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Laser-induced retinal injury thresholds:

Variation with retinal irradiated area.

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ABSTRACT

The retinal injury threshold for exposure to a laser source varies as a function of the irradiated area on the retina. Currently accepted guidelines for the safe use of lasers provide that the MPE will increase as the diameter of the irradiated area for retinal diameters between 25 μm and 1700 μm, based on the ED_{50} data available in the late 1970s. Recent studies by Zuclich and Lund produced data showing that the ED_{50} for ns-duration exposures at 532 nm and μs duration exposures at 590 nm varied as the square of the diameter of the irradiated area on the retina. This paper will discuss efforts to resolve the disagreement between the new data and the earlier data though an analysis of all accessible data relating the retinal injury threshold to the diameter of the incident beam on the retina and through simulations using computer models of laser-induced injury. The results show that the retinal radiant exposure required to produce retinal injury is a function of both exposure duration and retinal irradiance diameter and that the current guidelines for irradiance diameter dependence do not accurately reflect the variation of the threshold data.

Keywords: Laser bioeffects, retinal injury, ocular thresholds, thermal model, spot-size dependence

1. INTRODUCTION

Zuclich et al[1,2] recently published new data bringing into question provisions of the current guidelines relating the MPE to the diameter of the irradiated area. In the current laser safety standards and guidelines published by ANSI [3], ICNIRP [4, 5], and IEC [6], the dependence on the retinal irradiance diameter (the retinal profile over which the energy that enters the eye is distributed) is represented in the MPEs by the correction factor α/α_{min} (C_E in ANSI and ICNIRP, C_6 in IEC) where α is termed the 'angular subtense of the apparent source' and describes the angular extent of the laser profile on the retina[7] (the angle α can be determined by dividing the retinal irradiance diameter with the effective focal length of the relaxed eye). The angle α is limited to small angles by α_{min} = 1.5 mrad, which is the nominal smallest angle that can be achieved due to the optical limitations of the eye (for the human eye, 1.5 mrad corresponds to a retinal diameter of 25.5 μm). For the determination of the correction factor, α is not to exceed α_{max} = 100 mrad, provided that the angle of acceptance for measurement of the radiant exposure which is compared to the MPE is also limited to 100 mrad. For the case that the retinal spot diameter is larger than 100 mrad and the irradiance profile is sufficiently homogeneous, the following formula may be used when the measurement angle of acceptance is not limited [8], i.e. the total energy that passes through the 7 mm aperture is compared to the MPE (i.e. using an 'open' field of view for the measurement or exposure assessment):

$$C_6^{open} = 66.6\,\frac{\alpha^2}{\alpha_{max}^2} = \frac{\alpha_{max}}{\alpha_{min}}\,\frac{\alpha^2}{\alpha_{max}^2} = \frac{\alpha^2}{\alpha_{min}\,\alpha_{max}}$$

This formula reflects the square dependence of the MPE on the retinal irradiance diameter for retinal irradiance diameters larger than 1.7 mm (0.1 rad x 17 mm for the human eye). Thus, the angle α_{max} is the breakpoint between the region of $\alpha < \alpha_{max}$ where the MPE (in 'corneal' space) increases with the diameter of the retinal irradiance profile, while for profiles larger than the breakpoint, the MPE increases as the square of the diameter (provided that the exposure level which is compared with the MPE is not limited by the angle of acceptance, i.e. a value equivalent to the TIE is used).

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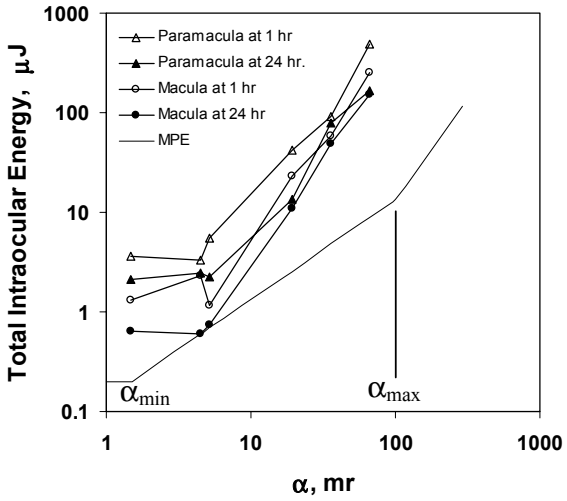


