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Do *in vivo* terahertz imaging systems comply with safety guidelines?

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Techniques for the coherent generation and detection of electromagnetic radiation in the far infrared, or terahertz, region of the electromagnetic spectrum have recently developed rapidly and may soon be applied for *in vivo* medical imaging. Both continuous wave and pulsed imaging systems are under development, with terahertz pulsed imaging being the more common method. Typically a pump and probe technique is used, with picosecond pulses of terahertz radiation generated from femtosecond infrared laser pulses, using an antenna or nonlinear crystal. After interaction with the subject either by transmission or reflection, coherent detection is achieved when the terahertz beam is combined with the probe laser beam. Raster scanning of the subject leads to an image data set comprising a time series representing the pulse at each pixel. A set of parametric images may be calculated, mapping the values of various parameters calculated from the shape of the pulses. A safety analysis has been performed, based on current guidelines for skin exposure to radiation of wavelengths 2.6 μm–20 mm (15 GHz–115 THz), to determine the maximum permissible exposure (MPE) for such a terahertz imaging system. The international guidelines for this range of wavelengths are drawn from two U.S. standards documents. The method for this analysis was taken from the American National Standard for the Safe Use of Lasers (ANSI Z136.1), and to ensure a conservative analysis, parameters were drawn from both this standard and from the IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields (C95.1). The calculated maximum permissible average beam power was 3 mW, indicating that typical terahertz imaging systems are safe according to the current guidelines. Further developments may however result in systems that will exceed the calculated limit. Furthermore, the published MPEs for pulsed exposures are based on measurements at shorter wavelengths and with pulses of longer duration than those used in terahertz pulsed imaging systems, so the results should be treated with caution.

Key words: terahertz pulsed imaging, hazard analysis, maximum permissible exposure (MPE), human, *in vivo*, skin, safety

I. INTRODUCTION

Electromagnetic radiation in the far infrared, or terahertz, region of the electromagnetic spectrum is usually defined as including wavelengths between 3 μm and 3 mm (100 GHz–100 THz). The radiation was not widely exploited until recently because only incoherent, low brightness radiation could be generated, and detection was a slow process with poor signal to noise ratio. Developments in technology[1,2] have led to much interest in using the radiation to perform spectroscopy and imaging in several areas of application.[3–5]

One such application is *in vivo* medical imaging. There is optimism, supported by initial experimental results, that images formed from pulses of terahertz radiation have contrast generated from both biochemical[6] and morphological features of the subject. Applications such as wound healing and burn diagnostics,[4,7] dermatology,[8,9] and dentistry[10,11] have been subject to most interest. This is because they are applications where the limited penetration depth of the radia-

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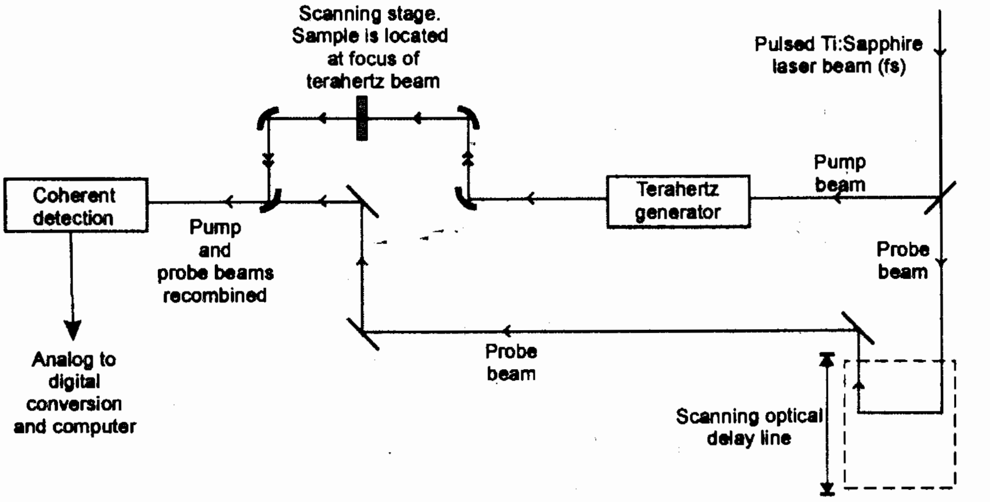

