds from the NHP thresholds. In terms of TIE, the NHP thresholds remain almost constant for smaller laser spots, while both the ex-vivo bovine as well as the computer model continues to decrease with basically linear spot diameter dependence. At a nominal laser spot diameter of 25 µm, the ex-vivo bovine and the computer model thresholds are a factor of about 3.5 lower than the interpolated NHP threshold. The reduction factor, the ratio between the NHP thresholds and the EL, is about a factor of 10 for the minimal spot size condition only. The ratio between the *ex-vivo* and computer-model thresholds and the EL for the minimal spot size is of the order of 3. For spot sizes above about 80 µm, the factor is also about 3. Very similar small spot - spot size behavior is also noted for NHP 532 nm nanosecond thresholds and to some extent the microsecond data of Zuclich et al. (2000) (Fig. 2). As discussed by Lund et al. (2007), equivalent small spot – spot size dependence can also be observed for millisecond pulses and ultrashort pulses. Till et al. (2003) developed a "slow damage" model based on melanosome membrane melting to explain the microsecond small spot data, which could, however, not be applied to explain the small spot behavior for other time domains and damage mechanisms where the same small spot - spot size dependence was also observed. The existence of this small spot behavior for pulse durations regimes that clearly encompass different damage mechanisms (for instance also including bubble formation around melanosomes) indicates that the underlying effect is more generic or basic and does not depend on the damage mechanism.

There is no validated explanation for the observed spot size dependence. In addition to the generally recognized (Sliney and Wolbarsth 1980) intraocular scatter, that would contribute substantially to loss of energy in a minimal image, recently, Schulmeister et al. (2008a) have proposed that scatter by the nerve fiber layer of the retina could be a contributing factor. Also the difficulty to visually discern minimal lesions at threshold for very small irradiance diameters could be a factor (Lund et al. 2008). Consequently, it can not be excluded at this point in time that damage at the lower levels that are predicted by the computer model and the bovine data could occur for the human case, even if only in the fovea, where the pre-RPE induced scattering is minimal.

Time dependence

The ex-vivo bovine and the computer model threshold data were plotted in Fig. 4 as a function of pulse duration for the range of retinal spot sizes. The pulse duration dependence of the spot size-inflection point also results in a variation of the time dependence for the different retinal spot sizes which is not reflected in the ELs. Due to the constant value of α_{max}, the pulse duration dependence of the EL for the visible wavelength range and for pulse durations between 18 µs and 10 s of $t^{0.75}$ applies to all spot sizes. However, this steep time dependence is shown by the threshold data only for the small spot case. The larger the spot size becomes, the more the region of shallower time dependence, seen for 1 ms pulses, extends to longer pulse durations, so that for a spot diameter of 2 mm the time dependence slope in log-log scale becomes 0.4 ($t^{0.4}$). For pulse durations less than about 0.1 ms, all the curves of the computer model for the different spot sizes merge as they approach the thermal confinement condition for a homogeneous absorber. Regarding the shallower time dependence for large spots, it can be noted

that this is reminiscent of the time dependence of the ELs for thermal corneal and skin damage, which is $t^{0.25}$. These corneal and skin ELs are based on threshold studies which used laser spot diameters of the order of millimeters, which would also exhibit a shallower time dependence than image sizes of less than 1 mm, relevant for retinal laser exposure.