Figure 1. The ED_{50} for retinal injury induced by exposure to 5 ns, 532 nm laser pulses compared to the maximum permissible exposure (MPE)

The exposure limits (MPEs) are defined in terms of radiant exposure or irradiance at the position of the cornea. When the MPE is multiplied by the area of a circle with 7 mm diameter, a value that is equivalent to the energy that enters the eye, the total intraocular energy (TIE) can be derived. In this sense the MPEs are defined in corneal space. The TIE is a useful measure of the dose in bioeffects studies in that the experiment is usually designed so that the laser beam incident at the cornea is smaller than the pupil of the subject eye, and the TIE can be and is directly measured. It should be also noted that while the investigator can measure the angular distribution of the beam entering the eye they cannot directly measure the irradiance diameter at the retina. Large retinal area exposures are made in Maxwellian view such that α, the angle subtended by the retinal irradiance profile is equal to θ, the divergence angle of the incident beam.

Zuclich et al reported the ED_{50} for laser-induced retinal alteration over a range of α for exposure to 5 ns, 532 nm Nd:YAG laser irradiation (Figure 1). The ED_{50} was defined as that incident energy (TIE) at the cornea having a 50% probability of producing retinal injury. The data show no range in which the ED_{50} varied as α/α_{min}. The threshold for retinal injury remained essentially constant when α was decreased below 5 mrad and was proportional to α^2 for α greater than 5 mrad. Further, the ED_{50} was essentially equal to the MPE when α = 5 mrad, leaving no margin of safety.

These new data indicate a need to re-examine the provisions of the guidelines. To that purpose the authors revisited the literature to collect all accessible data relating the radiant exposure required to produce retinal damage to the diameter of the irradiated area on the retina. In addition the authors revisited existing thermal models using the availability of more powerful desktop computers to examine in detail the behaviour of computed thresholds as a function of retinal irradiance diameter and exposure duration.

2. METHODS

The present form of C_E and C_6 was largely based on in-vivo experiments reported by Beatrice[9, 10], Ham[11], Goldman[12], and Lund[13] before 1980, which suggested that the ED_{50} varied linearly with α for retinal irradiance diameters smaller than 1 mm . Other data are available from the literature. Data relating the threshold energy for retinal alteration to the diameter of the irradiated area were extracted from reports of studies intended to obtain dose-response data for laser irradiation of retinal tissue in vivo [1, 2, 9-29].

It was not always straightforward to derive comparable data from these reports. Investigators can measure the quantity of the energy entering the eye and the parameters characterising the beam propagation but cannot directly measure the radiant exposure at the retina, nor can they directly observe the retinal alterations resulting from the incident energy. The distribution of energy at the retina can only be inferred based on the properties of the laser beam incident at the cornea. Nonetheless, the commonly reported values were the retinal radiant exposure (H_R) and the diameter of the irradiated area on the retina. These are computed quantities that by necessity invoke assumptions about the size and focal length of the eye, the optical quality of the eye and the transparency of the pre-retinal ocular media. The assumed values were not always immediately evident from the reports. In practice, the exposures are made in a modified Maxwellian view with the beam waist positioned a distance in front of the eye so that the incident beam at the pupil has a diameter of 3-4 mm. The smallest retinal images are produced using a collimated beam. Aberrations, diffraction, scattering by the ocular media, and refractive errors all play a part in determining the smallest possible image. In spite of considerable study, the minimum image size is still a topic of debate. [30]

Lack of access to the target tissue also impacted the observation of a retinal response. Most commonly the retina was observed using an ophthalmic instrument such as an ophthalmoscope, fundus camera, or slit biomicroscope. It is not possible with these devices to directly see the induced retinal alteration for near-threshold exposures. Rather,

