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PROPOSED CHANGES FOR THE RETINAL THERMAL MPE

Paper 404

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Abstract

Recent in-vitro, computer model and non-human primate threshold data provide for a more complete set of information of the dependence of the retinal thermal damage threshold values on retinal irradiance profile diameter for the complete range of relevant pulse durations. Based on this data it would be possible to reduce the unnecessarily large safety factor by increasing the current laser and broadband exposure limits for extended sources for pulsed durations up to the millisecond range. A pulse duration dependent parameter α_{max} is proposed which equals 100 mrad only for longer pulses and decreases to 5 mrad for shorter pulses. At the same time, for nanosecond pulses, the exposure limits need to be lowered, as in that pulse duration regime, microcavity formation around melanosomes results in a lower damage threshold than would be expected in the thermal confinement regime.

Introduction

Maximum permissible exposure (MPE) values for laser radiation are defined on the international level by ICNIRP [1,2], where they are referred to as exposure limits (EL). Other documents, standards and regulations either copy the ICNIRP limits [3,4,5] or, if nationally defined, are usually well harmonised with the ICNIRP set of ELs [6].

The laser MPEs for thermally induced retinal damage depend on the parameter named "angular subtense of the apparent source" (symbol α with units of mrad) which characterises the thermally effective diameter of the retinal irradiance profile (for a discussion on this parameter see for instance [7,8]). Since this paper is concerned with the basic dependence on the retinal irradiance profile diameter and not for instance with the issue of determining α for different types of irradiance profiles, here we simply refer to the "retinal spot size". Most laser beams produce a minimal retinal spot on the retina and this condition, referred to as "small source", is the most hazardous one, since the highest retinal irradiance is produced. It is also the "default" condition, i.e. it applies to Gaussian beams, to well collimated beams and generally to beams with good beam quality. Only for special laser beams, such as line lasers or low quality laser beams, a retinal image that is larger than the minimal retinal image is possible, an exposure condition which is referred to as "extended source". In the remainder of the paper, whenever the term MPE is used, the *retinal thermal* MPEs are meant. In this paper we will present threshold data both in terms of intraocular energy (IOE) (being directly related to corneal radiant exposure, in which the laser MPEs are expressed) as well as in terms of retinal radiant exposure (being directly related to radiance, in which for instance the broadband MPEs are expressed), the latter can be calculated by division with the retinal exposure area (see [9] for a detailed treatment of the transformation).

The current linear retinal spot size dependence of the thermal retinal MPEs, in principle, reflects that a larger spot, for the same retinal radiant exposure, produces a higher temperature rise than compared to a smaller spot where radial heat flow reduces the temperature in the centre of the spot. If there were no radial cooling, the damage threshold in terms of retinal radiant exposure (or radiance) would not depend on the spot size. When specifying the thresholds in terms of intraocular energy (or corneal radiant exposure) the dependence would be on α^2 since retinal radiant exposure is calculated from the intraocular energy by division with the area of the laser beam incident on the retina. When radial cooling decreases the temperature of the center of the irradiated spot, the threshold for damage is increased compared to the threshold if there were no radial cooling. This produces the α rather than the α^2 dependence, as expressed in the retinal thermal ELs for angular subtenses less than α_{max}. When the spot size becomes so large that the effect of radial cooling does not reach the centre of the spot during the time relevant for thermal damage, the temperature in the centre of the spot is determined by

the local radiant exposure only, independent of the retinal spot size. It follows that for this condition, the damage threshold in terms of retinal radiant exposure does no longer depend on the spot diameter, which is the physical background of the spot size dependence breakpoint, i.e. of α_{max}. The value of α_{max} = 100 mrad of the current MPEs is based on very limited and early experimental spot size dependence threshold studies, the basic one was conducted with a rabbit model [10]. Recently, more complete sets of threshold data related to thermally induced damage of the retina became available [9,12] that provide for a more complete understanding and subsequently for improving the retinal thermal exposure limits for laser and for broadband radiation.

