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Abstract. The corneal damage effects induced by 1319-nm transitional near-infrared laser have been investigated for years. However, the damage threshold dependence on exposure duration has not been revealed. The *in vivo* corneal damage thresholds (ED_{50}s) were determined in New Zealand rabbits for 1319-nm laser radiation for exposure durations from 75 ms to 10 s. An additional corneal ED_{50} was determined at 1338 nm for a 5-ms exposure. The incident corneal irradiance diameter was fixed at 2 mm for all exposure conditions to avoid the influence of spot size on threshold. The ED_{50}s given in terms of the corneal radiant exposure for exposure durations of 5 ms, 75 ms, 0.35 s, 2 s, and 10 s were 39.4, 51.5, 87.2, 156.3, and 311.1 J/cm^2, respectively. The 39.4 J/cm^2 was derived from the ED_{50} for 1338 nm (27.0 J/cm^2). The ED_{50}s for exposure durations of 75 ms to 10 s were correlated by a power law equation, $ED_{50} = 128.9t^{0.36}$ in J/cm^2, where t was the input in the unit of second, with correlation coefficient (R) of 0.997. Enough safe margins existed between the ED_{50}s and the maximum permitted exposures from current laser safety standard.
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Keywords: corneal thermal damage; damage threshold; transitional near-infrared laser; exposure duration.

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1 Introduction

The transitional infrared wavelength range refers to the wavelength band from 1.3 to 1.4 μm.[1–3] In this region, the most sensitive tissue changes gradually from the retina to the cornea. Developments of lasers in this wavelength range promote increased applications throughout telecommunication, medicine, and military.[4,5] Due to the rapid increase of laser power or energy, ocular damage risk becomes serious and thus receives increasing concern. In the past two decades, investigations on ocular bioeffects induced by transitional near-infrared (NIR) laser have revealed some unique characteristics. First, the absorption of incident laser beam in this region is more evenly distributed across the ocular components.[1–3] Damage may be induced in one or more of the cornea, lens, and retina/choroid, depending on the precise exposure parameters.[1,2,6–8] Second, strong spot-size dependence exists for this wavelength range. Threshold-level damage occurs at the retina for a relatively large corneal beam spot, while it occurs at the cornea for a relatively small spot.[3] Third, a retinal or corneal threshold lesion involves full thickness of that layer.[9–11] Up to now, corneal damage thresholds for diverse exposure conditions have been determined, which provided important reference to the revision of laser safety standard.[12–14]

For given wavelength, one important issue is to determine the dependence of ocular damage threshold on exposure duration, especially for the range from submillisecond to tens of seconds.[15–17] For IR laser radiations, the ocular damage is dominated by thermal-mechanical mechanism for exposures below ~50 μs and by thermal mechanism above ~50 μs.[16–18] In the thermal-dominated regime, the corneal damage threshold follows a power function law: $^{k}ED_{th} \propto t^k$, where k is the slope of the fitted line in the log-log space.[16] For the wavelengths of 1.54, 2.02, and 10.6 μm, the values of k are all about 0.5 for exposure durations of 20 ms to 10 s,[16,18–20] as shown in Fig. 1.

However, for the transitional NIR region, the k seems greatly different from those of other infrared wavelengths. The existing corneal damage thresholds for 1319 nm are summarized in Fig. 1.[1,3,9,10,21] Good linear relationship could be found for the right four points. Through regression analysis, k equals 0.92, which is much larger than those of the other three wavelengths. The large k value at 1319 nm implies that the corneal damage for transitional NIR wavelengths may obey a new rule. It may be due to the volumetric absorption characteristic, which is obviously different from the thin-layer absorption of longer infrared wavelengths.

For the determination of damage threshold, spot size is an important influence factor.[18–20] According to previous studies, the corneal epithelial damage thresholds increase dramatically as the spot size decreases to a certain value which depends on the exposure duration.[16,18,20] For example, the corneal damage threshold at 0.5-mm spot size is four times higher than that at 2 mm for 2-s exposure duration and 1.54-μm wavelength.[18] A strong dependence of damage threshold on spot size also exists for the transitional NIR region, as can be seen from the left three points in Fig. 1. Also, it should be noted that the four points on the upright of Fig. 1 are from different studies and the spot sizes