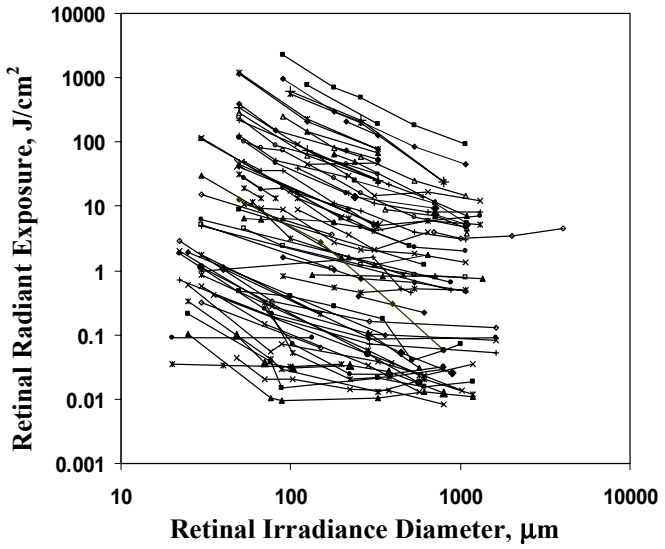


Figure 2. The variation of ED_{50} for laser-induced retinal injury (retinal radiant exposure, J/cm^2) with the retinal irradiance diameter These data included exposure durations from fs to ks and wavelengths from 400 nm to 1100 nm..

one sees the biological/metabolic response to the induced damage. This response is not instantaneous but develops over a period of time following the exposure. Early studies used a minimum visible lesion (MVL) visible at 5 minutes after exposure as the endpoint for the determination of the presence of a retinal response. Most subsequent studies have reported 1 hour and/or 24 hour MVL endpoints. Some investigators employed fluorescein angiography as an indicator of retinal alteration. While the non-human primate is the current model of choice, many of the early studies used the rabbit as an animal model, notably those studies that exposed retinal tissue to broadband radiation from a xenon lamp.

The collected data are shown in Figure 2 wherein the ED_{50} is given as a function of the retinal irradiance diameter. The data are expressed in units of radiant exposure (J/cm^2) at the retina. The retinal radiant exposure H_R is related to the incident energy at the cornea by the relationship $H_R = 4 * T_\lambda * TIE/\pi * D^2$ where T_λ is the transmission of the pre-retinal ocular media at the wavelength of exposure, D is the retinal irradiance diameter and TIE is the energy incident at the cornea within the area of the pupil. In all cases the retinal image diameter has been computed at the point where the radiant exposure fell to 1/e of the peak radiant exposure and has been adjusted to the appropriate value for a 13.5 mm focal length eye if the subject animal was a rhesus monkey or a 10 mm focal length eye if the subject animal was a rabbit.

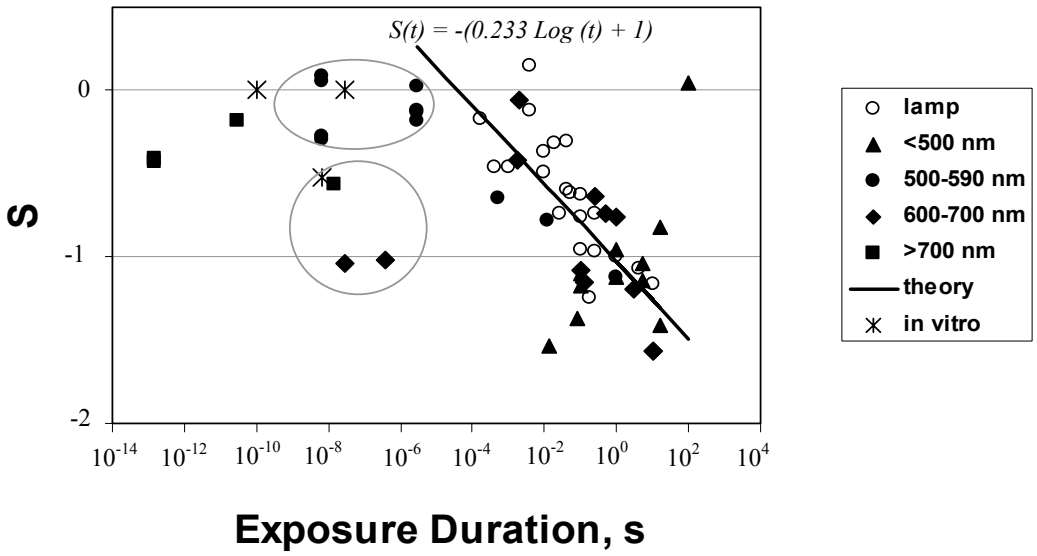


Figure 3. The exposure duration dependence of the slope of the ED_{50} vs retinal irradiance diameter data. Each point is the value S obtained by fitting the data of a single line in Figure 2 to an equation of the form $H_R = k * D^S$. The oval encloses the new data of Zuclich et al. The circle encloses the data of Beatrice and Lund. The line is a regression fit to the data for exposure duration longer than 20 μs. The equation of the line is $S(t) = -(0.233 \text{ Log } (t) + 1)$