Review of available threshold data

Spot size threshold data for µs and ns pulses

The current spot size dependence of the MPEs is under doubt for some time, especially for pulse durations in the microsecond range and for shorter pulses, since in the condition of thermal confinement (i.e. when the pulse duration is shorter than the time it takes for heat flow to have an effect) it would not be expected that the threshold in terms of retinal radiant exposure would depend on the diameter of the retinal spot, but should depend only on the local radiant exposure value. This concern was also supported by a spot size dependence study published in 2000 [13] for nanosecond and microsecond pulse durations (i.e. pulse durations in the thermal confinement regime). These experimental thresholds (figure 1) exhibit an α^2 dependence for spot sizes above about 80 µm, as would also be predicted by thermal models.

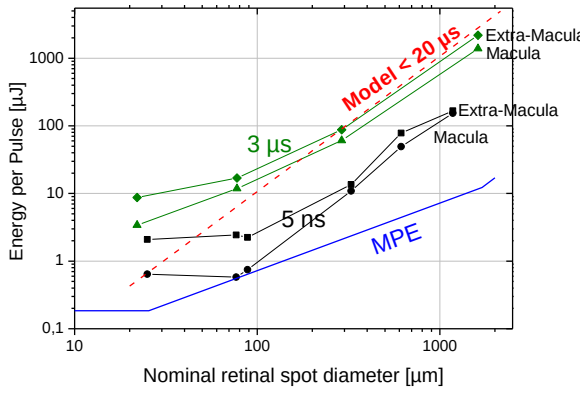

Figure 1. Experimental 24h threshold values for 3 µs (590 nm) and 5 ns pulses (532 nm) from Zuclich et al. [13]. Model data from [5].

In figure 1, the current MPE 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 is almost equal to the EL.

In vitro bovine and computer model data

In vitro damage thresholds (ED50) of bovine ex-plant retinas are shown in figure 2 for a wavelength of 532 nm, together with results of a computer model [5]. Data are provided for the pulse duration range of 0.1 ms to 655 ms and a spot size diameter range of 23 µm to 2 mm. The in-vitro 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 a Arrhenius integral damage criterion of the RPE layer. The slope S (ED84/ED50) of the ex-plant *in vitro* thresholds is close to 1 (typically around 1.1, but never larger than 1.4), 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: 13000 exposures are the basis of the thresholds shown in figure 2.

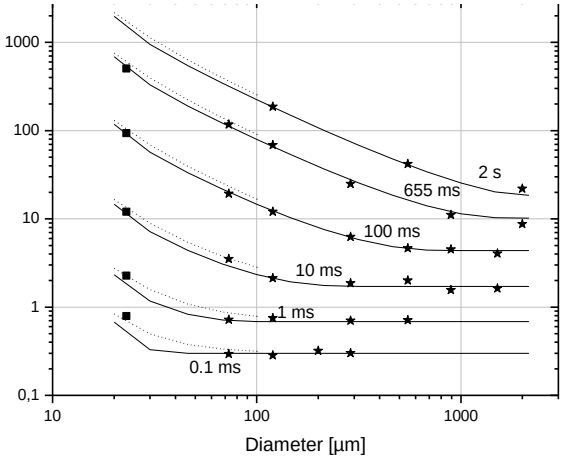

Figure 2. Damage threshold values for bovine *in vitro* samples plotted as retinal radial exposure. Square symbols indicate a Gaussian beam profile (small spot sice), star symbols represent top-hat profiles. The lines are the result of a computer model (full for TH, dotted for Gaussian).

Two regions can be clearly distinguished in figure 2, 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, where d is the retinal irradiance profile diameter, and another where the thresholds do not depend on the diameter d, i.e. a logarithmic slope of 0. These two regions are separated by a "knee" in the curve, which can be approximated by a breakpoint 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 threshold data can also be plotted as function of pulse duration for a given spot size (figure 3). 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.