The thermal damage model predicts that under thermal confinement conditions that apply to a homogeneous layer, the thresholds in terms of energy per pulse (or radiant exposure per pulse) would no longer depend on the pulse duration. However, as seen in Fig. 6, it is important to note that the threshold values for bubble induced injury continue to decrease for shorter pulse durations down to pulse durations of about 10 – 100 ns, below which the bubble induced thresholds appear to remain constant. NHP data reviewed by Roach et al. (1999) shows only a limited temporal dependence for pulse durations between 1 ns and 100 fs, i.e. four orders of magnitude in terms of pulse duration. The factor between this lower threshold plateau in the nanosecond regime and the thermal model threshold is about 10. The ex-vivo bubble induced thresholds also compare quite well with the 3 µs and 7 ns Rhesus monkey data of Zuclich et al. (2000) also shown in Fig. 6, which explains the difference of the thermal model data with the 5 ns NHP data of about factor 10. For 3 µs pulses, according to the work of Schuele et al. (2005) and Lee, Alt et al. (2007) the bubble induced thresholds are not significantly lower than the thermally induced thresholds. For this pulse duration, the thermal model is also a good fit for the NHP 3 µs data of Zuclich et al. (2000), which therefore might be either thermally induced or might be bubble induced damage. Computer models based on the Arrhenius integral can not model the damage threshold for bubble induced injury, but for these conditions it can be assumed that the local radiant exposure level governs any spot size dependence. However, the bovine and porcine ex-vivo model still appear to be a viable alternative for *in-vivo* animal experiments in the regime of bubble induced damage, i.e. for pulse durations down to the nanosecond regime. Due to the continued decrease of bubble induced thresholds for pulse durations in the thermal confinement regime which is in contrast to the constant value of the EL for pulse durations less than 18 µs, the reduction factor between the EL and the damage threshold also decreases with decreasing pulse duration, leading to basically to the case of no reduction factor seen for the nanosecond NHP data for a spot size of 80 µm (Fig. 2). The reason for the decrease of the damage threshold with shorter pulses for bubble induced damage is believed to be reduced cooling of the melanosome surface during the laser pulse for shorter pulses compared to longer ones. This effect should level off for pulse durations of about 50 ns when the heat flow during the pulse becomes negligible regarding the cooling of the melanosomes[‡‡].

So far, we have discussed single pulse exposure only. For the evaluation of exposure to multiple pulses, additional criteria need to be considered. IEC, ANSI and ICNIRP define an "average power" criterion and a "$N^{-1/4}$" criterion, where N is the number of pulses within the evaluation duration. The more generally applicable form of the $N^{-1/4}$ criterion is the "total-on-time" (TOT) criterion, as for instance specified in IEC 60825-1 Edition 2. Schulmeister et al. (2007) showed that for constant peak powers, the TOT criterion either reflects retinal thermal injury thresholds for multiple pulse exposure very well, or for larger spots, short pulse durations and repetition rates less than about 1 kHz, is a conservative approach where the multiple pulse injury thresholds are higher than would be calculated with the TOT criterion (even when a pulse duration

[‡‡] private communication Brinkmann R.

dependent α_{max} is assumed). A detailed discussion of multiple pulse threshold data and evaluation criteria that would reflect the trends of the threshold data is beyond the scope of this review.

POTENTIAL IMPLICATIONS TO EXPOSURE LIMITS

General reduction factor

An analysis of the NHP data shown in Fig. 5a and 5b shows that the reduction factor of 10 that is often stated as a *"general reduction (or "safety") factor that is chosen by the committees setting laser exposure limits"* only applies to the minimal nominal laser spot sizes; for spot sizes above about 80 µm - 100 µm (5 - 6 mrad in the human standard eye) the reduction factor in the millisecond pulse duration regime for green wavelengths is a factor of three in the current ICNIRP and ANSI exposure limits. Compared to the often mentioned reduction factor of 10, this might appear quite low. Actually, the reduction factor is based upon the level of uncertainty of the available data (ICNIRP 2000, Sliney et al. 2002). Thus, when the threshold values are determined with small experimental uncertainty and exhibit little spread by variability, which is the case for instance for the new 100 ms Rhesus monkey data, then the dose response curve is quite sharp, close to a real step-function threshold, and the reduction factor could be as small as 2.5 to 3, while still assuring that for exposure at the EL, no damage will occur (see also discussion in Sliney et al. 2002 and Schulmeister et al. 2008a).