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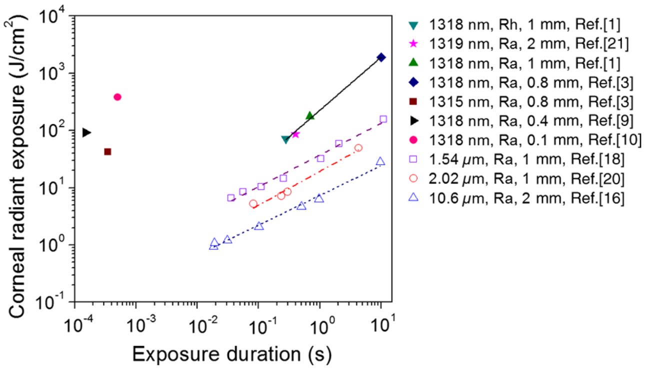

Fig. 1 Previous corneal damage thresholds (ED_{50} or H_{th}) in terms of J/cm^2.[1,3,9,10,16,18,20,21] The parameters behind the symbols denote the laser wavelength, the animal species (Rh: Rhesus; Ra: Rabbit), and the corneal spot diameter. The four lines are the least square fits to damage thresholds: solid line: $ED_{50} = 225.9t^{0.92}$ ($R = 0.997$); dashed line: $H_{th} = 37.3t^{0.55}$ ($R = 0.998$); dashed-dotted line: $H_{th} = 19.4t^{0.59}$ ($R = 0.983$); and shot-dotted line: $H_{th} = 7.36t^{0.52}$ ($R = 0.995$).

differ from each other. So the linear relationship may be a coincidence and $k = 0.92$ may be a misleading tendency. In this paper, we aim to determine the corneal damage thresholds for 1319 nm at 2-mm fixed spot size and their dependence on exposure duration.

2 Materials and Methods

2.1 *Experimental Setup*

The experimental setup for corneal exposure was shown in Fig. 2. Corneal exposures were conducted with a diode pumped continuous-wave (CW) Nd:YAG laser (Fujian Institute of Research on the Structure of Matter, Chinese Academy of Science, Fujian, China) at 1319 nm and a Xe-lamp pumped pulsed Nd:YAG laser (Beijing Hongxiang Optoelectronic Technology Co., Ltd., Beijing, China) at 1338 nm. The maximum output of the CW 1319-nm laser was ~50 W, with power stability within ±2% for 1-h operating time. The pulsed 1338-nm laser emitted 5-ms single pulse with ~3-J maximum pulse energy and ±5% energy repeatability. The intensity of the incident radiation was nearly "top hat" distributed which was provided by the laser manufactures and verified through the exposure of photosensitive paper. A beam splitter placed slightly off the axis reflected a small portion of laser energy to a power/energy meter (3A, Ophir, Jerusalem, Israel) for monitoring the laser power/energy arrived at the cornea. Another power/energy meter (30A, Ophir) was placed at the animal eye's position to measure the power/energy arriving at the cornea. An electronically controlled mechanical shutter was employed to control the exposure duration for the CW 1319-nm laser. A low-power 633-nm He-Ne laser, coaxial with the 1319- or 1338-nm laser, was

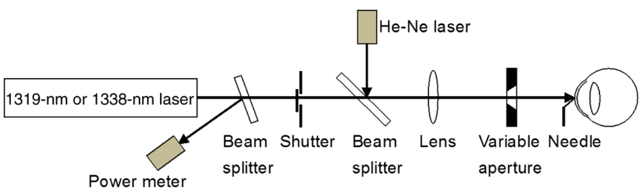

Fig. 2 Experimental setup.

used as a pointer for corneal exposure position. A lens and a circular variable aperture were positioned to control the corneal spot diameter and select the central portion of the beam. Though measuring the spot diameters at different positions, the exact position corresponding to the desired corneal spot diameter could be determined and then located by a needle.

2.2 *Animals and Laser Damage*

New Zealand white rabbits of either sex weighting 2.5 to 3.0 kg were used for the experiments. The rabbits were procured, maintained in the Center for Laboratory Animal Medicine and Care, Beijing, China, and used in accordance with the institutional guidelines of the Animal Care and Use Committee and the ARVO Resolution on the Use of Animals in Research. Subjects were preexposure examined by a slit-lamp to ensure clear ocular media and normal ocular tissue. To ensure the subjects did not experience pain and distress, all animals were anesthetized with an intramuscular injection of a mixture of ketamine hydrochloride (40 mg/kg) and xylazine (12 mg/kg). Full pupil dilation was performed with two drops each of proparacaine hydrochloride 0.5%, phenylephrine hydrochloride 2.5%, and tropicamide 1% at 5-min interval. The anesthetized animals were placed in a conventional holder where they were positioned with the aid of the He-Ne laser. The eyes were positioned to ensure the incident beam was perpendicular to the central cornea. Six to seven exposures were delivered to each eye. Overlapping of corneal lesions was avoided with the aid of the He-Ne laser pointer.