FIG. 1. Schematic of a terahertz pulsed imaging system, arranged for transmission imaging. The terahertz generator may be an antenna or a nonlinear crystal. The terahertz beam is collimated (heavy double arrows) and focused (heavy single arrow) by parabolic mirrors. The scanning optical delay line is used to obtain measurements at a range of time points in the pulse, whilst the raster scanning for image formation is achieved by a scanning stage holding the sample at the focus of the terahertz beam. Adaptations are possible for reflection imaging and scanning of the beam rather than the sample.

tion is unimportant, and the tissue is easily accessible with no need for waveguides to direct radiation to the area of interest. The use of near infrared and visible light is also being investigated with respect to these applications, but terahertz frequency radiation is less affected by Rayleigh scatter than radiation at the higher frequencies, which may reduce the need for special scatter-reducing imaging techniques and postprocessing.

The technique of terahertz pulsed imaging is based on the pump and probe technique of optical spectroscopy, using an ultrafast infrared laser such as a Ti:sapphire laser (Fig. 1). The beam is split in two with one part used as the pump beam, to generate terahertz pulses, while the other forms part of the detection system and is used as a probe beam to detect coherently the amplitude of the terahertz electric field after it has interacted with the subject. Picosecond pulses of terahertz radiation are generated using the pump beam by one of two techniques. In the first a voltage-biased photoconductive antenna[12] is illuminated with pulses from the ultrafast infrared laser. In the second, known as optical rectification or optical mixing, the infrared pulses are used to illuminate a crystal with high nonlinear susceptibility.[13,14] The second method can yield pulses with frequencies up to 70 THz. A typical terahertz pulse, generated by optical rectification, is shown in Fig. 2. Currently, the average power of the resultant terahertz beam is under 1 mW. The terahertz beam is directed onto the subject using parabolic mirrors, focused to a spot roughly 0.5 mm in diameter. The transmitted or reflected terahertz pulse profile is measured at a discrete number of time points by scanning with an optical delay stage. The spatial mapping of measurements for image formation may most simply be performed using raster scanning of the subject, or of the terahertz beam, although this is a slow method. Alternative schemes are under development involving illumination of a larger area by the pump beam, a multielement array detector such as a charge coupled device is used for detection.[15,16] The acquisition process results in a time series, representing the pulse profile, at each point in the raster scan. The pulse will be broadened and delayed in a manner that depends on the material through which it has passed. A reference pulse is also acquired without the sample in place. Sets of parametric images may be generated by plotting values generated from each measured pulse, or from its Fourier transform. The latter option means that frequency dependent effects may be isolated. Examples of parametric images from one image acquisition are shown in Fig. 3. Fuller descriptions of terahertz imaging systems may be found in Refs. 4, 7, and 17.

In systems intended for *in vivo* use, the Class 4 infrared laser used in the pump and probe system is enclosed in order to safeguard the subject. The hazard arising from skin exposure to terahertz radiation is addressed in this article. Although scanning systems are very slow, they are likely to be the technology used in the first *in vivo* studies on volunteers, and it is primarily these that have been considered in the analysis here.

II. SAFETY ANALYSIS

The frequencies present in a typical pulsed terahertz imaging system range from several gigahertz to several terahertz. Safety guidelines for electromagnetic radiation are presented in standards documents covering two wide frequency

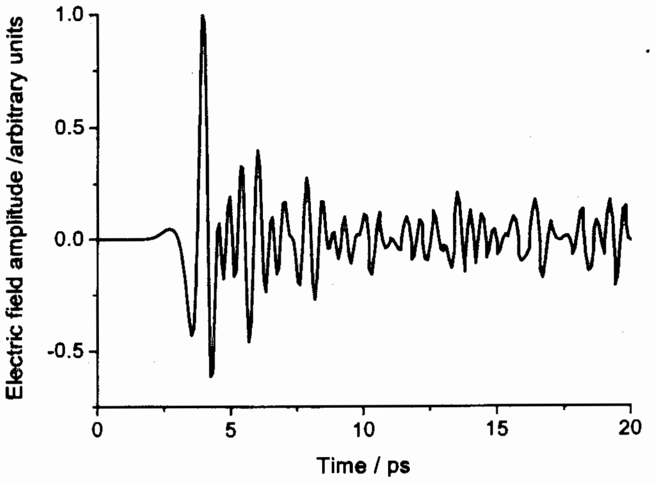

FIG. 2. Example of a terahertz pulse generated by optical rectification. The full width half maximum extent of the pulse peak is roughly 100 fs.