At this stage it can not be ruled out that for nominal minimal retinal spot sizes, where ELs tend to be a factor of 10 below experimental Rhesus monkey thresholds, RPE cell damage could occur at levels potentially only a factor of three above the EL. It therefore appears that the choice of a reduction factor of 10 for minimal images is a prudent one, since the actual threshold for an injury relevant on a medical and physiological level for vision is not certain but will most likely be somewhere between the levels predicted by the computer and ex-vivo bovine model and the levels determined in NHP in-vivo experiments. Also the transfer of the results to the human case need to be done with caution – the impact of different pigmentation and racial differences for human exposure needs to be considered and would also depend on wavelength, pulse duration and retinal image size.

Time dependence of laser EL

Zuclich et al. (2000) have pointed out a need to reduce the ELs so that the reduction factor for the 5 ns pulse duration 80 µm spot size threshold is increased to an appropriate level. A reduction factor of 2.5 to 3 would be comparable to the reduction factor for other extended source ELs. As shown in Fig. 6, the small reduction factor seems to be due to the constant EL in terms of energy or radiant exposure for pulse durations between 1 ns and 18 µs. This is based on the thermal confinement regime of homogeneously absorbing media, however, the damage thresholds, due to bubble formation (which exhibits a lower threshold than thermally induced damage), continue to decrease. Any lowering of the ELs (and of the product safety emission limits that are derived from the ELs, the Accessible Emission Limits, AELs) needs to be done with care and should be ideally done so that existing laser products are affected as little as possible, i.e. only for those conditions where the ELs was found to be too high. There are basically two possibilities to resolve this:

1) Increase α_{min}

2) Decrease the EL in the nanosecond time regime

On first examination of Fig. 1, an increase of α_{min} to a value of about 5 mrad (85 µm) would establish the usual safety factor for the 5 ns threshold data, and with the

proposed time dependent α_{max}, the ELs for spot sizes larger than that would increase with α^2 and would keep a corresponding reduction factor for all spot sizes. However, the problem of this solution is that a change of α_{min} would affect all laser products that are classified based on an extended source size, where the AELs and ELs would be correspondingly lowered. It was shown in this work that this is not necessary for pulse durations in the millisecond and second range and would unnecessarily lower the limits there, where a significant number of products already exist.

It follows that a reduction of the basic ELs in the nanosecond regime, possibly up to a few microseconds, would appropriately reflect the reduction of damage thresholds due to bubble induction. With the currently available damage threshold data it is difficult to determine where exactly the EL would have to be lowered to assure a minimum reduction factor of at least 2.5 for sources above 80 µm and a factor of 10 for the minimal spot size. Also the treatment of multiple pulses in the regime of bubble induced injury, where the pulse additivity exhibits different trends than for thermally induced damage, would need to be considered.

Pulse duration dependent α_{max}

The computer model and the ex-vivo model data by Schulmeister et al. (2008a) for pulse durations in the µs and ms range show that in that pulse duration regime, the reduction factor increases steadily for extended sources. This is due to the constant α_{max} of 100 mrad, which reflects the trend of the retinal damage thresholds only for pulse durations in the seconds time regime. The location of the inflection point in the damage thresholds, which in meaning is equivalent to α_{max}, decreases for shorter exposure duration.

The spot size dependence of the retinal damage thresholds would be reflected by the exposure limits if a pulse duration dependent α_{max} were introduced. Such a pulse duration dependent α_{max} would be defined conservatively based on the 'beginning' of the constant (horizontal) parts of the threshold curves. These points are shown in Fig. 10 and are found to exhibit a square-root dependence on pulse duration, which is also supported by the time dependence of thermal diffusion theory. The experimental and theoretical damage threshold data would suggest a square-root dependence for the pulse duration dependence of the parameter α_{max}. It is suggested not to decrease α_{max} to values below 5 mrad, since the value of 5 mrad also approximately corresponds with the break point of the small spot-spot size behavior where any increase in the exposure limits would have to be done with caution. Decreasing the value of α_{max} to angular subtenses smaller than 5 mrad would, for short pulse durations, also amplify the amount by which the EL for the nanosecond region would have to be decreased. When the pulse duration dependence of α_{max} is defined so that 100 mrad is reached for a pulse duration of 0.25 s, then, with a square-root dependence, a value of 5 mrad is reached for a pulse duration of 625 µs, as is also shown in Fig. 10.