Following each exposure session, lesion/no lesion determinations were made by two experienced investigators for each irradiation site at 1 h postexposure, a time point that is approved for corneal damage threshold determination.[11,22] Corneal lesions were examined with unaided eye and confirmed by slit-lamp microscopy. Also, the lens and the retina were observed through slit-lamp microscopy and ophthalmoscope to examine whether damages occurred or not. The lesion/no lesion data were collected and analyzed using SAS statistical package (version 6.12, SAS Institute, Inc., Cary, North Carolina). Bliss probit analysis was performed to determine the ED_{50} thresholds, fiducial limits at the 95% confidence level, and probit slope (ED_{84}/ED_{50}). The ED_{50} refers to the effective dose corresponding to 50% damage probability.[23,24] After determination of ED_{50}s, the development of laser-induced corneal injury at ~1.5 times threshold were followed with slit-lamp microscopy for 1319 nm, 0.35 s and 1338 nm, 5 ms exposure conditions. Only one to two exposures were made on each cornea for observation convenience. The corneal injuries were observed immediately, 1 h, 6 h, 12 h, 24 h, and 3 days postexposure.

2.3 *Data Analysis*

As two laser wavelengths were involved in this experiment, the influence of wavelength should be eliminated in data analysis for investigating the corneal damage threshold dependence on exposure duration. According to the action spectrum theory introduced by Lund and coworkers,[25,26] the same absorbed energy induces the same injury effect, i.e.,

$$Q_{c,\lambda_1} = Q_{c,\lambda_2}, \tag{1}$$

where Q_{c,λ_1} and Q_{c,λ_2} are the energy absorbed by the corneal at the wavelength λ_1 and λ_2, respectively. For thin layer tissue, using first-order approximation, the absorbed energy $Q_{c,\lambda}$ can be expressed as

$$Q_{c,\lambda} = Q_{0,\lambda} \cdot A_\lambda \cdot L, \tag{2}$$

where $Q_{0,\lambda}$ is the incident energy, A_λ is the corneal absorption coefficient, and L is the tissue thickness.

According to the absorption coefficient of water at 1319 and 1338 nm (1.79 and 2.62 cm^{-1}, respectively[27,28]) and the thickness of rabbit cornea (0.04 cm), $A_\lambda \cdot L \ll 1$, which satisfies the first-order approximation. So the ED_{50} determined at 1338 nm can be transformed to that at 1319 nm,

$$Q_{0,1319} = \frac{Q_{0,1338} \cdot A_{1338}}{A_{1319}} = 1.46 \cdot Q_{0,1338}. \tag{3}$$

3 Results

A total of 765 data points were obtained for the five exposure conditions. All the experimental conditions, the ED_{50}s termed in corneal radiant exposure, the 95% fiducial limits, and the probit slopes, were summarized in Table 1.

Using the above-mentioned method, the ED_{50} for 1319 nm at 5 ms, derived from that for 1338 nm, was 39.4 J/cm^2. All the ED_{50}s, in terms of radiant exposure, were plotted in Fig. 3. It can be seen that the ED_{50}s kept nearly constant for exposure durations shorter than 5 ms, while for exposure durations longer than 75 ms, the ED_{50}s followed a linear function. Through regression analysis, the dependence of ED_{50} on exposure duration was determined, i.e., $ED_{50} = 128.9t^{0.36}$ in J/cm^2, where t is the input in the unit of second, with the correlation coefficient of 0.997. The maximum permitted exposures (MPEs) from the new ANSI Z136.1-2014 and ICNIRP-2013 guidelines were also included in Fig. 3 for further discussion.

At threshold levels, corneal lesions induced by 1319- and 1338-nm lasers appeared as light gray-white spots. Some of the lesions which were barely visible right after laser exposure became distinctive at 1 h and then obscure again at 24 h postexposure. Lesions distinctive immediately also became obscure at 24 h. Lens or retinal damage was not found for all observation time points.