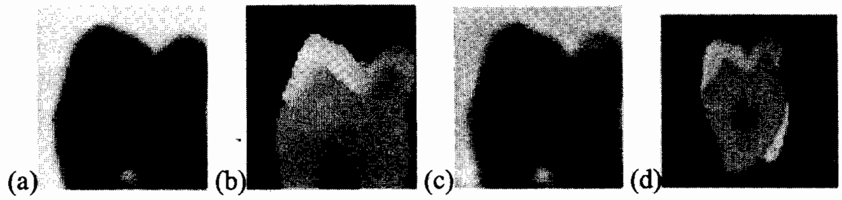

FIG. 3. Parametric terahertz pulsed images taken from a data set acquired from transmission through a slice of tooth of thickness 200 μm (a) Pulse amplitude relative to reference pulse amplitude, in time domain. (b) Time delay between transmitted pulse peak and peak of reference, in time domain. (c) Transmittance (ratio of transmitted and incident intensities after Fourier transformation of pulses) at 1.06 THz. For comparison, a radiograph of the tooth slice, which covers a larger field of view, is shown in (d).

ranges that meet at 300 GHz (corresponding to a wavelength of 1 mm and thus within the terahertz band). The international guidelines[18,19] are drawn from two U.S. standards documents. Optical wavelengths are covered by ANSI Z136.1, 2000[20] and millimeter waves and longer wavelengths by IEEE C95.1, 1999.[21] Each of the ranges is further subdivided into smaller ranges for which different safety limits apply.

In the IEEE document[21] it is stated that "These recommendation are not intended to apply to the purposeful exposure of patients by, or under the direction of, practitioners of the healing arts." and "Exposures in excess of the MPEs are not necessarily harmful. However, in the absence of intended benefits (e.g., medical or lifesaving procedures), exposures above the maximum permissible exposure (MPE) are not recommended." The implication of these statements is that higher limits may be justifiable if some medical benefit were expected. However, certainly in initial work, exposure of volunteers and patients to terahertz radiation will be for research purposes only, and no benefit to the individual can be promised. Thus the limits should be applied without relaxation. The ANSI document makes a similar comment on use for medical applications, and the guidelines have previously been applied to clinical tools, for example the scanning laser ophthalmoscope[22] and optical coherence tomography.[23]

MPEs for wavelengths in the terahertz band are expressed in terms of power density (irradiance), MPE:E (W cm^{-2}) for continuous exposures, and for a single pulsed exposure in terms of energy density (radiant exposure), MPE:H (J cm^{-2}). Similarly, Q_{MPE} and ϕ_{MPE} represent MPE values in terms of energy and power, respectively. The MPEs for skin exposure for wavelengths in the terahertz band are shown in Table I. Note that different limits apply according to the wavelength and exposure duration. As part of the safety analysis for a pulsed system, these limits are converted to a Q_{MPE} in joules for a single pulse. Whilst it would be possible to carry out two safety analyses, each following the style of one of the two standards documents, it is possible to justify performing an analysis based on the methods of the ANSI standard. This is because although the wavelength range 1–20 mm is included in C95.1, 1999,[21] the guidelines in the latest version for all wavelengths under 50 mm (over 6 GHz), were set to be consistent with those in Z136.1 for large area (>0.1 m^2) exposure to wavelengths between 2.6 μm and 1 mm (Table I). The guidelines were harmonized in this way because the exposures are considered to be quasioptical for wavelengths under 50 mm, so it was sensible for the limits based on optical measurements to be extended. This harmonization was not present in earlier versions of the guidelines, and there was previously a discrepancy between the guidelines set in the two documents at wavelength 1 mm (300 GHz). As the limits have been harmonized, it is justifiable also to harmonize the method of analysis for wavelengths under 50 mm. For this reason, the procedural approach taken here to safety analysis for the full range of wavelengths is that recommended in Z136.1, 2000.[20,24,25] This approach also has the advantage of being more appropriate to terahertz pulsed imaging systems that use streams of ultrashort (picosecond) pulses focused on a small area of the skin rather than the whole body.