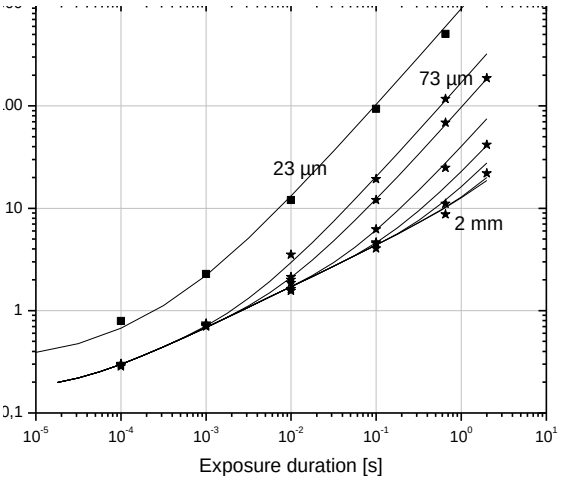

Figure 3 Threshold data plotted as function of pulse duration for a range of retinal spot size diameters.

2.3 NHP 100 ms threshold data

Recently, a series of NHP thresholds were determined with a 514 nm Argon laser and a pulse duration of 100 ms with varying retinal retinal spot diameters [12] as shown in figure 4. The profile was Gaussian for the smaller spots and top hat for the larger spots. In figure 4, the diameter is not the actual diameter at the monkey 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 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.

The rhesus monkey data (1 hour and 24 hour endpoint, macula and extramacula) are shown in figure 4 together with damage threshold data of the bovine *in vitro* model as well as the computer model of the previous subsection.

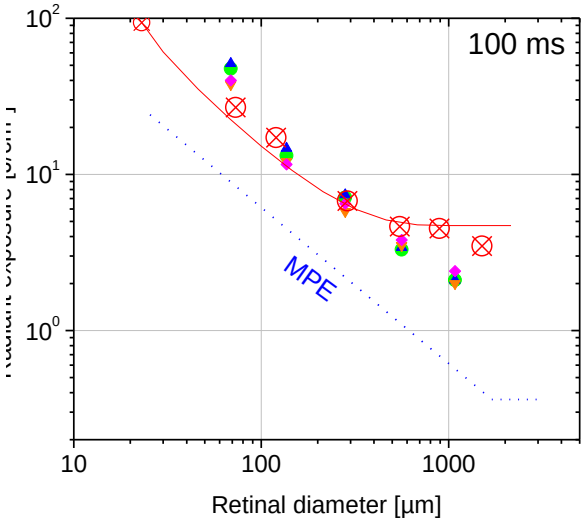

Figure 4. Rhesus monkey threshold data (small symbols), bovine *in vitro* threshold data (large crossed circles), model data (full line) and the current MPE values (dotted line). The data is plotted as retinal radiant exposure (not corrected for transmission losses for the case of Rhesus monkey).

Microcavitation in-vitro data

Porcine *in vitro* threshold experiments by Schüle et al. [14] distinguished between thermally induced damage and cell death where bubble formation around the melanosomes (microcavitation) could be detected. They decreased the pulse duration from 3 ms downwards and showed that for pulse durations of less than about 50 µs, the damage mechanism at threshold level changes from a thermal one (that can well be modelled by the Arrhenius integral) to a damage mechanism which is based on the formation of to microcavities (referred to also as 'bubbles') around the heavily absorbing melanosomes in the RPE, which reach relatively high temperatures (figure 5). Bubble induced in vitro threshold values are from several studies [14,15,16].