At ∼1.5 times threshold level, the cornea was seriously damaged by 1319 and 1338 nm lasers. Immediately postexposure, the corneal lesions appeared as distinctive white spots under unaided eye [Figs. 4(a) and 4(c)], obvious corneal distortions and lenticular damage could be observed under slit-lamp microscope with direct broad-beam illumination [Figs. 4(b) and 4(d)], and highly reflective white straps with a thickness identical to the unexposed region could be seen under direct slit-beam illumination [Figs. 4(e) and 4(i)], indicating the damage involved the full thickness of the cornea. At a specific illumination angle, the corneal and lenticular damages could be observed simultaneously and the lenticular damage appeared as a white strap at the anterior lens capsule [Figs. 4(e) and 4(i)]. The corneal thickness of the damaged and adjacent regions increased remarkably at 6 to 24 h and recovered at 3 days postexposure [Figs. 4(f)–4(h) and 4(j)–4(l)]. The retinal lesions were not observed at all check time points for both lasers.

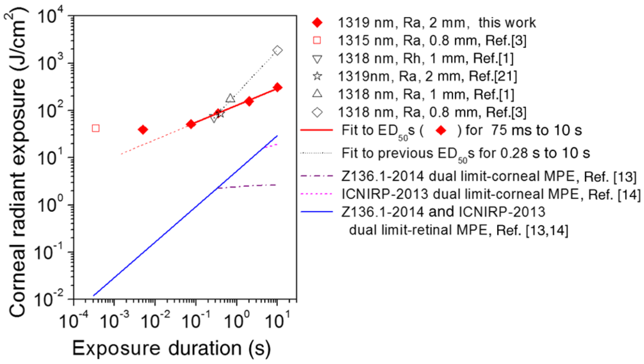

Fig. 3 Corneal damage thresholds determined in our experiment and reported by previous investigations, and MPEs from ANSI Z136.1-2014 and ICNIRP-2013 for 1319 nm.[1,3,13,14,21] The 5-ms point was transformed from that at 1338 nm. The solid line was a least square fit to a power law, $ED_{50} = 128.9t^{0.36}$ ($R = 0.997$).

4 Discussion

During the last two decades, corneal damage experiments for transitional NIR lasers have been conducted for different wavelengths, exposure durations, and spot sizes. However, the damage threshold dependence on exposure duration is still inconclusive. This study determined corneal ED_{50}s for 1319-nm laser with exposure durations from 5 ms to 10 s at fixed incident spot size and analyzed its exposure duration dependence. Our results will provide reference to the revision of laser safety standards about the MPEs for transitional NIR lasers.

Previous corneal damage studies were conducted using rabbits and rhesus monkeys. For the corneal damage threshold, no obvious difference could be found between rabbit and rhesus.[1] We chose the rabbit as the experimental animal. Bliss probit analysis is a widely accepted method for the determination of damage threshold. The probit slope of the dose response

Table 1 Summary of the data obtained from the corneal damage thresholds for 2-mm spot diameter.

Wavelength (nm)	Exposure duration (s)	Number of eyes	Number of exposures	ED_{50} (95% fiducial limits) (J/cm^2)	Probit slope (ED_{84}/ED_{50})
1338	5.0×10^{-3}	24	160	27.0 (25.8, 28.1)	1.14
1319	7.5×10^{-2}	24	168	51.5 (47.8, 55.0)	1.28
	0.35	24	166	87.2 (84.4, 95.1)	1.21
	2	24	157	156.3 (141.4, 172.1)	1.18
	10	18	114	311.1 (243.0, 335.9)	1.16