TABLE I. Maximum permissible exposure values for skin exposure, taken from ANSI Z136.1, 2000[a] and IEEE C95.1, 1999[b].

Wavelength range	Area of exposure, skin	Total exposure duration (T)	MPE:H /J cm^{-2}	MPE$_{\mathrm{CW}}$:E /W cm^{-2}	Standard
2.6 μm–1 mm	<0.01 m^2	10^{-9}–10^{-7} s	0.01	—	Z136.1, Table 7
2.6 μm–1 mm	<0.01 m^2	10^{-7}–10 s	$0.56\,T^{0.25}$	—	Z136.1, Table 7
2.6 μm–1 mm	<0.01 m^2	10 s–30 ks	—	0.1	Z136.1, Table 7
2.6 μm–1 mm	0.01–0.1 m^2	10 s–30 ks	—	10/A (A = exposed area/cm^{-2})	Z136.1, Section 8.4.2
2.6 μm–1 mm	>0.1 m^2	10 s–30 ks	—	0.01	Z136.1, Section 8.4.2
1–20 mm	Whole body (controlled environment)	No maximum specified	—	0.01	C95.1, Tables 1 and 2
1–20 mm	Partial body (controlled environment)	No maximum specified	—	0.04	C95.1, Table 3

[a]See Ref. 20.
[b]See Ref. 21.

TABLE II. Notation.

Pulse repetition frequency/Hz	F
Pulse duration of a single pulse/s	t
Total exposure duration per pixel/s	T
Total number of pulses in time F	$n = FT$
Limiting aperture diameter/cm	D_f
Maximum permissible exposure determined by application of ANSI standard Rule 1 procedures/J cm^{-2}	$\mathrm{MPE}_1 : H$
Energy transmitted through the limiting aperture, for Rule 1/J	$Q_{\mathrm{MPE\text{-}1}}$
Maximum permissible exposure determined by application of ANSI standard Rule 2 procedures/J cm^{-2}	$\mathrm{MPE}_2 : H = \mathrm{MPE}_{\mathrm{cw}} : H/n$
Energy transmitted through the limiting aperture, for Rule 2/J	$Q_{\mathrm{MPE\text{-}2}}$

A. Assumptions

It was assumed in this safety analysis that the maximum wavelength in the terahertz pulse was 20 mm, corresponding to a frequency 15 GHz, and the minimum wavelength considered was 2.6 μm (115 THz). 20 mm corresponds to the long wavelength limit of the 1–20 mm (15 000–300 000 MHz) range in C95.1, 1999,[21] and 2.6 μm corresponds to the short wavelength limit of the range 2.6 μm–1 mm (0.3–115 THz) range in Z136.1, 2000.[20] Thus, the full range considered was 2.6 μm–20 mm (15 GHz–115 THz). Although the terahertz pulse comprised many wavelengths, it was assumed that the power of wavelengths greater than 20 mm (<15 GHz) was negligible.

To ensure a conservative analysis, the lowest $\mathrm{MPE}_{\mathrm{CW}} : E$ for areas<0.01 m^2 (Table I) was applied: 0.04 W cm^{-2}, which comes from IEEE C95.1. Note that for skin exposure in the relevant wavelength ranges no MPE is defined in the standards for pulses of duration under 10^{-9} s (Table I). The limits for pulses of 10^{-9} s given in ANSI Z136.1 were used for the shorter pulses of terahertz pulsed imaging; this approach was previously recommended for optical wavelengths by Sliney.[26] Thus, the single pulse limit MPE:H used in this analysis was 0.01 J cm^{-2}.

It was assumed that the Class 4 laser that is used to generate the terahertz pulses is enclosed and that none of the radiation from that laser reaches the subject.