It is difficult to draw any conclusions concerning the true relationship between the ED_{50} and the retinal irradiance diameter by simple examination of this body of data. Each data set can be approximated by an equation of the form $H_R = k * D^S$. The values of *S* relate the retinal radiant exposure to the retinal irradiance diameter at the threshold for retinal injury (Figure 3). The results of the thermal model calculations show that it is an oversimplification to fit each dataset with a single value of *S*: nonetheless *S*, so derived has utility in understanding the collected data. The value of *S* for a dataset is not changed when all values of *D* are multiplied by a constant such as an adjustment to the eye focal length or a transform from the $1/e^2$ to 1/e diameter definition. *S* generally has a value between 0 and -1. About one-fourth of the data sets consist of two points, one at a small retinal irradiation diameter determined by the ability of the eye to focus a collimated incident beam and generally listed at 25-30 micrometers. The second data point was at a larger irradiation diameter between 150 and 900 μm. Because of the uncertainty of the determination of the minimum irradiance diameter, those data sets are less reliable than those presenting data for more than two irradiance diameters.

In general the values of *S* follow the dependence on exposure duration predicted by heat flow considerations. For exposure durations shorter than a few μs, thermal flow is ineffective in removing heat from the exposed area and the temperature rise (and resulting tissue injury) is proportional to the radiant exposure for all irradiance diameters. The value of *S* is expected to be zero. As the exposure duration is increased, the value of *S* will decrease because thermal conduction becomes increasingly more important, and, because of aspect ratio, is more efficient for small irradiance diameter exposures than for large diameter exposures. The value of *S* is expected to be approximately equal to -1 for 1-second exposures. The values of *S* for the ns- and μs-duration data of Zuclich are close to zero, in agreement with this prediction. In contrast a grouping of 3 data points representing ns-duration exposures to red and near-infrared lasers have a value of *S* nearer to -1. These older data sets, attributed to Beatrice [9,10] and Lund [25], were influential in the definition of C_e and C_6 in the current guidelines. As a result it has become important to reconcile the older data and the new data.

It has been noted that the recent data differs from the older data in that the recent experiment reported a 24 hr MVL endpoint, exposed macular tissue, and used a top-hat beam profile. An examination of the available data shows that none of these factors have an effect on the value of *S*. The older data sets were collected in experiments conducted prior to 1980. Certainly there have been significant advances in laser quality, dosimetry, and beam diagnostics in the intervening years. The lasers utilized in the earlier studies were capable of producing TEM_{00} output of several millijoules and dosimetry and beam diagnostics were adequate. There is no apparent rational for rejecting the older data of Beatrice [9,10] and Lund [25], nor is there any apparent reason for rejecting the new data of Zuclich et al [1,2]. If both results are valid, some other factor must be involved in affecting the value of *S*. The only other apparent factor is wavelength: The new data were obtained at wavelengths of 532 nm and 590 nm. The older data were obtained at wavelengths longer than 590 nm. There is no obvious mechanism that would differentiate the two wavelength regions in a way that would affect the value of *S*.

Thermal Model

Models to estimate the temperature rise in retinal tissue were first written in efforts to understand the retinal hazard of intense broad-band optical sources. The models evolved to incorporate more realistic description of energy deposition in retinal tissue, to include transient thermal events, and to include the Arrhenius integral to predict denaturization of tissue leading to damage. Available computer models for laser-induced thermal retinal injury differ in the definition of the heat source. One assumes absorption following Beers law in homogeneous retinal pigment epithelium (RPE) and choroid layers and solves the heat flow equations numerically with a finite difference method (Takata et al[31]) The other assumes absorption only within the discrete melanosome particles in the RPE. Temperature fields produced by the individual melanosomes are superimposed to produce the temperature distribution in the retina as a function of time. (Thompson et al[32]). Both models incorporate the Arrhenius integral to determine an end point for damage. Three of the authors (Schulmeister Seiser and Edthofer) modified these models to facilitate computation of damage thresholds over a range of exposure durations and retinal irradiance diameters as well as enable non-circular symmetry. A full description of the computations and the results can be found in Schulmeister et al[33]. Retinal injury thresholds were computed for a number of retinal irradiance diameters ranging from 30 μm to 2000 μm for each of several exposure durations from 1 μs to 1 s. Figure 4 shows results obtained with the homogeneous absorber finite difference model. The melanin-granule model produced essentially identical results. The thermal model results were obtained by providing a retinal irradiance diameter and radiant exposure profile as input data and allowing the program to obtain a solution for the threshold radiant exposure. A tophat beam profile was assumed as well as a square-wave temporal pulse shape. The computed thresholds, when expressed as retinal radiant exposure, vary approximately inversely as the diameter of the irradiated area for small spots and are