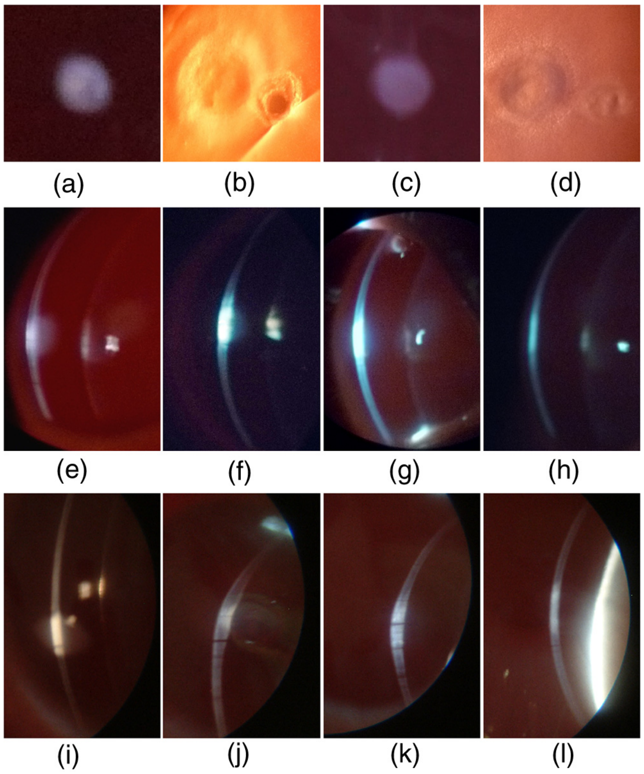

Fig. 4 Photographs of lesions induced by 1319- and 1338-nm lasers at ~1.5 times threshold level. The corneal radiant exposures for 1319 and 1338 nm were 133.7 J/cm^2 (0.35 s) and 40.5 J/cm^2 (5 ms), respectively: (a) and (c) lesions under unaided eye immediately postexposure for 1319 and 1338 nm, repectively; (b) and (d) lesions under slit-lamp microscope with direct broad-beam illumination immediately postexposure; (e)–(h) lesions for 1319-nm laser under direct slit-beam illumination at immediately, 6 h, 24 h, and 3 days postexposure; and (i)–(l) lesions for 1338-nm laser under direct slit-beam illumination at immediately, 6 h, 24 h, and 3 days postexposure.

curve reflects not only natural biological variations, but also the impact of experimental uncertainties.[23] For corneal damage threshold, the probit slopes are about 1.1 to 1.2 due to high homogeneity of corneal media and low variation among individuals. In this investigation, the probit slopes were between 1.1 and 1.3, similar to previous reports.[21,29]

Based on the corneal ED_{50}s from this work and previous reports, the ED_{50}s kept nearly constant for exposure durations shorter than 5 ms, while for exposure durations longer than 75 ms, the ED_{50}s followed a linear function in log-log space with slope of 0.36. By comparing Figs. 1 and 3, the slope for 1319 nm was not obviously different from those for other IR wavelengths (1.54,[18] 2.02,[20] and 10.6 μm[16]), which indicated the volumetric absorption characteristics of transitional NIR lasers would not significantly influence the dependence of corneal damage threshold on exposure duration. Furthermore, the damage thresholds for 1319 nm were obviously higher than those for other IR lasers, which resulted from its lower absorption. The absorption coefficients of pure water for 1319 nm, 1.54 μm, 2.02 μm, and 10.6 μm are 1.79, 11.9, 56.2, and 826.7 cm^{-1}, respectively.[16,18,21] As the decrease of absorption coefficient, less energy deposits in cornea layer and thus more energy is needed to induce corneal damage.

Obviously, the exposure duration dependence from our experiments (0.36) was far less than that from previous data (0.92), as shown in Fig. 3. It could be seen that for short exposure duration ($< \sim 0.5$ s), the threshold from our experiment approximated the previous reported data, while for longer exposure duration ($> \sim 0.5$ s) they departed gradually from each other. At the 10-s exposure duration, our threshold was only one sixth of previous reported data. One important fact must be noted that the spot size in our experiments was 2 mm, obviously larger than those in other reports. It is well known that the spot size is an important factor in determining damage threshold. According to Schulmeister et al.,[30,31] for thermally induced ocular damage, there is an inflection point which separates the curve of damage threshold dependence on spot size. For spot sizes smaller than the inflection point, the damage threshold is approximately inversely proportional to spot size. While for spot sizes larger than the inflection point, the thresholds are independent of spot size. More importantly, the position of the inflection point depends on the exposure duration. From the report by McCally et al.,[18] for corneal damage, the inflection point locates at ~0.8 mm for 0.5-s exposure duration and increases to 2 to 3 mm for 10 s.[11] In Fig. 3, for the three points around the intersection of the two fitted lines, the exposure durations were shorter than 0.5 s and the spot sizes were larger than 0.8 mm, so the thresholds would be independent of spot size. However, for data points at longer exposure duration, such as 10 s, the spot size in previous report was 0.8 mm, which was smaller than the inflection point corresponding to 10 s. This explained their much higher damage threshold as compared with our result. Therefore, the higher slope in Fig. 1 was only a coincidence. According to above discussion, both the threshold point under the exposure condition of 0.35 ms, 0.8 mm (shown in Fig. 3) and our threshold point under 5 ms, 2 mm obviously belong to the region where the thresholds are independent of spot size. In addition, according to the model prediction by Polhamus et al.,[32] these two points locate in a time region where the damage thresholds are independent of exposure duration. As a result, their ED_{50}s are nearly identical.