B. Analysis

The analysis follows the procedure and notation of Thomas *et al.*,[25] who present a tutorial that clarifies the proper application of the rules for safety analysis defined in ANSI Z136.1. There are three rules for determining the appropriate MPE values for repetitively pulsed lasers. The hazard analysis involves calculating an MPE in terms of energy from each rule, and choosing the lowest for a particular limiting aperture diameter. The limiting aperture is defined as the maximum diameter of a circle over which radiance and radiant exposure are averaged for purposes of hazard evaluation. There are two limiting apertures defined in Table 8 of ANSI Z136.1 for skin exposure to pulses from 10^{-9} to 3×10^4 s duration: these are 3.5 mm for wavelengths 1.4 μm–0.1 mm, and 11 mm for wavelengths 0.1–1 mm. For the purposes of this analysis the 11 mm limiting aperture was applied also to wavelengths from 1 to 20 mm, although no limiting apertures are defined in IEEE C95.1. The MPEs should be applied to beams of at least several millimeters in diameter that are larger than the defined limiting apertures. Since our scanning beam is focused, in this analysis an alternative technique that converts the MPE to power or energy focused within the defined measurement aperture has been applied. Rule 1 protects against thermal injury from any single pulse in the pulse train. This is especially important if some pulses have greater than average energy. Rule 2 protects against two types of injury. Firstly injuries generated by photochemical damage mechanisms, which are cumulative in nature and secondly against thermal damage injuries caused by average power heat build up. Rule 3 protects against thermal injury caused by cumulative, subthreshold pulses. It applies only to ocular exposure and so is not included in the present analysis.

In the analysis the notation shown in Table II was used.

1. Rule 1: Single-pulse MPE

The duration t of a single pulse of terahertz radiation was set at 10^{-13} s (100 fs). From Table I, the MPE:H for skin exposure (<0.01 m^2), for pulses 1–100 ns, is 0.01 J cm^{-2}, and this was assumed also to apply to the 100 fs pulses used. This value for $\mathrm{MPE}_1 : H$ was substituted in Eq. (1) for each of the two limiting apertures

$$Q_{\mathrm{MPE\text{-}1}} = \mathrm{MPE}_1 : H \frac{\pi D_f^2}{4}. \tag{1}$$

The following results were obtained:

$$Q_{\mathrm{MPE\text{-}1}} = 9.62\times10^{-4}\ \mathrm{J} \quad D_f = 0.35\ \mathrm{cm}$$

$$Q_{\mathrm{MPE\text{-}1}} = 9.50\times10^{-3}\ \mathrm{J} \quad D_f = 1.1\ \mathrm{cm}.$$

2. Rule 2: Average power MPE

The first step in the Rule 2 analysis was to estimate the total exposure duration, T. In the system shown in Fig. 1, there are several factors that influence the imaging time. At each pixel in the image a sampled representation of the transmitted pulse is acquired. The total acquisition time will be the number of pixels scanned multiplied by the acquisition time per pixel. The fastest per pixel acquisition samples at only one time point on the pulse, which can provide sufficient data for an image but is inadequate for spectroscopic applications or parametric imaging. Slower acquisitions result from acquiring more samples along the pulse profile and performing averaging. Typical values may be 128 samples and 200 averages per pixel. For the purposes of this conservative analysis the total exposure duration was set to 10 min (600 s) representing a reasonable period for which a subject could be expected to keep still. In the limiting, high exposure, case this could represent exposure of a single area of skin if data were acquired from a single pixel at high time resolution with multiple averages. In practice, exposures to a particular area of skin are expected to be lower because raster scanning will mean that the several areas receive a shorter exposure during the total exposure time.

The continuous wave MPE expressed in irradiance may be expressed, for an exposure duration T, in terms of radiant exposure

$$\mathrm{MPE}_{\mathrm{CW}}:H=\mathrm{MPE}_{\mathrm{CW}}:E\times T\ \ \mathrm{J\,cm}^{-2}. \tag{2}$$

The MPE per pulse $\mathrm{MPE}_2:H$ is given by

$$\mathrm{MPE}_2:H=\frac{\mathrm{MPE}_{\mathrm{CW}}:H}{n}, \tag{3}$$

when $n=FT$.