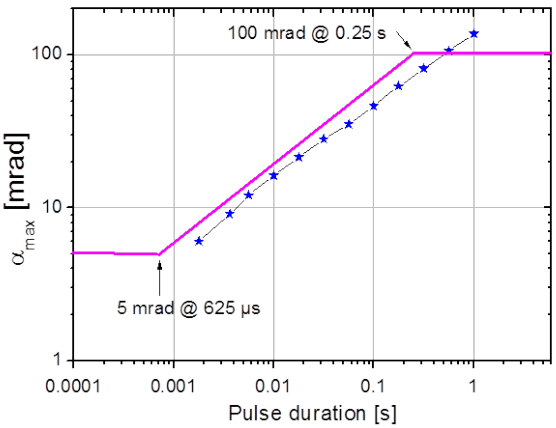

Fig. 10. Plot of the retinal spot sizes where the horizontal parts of the threshold curves shown in Fig. 3 begin (stars). Also shown is a possible way to define the pulse duration dependence of the parameter α_{max}.

It is noted that the introduction of a time dependent α_{max} would not affect the formula for the basic retinal thermal exposure as such. However, the application of a pulse duration dependent α_{max} "automatically" also produces a time dependence of the ELs which depends on the spot diameter. The pulse duration dependence of the factor α_{max} as presented here would, for pulses shorter than 625 µs and spot sizes larger than 100 mrad result in an increase of the EL of a factor of 20 while conserving a reduction factor between the damage threshold values and the EL of at least 2.5.

CONCLUSION

Experimental and thermal model threshold data for thermally induced retinal injury was reviewed. Two pulse duration regimes need to be distinguished due to different damage mechanisms. In the millisecond regime, the retinal injury mechanism, at threshold, is thermal in nature and can be well modeled with the Arrhenius integral. For pulse durations in nanosecond regime, cellular damage in the RPE cells is induced by microcaviation. The injury threshold for microcavitation induced retinal injury becomes lower than the thermal one in the lower microsecond pulse duration regime.

A comparison of the exposure limit with retinal injury thresholds shows that in the nanosecond regime, the reduction factor between the injury threshold and the exposure limit is not large enough. This is because the injury thresholds for micro-cavity induced injury continue to decrease for pulse durations shorter than 18 µs, while the exposure limit remains at a constant radiant exposure level. It appears necessary that the exposure limits in the nanosecond regime be reduced by a factor of between 2.5 and 3.

In the millisecond pulse duration regime of thermally induced injury, recent experimental and computer model studies provide for a more complete understanding of the dependence of the injury thresholds on spot size for varying pulse durations. While current exposure guidelines when expressed as radiance feature a $1/\alpha$ dependence on angular subtense of the retinal image, α, up to a value of 100 mrad (α_{max}) for all pulse durations (and no spot size dependence for larger angles), the data show that this is only applicable for pulse durations longer than of the order of 0.25 s. For short pulse durations, the threshold data show that the $1/\alpha$ dependence transforms into "no-spot-size dependence" at smaller critical angles than 100 mrad. The respective critical angle for this change of dependence is found to depend on the pulse duration. The constant parameter α_{max} = 100 mrad produces unnecessarily large reduction factors for pulsed exposure to extended sources. The spot size dependence of the damage thresholds would closely be reflected by the introduction of a time dependent α_{max} where α_{max} would be 5 mrad for short pulses and would increase with the square root of the pulse durations up to a value of 100 mrad for pulse durations of 0.25 s or longer. This would represent an increase of the exposure limit up to a factor of 20 for short pulses and large sources.

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