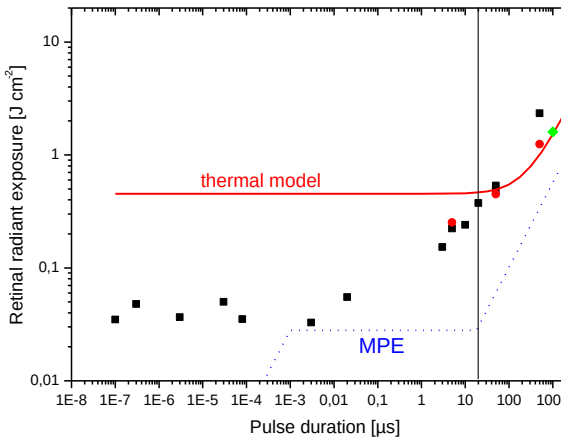

Figure 5. In vitro bubble induced damage thresholds from various sources (squares) compared with thermally induced RPE cell damage in a porcine model (circle), as well as thermally induced RPE cell damage in bovine model (diamond) and the thermal model data from [5].

Discussion

General spot size dependence

Both the computer model as well as the 532 nm bovine model data fits very well with the 514 nm NHP spot size dependence study with a pulse duration of 100 ms, 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. The discussion will be based on the spot size dependence of the bovine in-vitro data, since it is the most complete set of data.

When expressed as retinal radiant exposure values, the breakpoint between the 1/d threshold dependence and the constant threshold region for larger spots is not constant, as currently implied by the MPEs, but shifts to smaller diameters for shorter pulses. The breakpoint is in the region of 1.7 mm (100 mrad for the human eye) only for pulse durations longer than about 1 s. This pulse duration dependence of the breakpoint can also be explained based on thermal diffusion. If the spot diameter is larger than the zone that is affected by radial cooling, the central temperature will no longer depend the spot size. The lateral extent of radial cooling depends on the pulse duration (which is also close to the time it takes to induce the critical threshold radiant exposure) and the square root dependence of the diffusion distance upon time also is well reflected in the pulse duration dependence of the breakpoint.

The current broadband EL, expressed as radiance (directly related to retinal irradiance) decrease linearly with α^{-1} and the laser EL, being expressed as corneal radiant exposure (related directly to intra ocular energy) increase linearly with α, independent of the pulse duration. For spot sizes to the right of the breakpoint, this does not reflect the actual spot size dependence of the damage thresholds which is α^2 or a constant value ("α^0 dependence") for expressing the thresholds as retinal radiant exposure or corneal radiant exposure, respectively. Due to this decrease for the radiance case where the MPE should be constant and for the corneal radiant exposure case the too shallow increase, an unnecessarily large safety factor between the damage threshold and the MPE is created, especially for short pulses and large spots sizes.

Time dependence

The in-vitro bovine threshold data was plotted in figure 3 as function of pulse duration for the range of retinal spot sizes. The time dependence of the spot size dependence breakpoint also results in a variation of the time dependence for the different retinal spot sizes which is currently not reflected in the MPEs. For a diameter of 23 µm, the slope in log-log scaled time dependence is somewhat steeper than the value of 0.75 currently defined by the MPEs, it equals 0.9 for pulse durations longer than about 1 ms. For shorter pulse durations, the time dependence becomes shallower and according to the thermal model becomes zero (i.e. no time dependence) for pulse durations of less than about 10 µs, which is also referred to as the thermal confinement region. The larger the spot size becomes, the more the region of shallower time dependence extends to longer times, so that for a spot diameter of 2 mm, according to the model, the time dependence slope in log-log scale becomes 0.4. For pulse durations of less than about 0.1 ms, all the curves for the different spot sizes merge as they approach the thermal confinement region. Regarding the shallower time dependence for large spots, it can be noted that this is reminiscent of the time dependence of the MPEs for thermal corneal and skin damage, which is $t^{0.25}$. After all, these corneal and skin MPEs are based on threshold studies which used laser spot diameters in order of millimetres, 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, the thresholds in terms of energy per pulse (or radiant exposure per pulse) would no longer depend on the pulse duration.