For Rule 2, the MPE in terms of energy per pulse, $Q_{\mathrm{MPE\text{-}2}}$ is given in Eq. (4)

$$Q_{\mathrm{MPE\text{-}2}}=\mathrm{MPE}_2:H\,\frac{\pi D_f^2}{4}, \tag{4}$$

which, by substitution from Eqs. (2) and (3), may be written

$$Q_{\mathrm{MPE\text{-}2}}=\frac{\mathrm{MPE}_{\mathrm{CW}}:E}{F}\cdot\frac{\pi D_f^2}{4}. \tag{5}$$

From Table I, the lowest $\mathrm{MPE}_{\mathrm{CW}}:E$ for skin exposure ($<0.01\ \mathrm{m}^2$) for periods over 10 s is $0.04\ \mathrm{W\,cm}^{-2}$. This value for $\mathrm{MPE}_{\mathrm{CW}}:E$ was substituted in Eq. (5), with $F=82\ \mathrm{MHz}$, for each of the two limiting apertures and the following results were obtained

$$Q_{\mathrm{MPE\text{-}2}}=4.69\times10^{-11}\ \mathrm{J},\quad D_f=0.35\ \mathrm{cm},$$

$$Q_{\mathrm{MPE\text{-}2}}=4.64\times10^{-10}\ \mathrm{J},\quad D_f=1.1\ \mathrm{cm},$$

3. Selection of the correct MPE from the Rule 1 and Rule 2 analyses

For both of the limiting apertures $Q_{\mathrm{MPE\text{-}2}}$ is less than $Q_{\mathrm{MPE\text{-}1}}$, so the Rule 2 results were applicable to the hazard analysis. The final step was to compute the dependence of the energy transmitted by each limiting aperture on the beam diameter. If a Gaussian beam profile is assumed,[25] then the effective energy Q_f, which is the amount of energy transmitted through an aperture of diameter D_f, is given by Eq. (6)

$$\frac{Q_f}{Q_0}=1-\exp\left(\frac{D_f}{D_L}\right)^2, \tag{6}$$

where D_L is the terahertz beam diameter and Q_0 is the incident energy per terahertz pulse.

A plot of $(Q_f/Q_0)/Q_{\mathrm{MPE\text{-}2}}$ against beam diameter is shown in Fig. 4. The more conservative limit is the one where the ratio is higher, and for this particular assessment the ratio for the 0.35 cm limiting diameter was higher for all beam diameters. Thus the Q_{MPE} resulting from this analysis was 4.69×10^{-11} J.

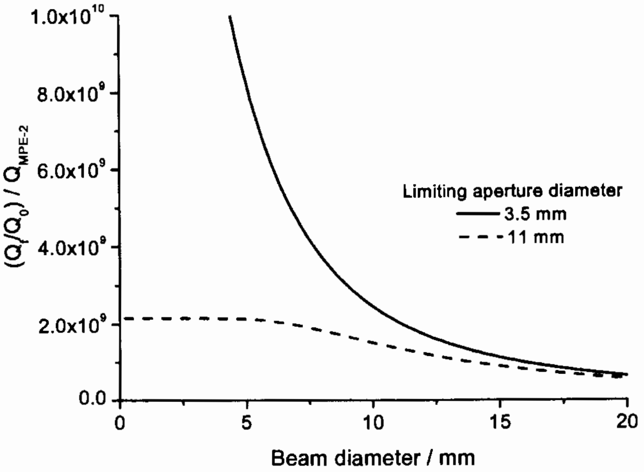

FIG. 4. A comparison of the ratio of $(Q_f/Q_0)/Q_{\mathrm{MPE\text{-}2}}$. $F=82\ \mathrm{MHz}$, $t=10^{-13}$ s, and $\lambda=2.6\ \mu\mathrm{m}$–20 mm.

A more general expression of this limit is shown in Fig. 5, where the $Q_{\mathrm{MPE\text{-}2}}$ for the 0.35 cm limiting aperture [Eq. (5)] is shown for a range of pulse repetition frequencies. The limit applies to pulse durations less than 100 ns. Note that the total exposure time does not appear in Eq. (5), and thus the calculated limit applies to total exposure times, which might include repeated exposures, from 10 s to 30 ks (or 8 h) (Table I).