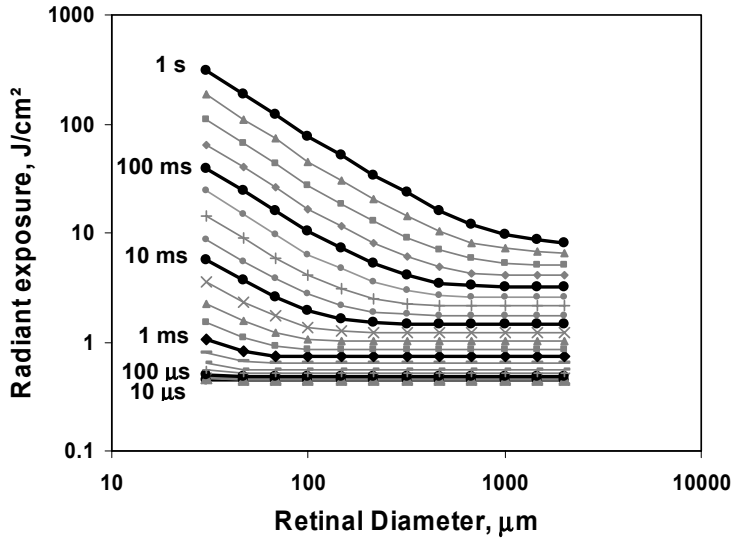


Figure 4. Thermal model computations of the dependence of the threshold for laser-induced retinal damage on exposure duration and retinal irradiance diameter. A tophat irradiance profile and a square temporal pulse shape were assumed. The computations were performed for 25 exposure durations from 1 µs to 1 s. a The computed thresholds, when expressed as retinal radiant exposure, vary approximately inversely as the diameter of the irradiated area for small spots and are independent of the irradiance diameter for large spots. The range of transition between the two zones in terms of retinal spot diameter is a function of the exposure duration. A breakpoint (Bp) can be obtained as the point of intersection of lines projected from the two zones.