The porcine *in vitro* thermal damage data given in [14] and shown figure 5 compare well with the bovine threshold and the computer model of this work, which is also plotted. It is important to note that the bubble induced threshold values 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. The factor between this lower threshold plateau and the thermal model threshold is about 10. The in vitro bubble induced thresholds plotted in figure 5 also compare quite well with the 3 µs and 7 ns Rhesus monkey data of Zuclich et al. [13] shown in figure 1, which explains the difference of the thermal model data with the 5 ns data of about factor 10. For the 3 µs data, according to the work of Schüle [13] the bubble induced thresholds are not significantly lower than the thermally induced thresholds, and for this pulse duration, the thermal model is also a good fit for the monkey 3 µs data of Zuclich et al., which therefore might be either thermally induced or might be bubble induced damage. Computer models based on the Arrhenius integral can not model the level of 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 *in vitro* model still appear to be a viable alternative for 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 but the constant value of the MPE for pulse durations less than 18 µs, the safety factor between the MPE and the damage threshold decreases also.

Conclusions - recommendations for review of MPEs

General safety factor

An analysis of the NHP data shown in figure 2 shows that the 'safety factor' of 10 that is often stated as a general 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 safety factor in the millisecond pulse duration regime for green wavelengths is only a factor three. Compared to the often mentioned safety factor of 10, this might appear quite low. However, 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 and for the bovine in vitro data, then the dose response curve is quite sharp, close to a real step-function threshold, and the safety factor can be as small as three, while still assuring that at the MPE, no damage will occur (see also discussion in [16 and 17]).

At this stage it can not be ruled out that for nominal minimal retinal spot sizes, where MPEs tend to be a factor of 10 below experimental Rhesus monkey thresholds, RPE cell damage occurs at levels potentially only a factor of 3 above the MPE, at least in the fovea: if intra-retinal scattering is the reason for the observed small-spot spot size dependence discussed in [5], then this scattering would not occur in the fovea and for this condition, RPE cell damage appears possible for the minimal image size at a factor of about 3 above the current EL, at least for heavily pigmented eyes. It therefore appears that the choice of a safety 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 *in vitro* bovine model and the levels determined in monkey *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 might be different depending on pulse duration and image size. Without further detailed information, it might well be prudent to assume that the damage thresholds determined by the models discussed here would also apply in absolute terms for heavily pigmented human retinas. RPE pigmentation might not be that different for different races and differences in choroidal pigmentation might not play a significant role for shorter pulses.

Raising limits with a time dependent α_{max}

The computer model and the bovine *in vitro* model show that there are unnecessarily high safety factor for short pulses and extended sources. This is due to the current constant α_{max} of 100 mrad, which in fact only applies to exposure durations in the seconds time regime. The breakpoint in the damage thresholds, which in meaning is equivalent to α_{max}, decreases for shorter exposure duration.

Since the spot size dependence of the damage thresholds for pulse durations of less than about 0.1 ms goes with α^2 instead of the current α, and the current α_{max} is fixed at 100 mrad, it follows that for short pulses, the safety factor could be decreased. As a conservative approach, we are basing the proposed time dependent α_{max} on the 'beginning' of the constant (horizontal) parts of the threshold curves. These points are shown in figure 6 together with a function that

would conservatively describe a time dependence of α_{max}, where α_{max} equals 100 mrad for 0.25 s, and decreases with the square root of the exposure duration to 5 mrad at 625 µs. The formula for a time dependent α_{max} would thus be

$$\alpha_{max} = 200\ t^{0.5} \quad (\text{for } 625\ \mu s < t < 0.25\ s)$$

where t is in seconds and α_{max} is in mrad. It is suggested to limit the decrease of α_{max} to 5 mrad, since the value of 5 mrad also approximately corresponds with the break point of the small spot spot size behaviour where any raise of the limits would have to be done with caution. Decreasing the value of α_{max} to angular subtenses smaller than 5 mrad for short pulse durations would also amplify the amount by which the MPE for the nanosecond region would have to be lowered. Figure 6 shows the new spot size dependence of the retinal thermal MPEs for a selection of pulse durations.