At longer exposure duration, the corneal damage thresholds from our experiments were much lower than previously reported data, so the corneal injury risk should be carefully evaluated in relation to the laser safety standard. There exists a safety margin between ED_{50} and corresponding MPE, which is defined as the ED_{50}/MPE ratio and generally preferred to be at least 2 for cornea and ~10 for retina.[12,14] In Fig. 3, the ocular MPEs ("dual-limit") for 1319 nm proposed by ICNIRP-2013 guideline and specified by new ANSI Z136.1-2014 were presented.[13,14] For assessing laser hazard, the lower value of the "dual-limit" should be employed. It can be seen that MPEs from ICNIRP and ANSI Z136.1 offer adequate safety margins for corneal protection. However, for setting the corneal MPEs, the damage threshold should be determined in the worst case. For 2-s exposure duration or shorter, the 2-mm corneal spot diameter is large enough. While for 10-s exposure duration, a spot size no less than 3.5 mm is appropriate (as shown by the limiting aperture in laser safety standard[13]). In other words, the ED_{50} for 10-s exposure duration determined in our experiment may not be the representation of "the worst case." However, from the tendency shown in Fig. 3, enough margin still exists between the ED_{50}s for "the worst case" and corresponding MPEs.

When assessing retinal damage risks, the ED_{50}s in terms of J (total intraocular energy, TIE) are convenient for comparison with MPEs. The ED_{50}s in terms of TIE for 1319 nm at 5 ms, 75 ms, 0.35 s, 2 s, and 10 s were 0.124, 1.62, 2.74, 4.91, and 9.77 J, respectively. The corresponding retinal MPEs are 0.0380, 0.290, 0.919, 3.40, and 11.4 J.[13,14] The ratios of ED_{50} to MPE for all conditions, including the 1.5 times ED_{50} exposures at 5 ms and 0.35 s, were lower than 10. Furthermore, the converging incident laser beam in our experiment leaded to enlarged retinal spot size. Therefore, the retina would not be damaged, which was consistent with our observations.

The highly scattering "white strap" in the illumination with the slit-lamp results from corneal lesion, while the weakly scattering "gray-white strap" represents unexposed region. For 1319 and 1338 nm, the thickness of the "white strap" is identical to that of the adjacent "gray-white strap," which indicated the damage involved the full thickness of the cornea. In contrast, for laser wavelengths with low-penetration depth such as 10.6 μm, the thickness of the "white strap" is much thinner than that of the adjacent "gray-white strap," as shown by Chen et al.[21] The lenticular damage could be observed at the anterior lens capsule at ∼1.5 times threshold level. However, according to Zuclich et al.,[1] the lens threshold is approximately twice the corneal threshold for 1318-nm exposure. The difference may be due to that the converging incident laser beam was employed in our experiment, which leaded to a higher exposure on the lens, comparing with the collimated beam by Zuclich et al.[1]

5 Conclusion

The ED_{50}s given in terms of the corneal radiant exposure for exposure durations of 5 ms, 75 ms, 0.35 s, 2 s, and 10 s were 39.4, 51.5, 87.2, 156.3, and 311.1 J/cm^2, respectively. The 39.4 J/cm^2 was derived from the ED_{50} for 1338 nm (27.0 J/cm^2). The ED_{50}s for exposure durations of 75 ms to 10 s were correlated by a power law equation, $ED_{50} = 128.9t^{0.36}$ in J/cm^2, where t was the input in the units of seconds, with correlation coefficient of 0.997, which was similar to those for other IR wavelengths. Enough safe margins existed between the ED_{50}s and the MPEs from both ANSI Z136.1-2014 and ICNIRP-2013 guidelines. The obtained results could be used for the refinement of the safety standards for transitional NIR lasers.

Acknowledgments

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