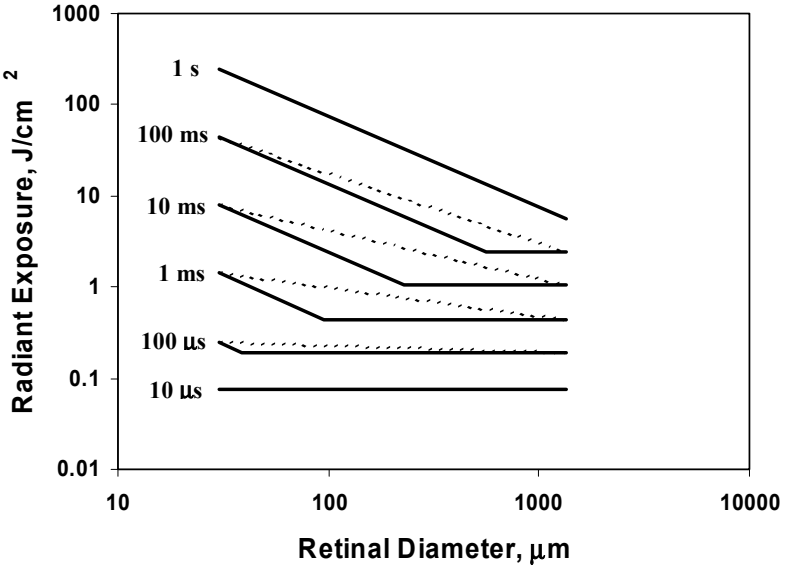
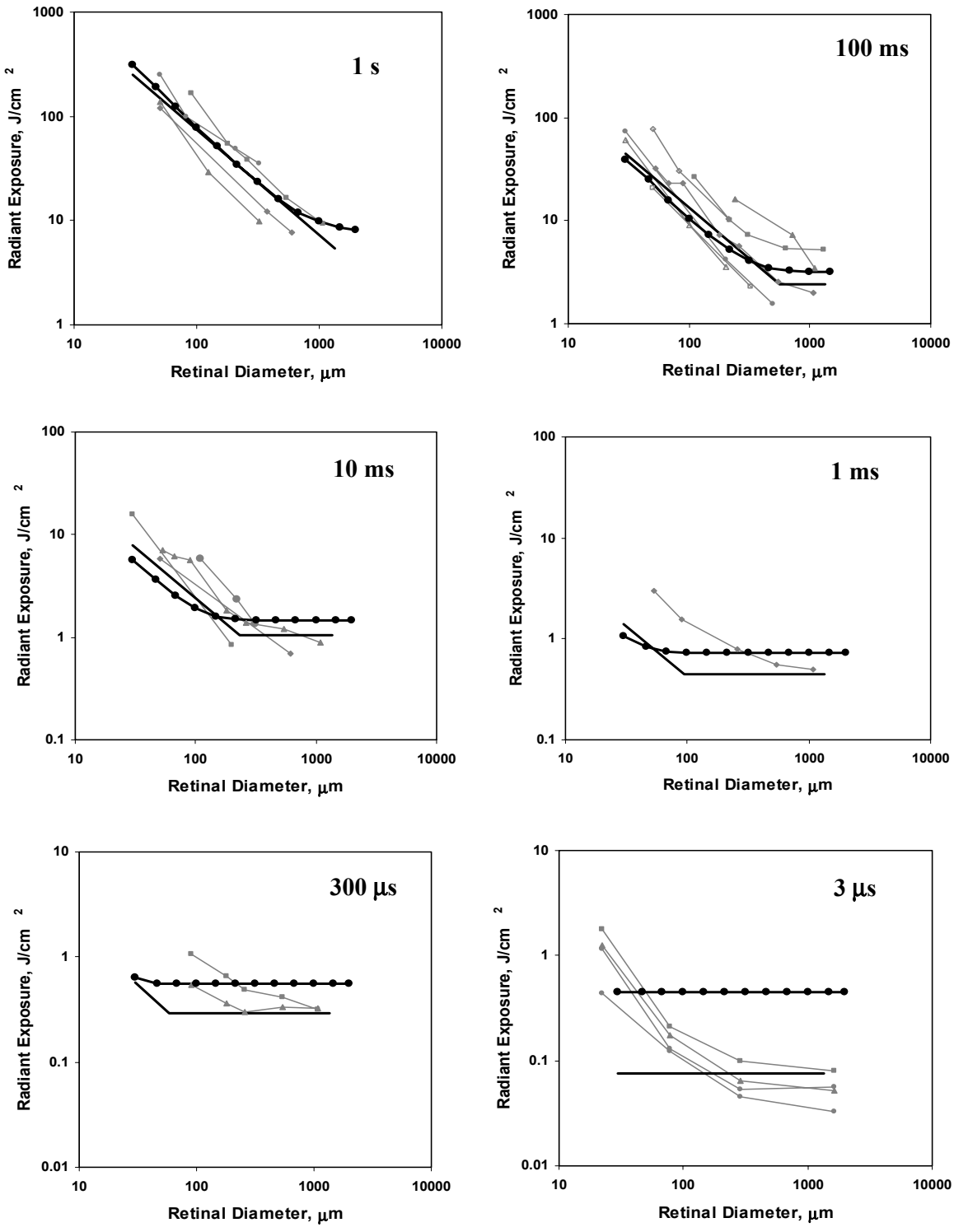


Figure 5 An empirical set of curves derived from the cumulative *S* vs exposure duration values. In Figure 4, the regression fit to the data for exposures longer than 20 us is given by Values of *S* were calculated using $S(t) = -(0.233\ Log\ (t) + 1$ for selected values of *t* and the radiant exposure, $H_r = k(t) * D^{S(t)}$ was determined for retinal irradiance diameters from 30 to 1350 um for each selected exposure duration. The value $k(t)$ was chosen such that $Hr = 250\ J/cm^2$ when $t = 1$ and $D = 30$ mm. This value was chosen to match the bioeffects data for 1 s exposures. For all other values of *t*, $k(t)$ was determined such that $k(t)/k(1s) = t^{3/4}$ The resulting retinal radiant exposure threshold values give the family of curves denoted by dotted lines. The thermal model computations indicate that these lines should be decomposed into two components. having slope -1 and slope 0



Figures 6 A comparison of the thermal model results and the empirical model results to the data for those exposure durations where data was available. The solid line represent the empirical model calculalations. The beaded line represent the thermal model calculations. For exposure durations of 1 s, 100 ms, and 10 ms, the model results are adequate predictors of the trend of the data. For shorter exposure durations, the model results continue to match the data for large irradiance diameters but become increasingly less predictive for irradiance diameters less than 100 µm.