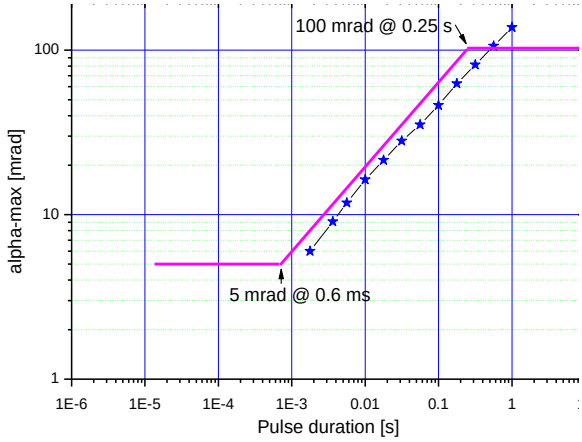

Figure 6. Proposed time dependence for α_{max}.

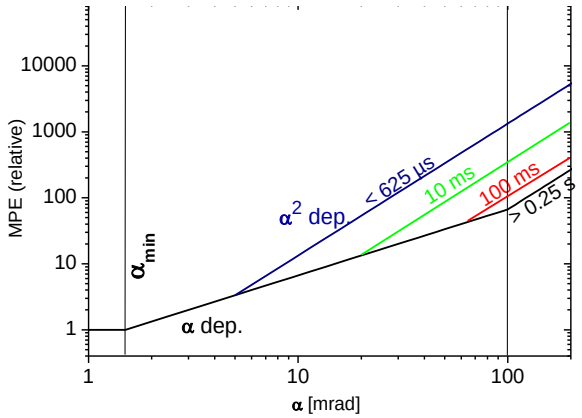

Figure 7: Proposed spot size dependence of retinal thermal MPEs for different pulse durations.

Time dependence

The data of Zuclich et al. [10] has brought up a need to reduce the current MPEs so that the safety factor for the 7 ns pulse duration 80 µm spot size threshold is raised to at least a level of 3, to make it comparable to the safety factor for other extended source MPEs. As shown in figure 5, this too small a safety factor seems to come about since the MPEs are held constant in terms of energy or radiant exposure for pulse durations less than 18 µs (based on the thermal confinement regime of homogeneously absorbing media), while the damage thresholds, due to bubble formation which exhibits a lower threshold than thermally induced damage, continue to decrease. The current MPEs only decrease further for pulse durations less than 1 ns, to account for lower threshold in the ultrashort pulse duration regime. Any lowering of the MPEs and 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 MPEs (and therefore also the AEL for Class 1) was found to be too high. There are basically two possibilities to resolve this:

1) Increase α_{min}

2) Decrease the MPE below about 50 ns with a different time dependence

On first examination of figure 1, an increase of α_{min} to a value of about 5 mrad (75 mrad) 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 safety factor for all spot sizes. However, the big problem of this solution is that a change of α_{min} would affect all laser products that are classified based on a source size of between 1.5 mrad and the new α_{min}, where the emission limits and MPEs 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 quite a number of products already exist. We would therefore propose that it is considered to lower the limits for pulse durations starting at around 30 ns, either with an exponent for the time dependence appropriate so that the log-log line joins the current 1 ps MPE level (below which the MPE is again a constant radiant exposure value, i.e. independent on pulse duration), or introducing an additional plateau for the EL between the current < 1ps and the current 1 ns < t < 18 µs plateau, so that the MPEs on either side of the plateau follow the 'usual' $t^{0.75}$ dependency, i.e. would decrease left of the plateau with $t^{0.75}$ equal to the current EL

values to meet the 1 ps level, and would increase right of the plateau with a $t^{0.75}$ dependence to meet the current 1 ns < t < 18 µs plateau at 50 ns.

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