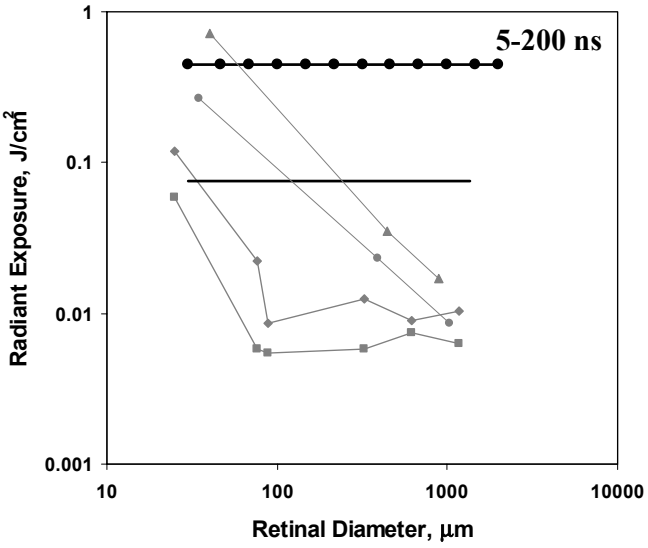


Figure 7 Comparison of data to model calculations for ns-duration exposures. The new data of Zuclich et al and the older data of Beatrice and Lund are included. The dichotomy between the newer and the older data is clearly shown. The model results predict the dependence of radiant exposure on retinal diameters shown by the newer data for retinal diameters larger than 100 µm, but completely fail to predict the behaviour of the data for small retinal diameters. The absolute level of the radiant exposure is off by 1 to 2 orders of magnitude. The models do not predict the irradiance diameter dependence of the older data.

independent of the irradiance diameter for large spots. The range of transition between the two zones in terms of retinal spot diameter is a function of the exposure duration. A breakpoint (Bp) can be obtained as the point of intersection of lines projected from the two zones

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The aspect ratio of the retinal region heated by the laser is an important factor controlling the dependence of threshold on irradiance diameter. For large images, the heated portion of retina behaves as a thin disc, and any cooling occurs by heat flow perpendicular to the disc. All regions of a large flat-topped image have equivalent exposure and dissipation opportunities, so the energy required to cause injury is proportional to the area of the image. The large-image injury threshold can be described by a retinal radiant exposure that is independent of image size. For small images, the diameter and thickness of the heated region become quite comparable, and dissipation can occur in three dimensions. Consequently, a higher level of retinal radiant exposure is needed to produce temperature increases which result in a higher damage threshold than when compared to the large-image value.

Empirical model.

An empirical set of curves can be derived from the cumulative *S* vs exposure duration values for comparison to the thermal models and the data. In Figure 4, the regression fit to the data for exposures longer than 20 µs is given by the equation $S(t) = -(0.233\ Log\ (t) + 1)$. Values of *S* were calculated for selected values of *t* and the radiant exposure, $H_R = k(t) * D^{S(t)}$ was determined for retinal irradiance diameters from 30 to 1350 µm for each selected exposure duration. The value $k(t)$ was chosen such that $H_R = 250\ J/cm^2$ when $t = 1$ and $D = 30$ µm. This value was chosen to match the bioeffects data for 1 s exposures. For all other values of *t*, $k(t)$ was determined such that $k(t)/k(1s) = t^{3/4}$ based on the knowledge that the ED_{50} varies as $t^{3/4}$ for small spot exposures of longer than 18 µs duration. The resulting retinal radiant exposure threshold values are plotted as a function of retinal diameter to give the family of curves denoted by dotted lines in figure 6. The thermal model computations indicate that these lines should be decomposed into two components, one having a slope of -1 and the other having a slope of 0 as indicated by the solid lines of Figure 5. The empirical curves in figure 6 are remarkably similar to the thermal model data of Figure 4.

3. RESULTS & DISCUSSION

Figures 6 and 7 compare the thermal model results and the empirical model results to the data for those exposure durations where data was available. For exposure durations of 1 s, 100 ms, and 10 ms, the model results are adequate predictors of the trend of the data. For shorter exposure durations, the model results continue to match the data for large irradiance diameters but become increasingly less predictive for irradiance diameters less than 100 µm. The results for ns-duration exposures are shown in Figure 7 wherein the model results are compared to the new data of Zuclich et al and the older data of Beatrice and Lund. The dichotomy between the newer and the older data is clearly shown. The model results predict the dependence of radiant exposure on retinal diameters shown by the newer data for retinal diameters larger than 100 µm, but completely fail to predict the behaviour of the data for small

retinal diameters. The absolute level of the radiant exposure is off by 1 to 2 orders of magnitude. The models do not predict the irradiance diameter dependence of the older data.

Both the thermal model, based on the thermal properties of the tissue, and the empirical model based on the data support a breakpoint, Bp, separating the small spot regime from the large spot regime which varies with the exposure duration. Figure 8 shows the breakpoint as a function of exposure duration. For durations longer than 100 μs, the empirical data are fit by the function $Bp = g * t^{3/8}$. The thermal model results and the empirical model have very comparable dependencies of the breakpoint on exposure duration.

The breakpoint we have defined here is the point which separates the zone wherein the ED_{50} , expressed as H_R, varies inversely as the retinal irradiance diameter from the zone wherein the ED_{50} is independent of the exposure diameter. .In terms of the TIE, (J at the cornea), this is equivalent to the point separating the zone wherein the ED_{50} varies as the diameter of irradiated area on the retina from the zone wherein the ED_{50} varies as the square of the diameter of the irradiated area on the retina. Remembering that D_R is proportional to α, this is also the definition of α_{max}. Thus the observation that Bp varies as the exposure duration is an observation that the value of α_{max} should also vary as a function of the exposure duration.

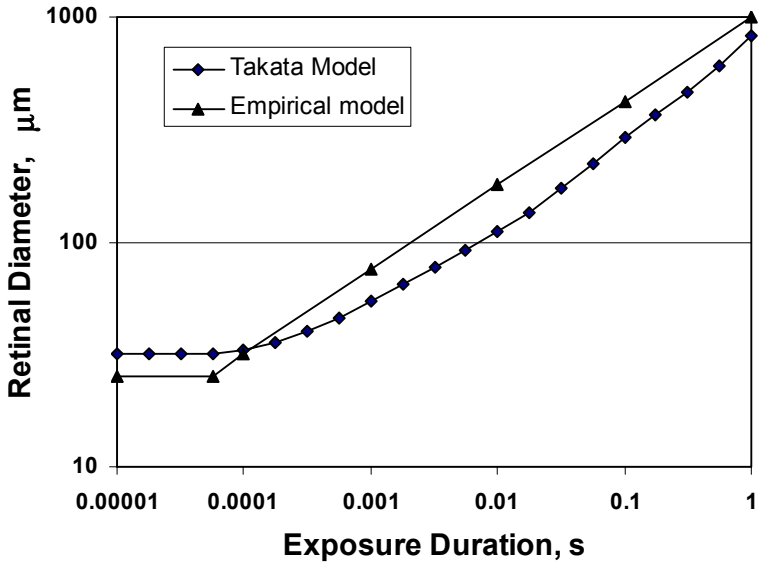

Figure 8. The breakpoint Bp as a function of exposure duration. For exposure durations greater than 100 μs, the empirical data are fit by the function $Bp = g * t^{3/8}$. The thermal model results and the empirical model have very comparable dependencies of the breakpoint on exposure duration.

4. CONCLUSIONS

Recent data regarding the relationship of laser-induced retinal injury to the diameter of the irradiated area on the retina present a problem for the current guidelines. These new data do not agree with the older data that provided the basis for the formulation of C_E and C_6 and there is no overwhelming reason to reject the old data. The new data are in better agreement with an empirical model based on a larger body of bioeffects data and with thermal model computations of the variation of threshold retinal radiant exposure with the diameter of the irradiated area. The new data strongly suggest that the form of C_E and C_6 must be changed. The empirical and thermal models suggest that the value of α_{max} should vary with exposure duration. However, the new data and other data also challenge the value of α_{min}. Issues concerning the injury threshold variation as the retinal diameter approaches the minimum achievable retinal irradiance diameter must be resolved before reformulation of the form of C_E and C_6.

5. DISCLAIMER

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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