III. COMPARISON WITH SYSTEM MEASUREMENTS

The energy of a terahertz beam is most conveniently measured as an average beam power. The Q_{MPE} in terms of energy per pulse was converted to a limiting average beam power by multiplying by the pulse repetition frequency, and the result for all pulse repetition frequencies was 3.85 mW. In our terahertz pulsed imaging system the average power for

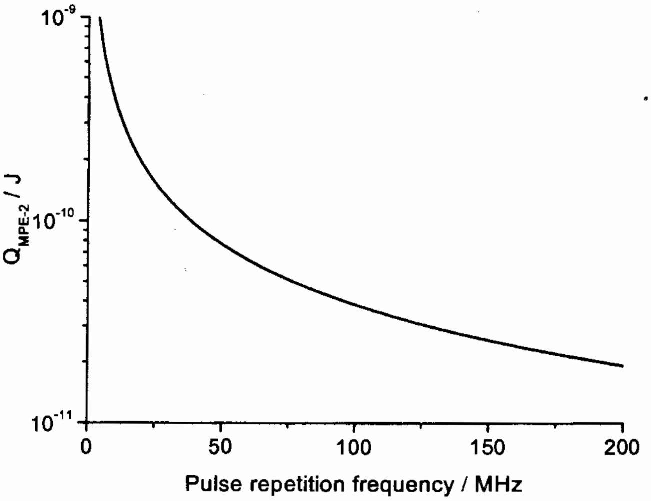

FIG. 5. The variation in the Q_{MPE} per pulse with pulse repetition frequency, for area of exposed skin $<0.01\ \mathrm{m}^2$, pulse duration under 100 ns, and total exposure time 10 s to 8 h.

a stream of pulses has been measured using a Golay cell to be of the order of 3 nW for terahertz radiation produced by both a photoconductive antenna and by optical rectification. Thus this system operates within the guidelines for skin exposure, providing cumulative exposure of the same area does not exceed 8 h.

IV. LIMITATIONS OF THE ANALYSIS

Biological effects resulting from incident electromagnetic radiation are a result of one or more competing biophysical interaction mechanisms.[18] The candidates are thermal, acoustic, optical, and photochemical mechanisms, and the combination of interactions depends on the spectral region and exposure duration. The damage thresholds on which the MPEs in the guidelines are based were derived from animal studies using the monkey retina and rabbit cornea.[27] No wavelength longer than 10.6 μm nor pulse duration shorter than 1.4 ns was used in these studies.[27] While use of data from the eye can be considered to give conservative thresholds for skin, it is possible that the values obtained at these wavelengths, which are shorter than many in the terahertz band, are inappropriate at longer wavelengths. This is because terahertz radiation is known to be strongly absorbed by water, which is an important component of tissue, and other polar molecules.[28] Terahertz photon energies correspond to the vibrational and rotational molecular energy levels of relevant biomolecules including proteins and DNA,[29] and water has absorption peaks in the terahertz region at 15 and 50 μm.[30] Nor are long term effects well understood. These important interaction mechanisms have not yet been widely studied[29] and are the subject of a continuing investigation.[31,32]

The pulses used in terahertz systems are under a picosecond duration, but the published MPEs were defined for nanosecond or longer pulses. In the analysis, the limits derived for nanosecond pulses were used,[26] but this recommendation was intended for the visible band, as were recently revised limits for ultrashort pulses.[33] For the part of the spectrum with wavelengths from 2.6 μm to 1 mm the damage mechanism is believed to be thermal, at least for exposure durations greater than 1 μs. However, for pulses of duration less than 1 μs the mechanism may be thermomechanical.[18] Thus an additional damage mechanism may operate for ultrashort (picosecond) pulses, and this was not considered in this analysis.

No account was taken of the effect of wavelengths greater than 20 mm. The damage mechanisms for these long wavelengths arise from increased body temperature, but the safety consequences of ignoring these components are believed to be negligible, as in a typical terahertz pulse, the spectral power at low frequencies is less than the power at 1 THz by a factor of 100 or more.

V. CONCLUSIONS

Presently, the average beam power in terahertz scanning imaging systems is under 1 μW or up to 1 mW where amplification is used.[9,34] Such scanning systems comply with current guidelines, which our analysis showed set a limit on average beam power of the order of 3 mW. Improvements to transducers and optics, and the use of amplified pulses, are expected to lead to average beam powers of several mW within two years, this is of concern as such average beam powers exceed the calculated maximum permissible exposure. Similarly, high power terahertz generation using linear accelerators and free electron lasers will not fall within the limits of the guidelines for skin exposure.

The faster imaging methods,[15,16] which were mentioned briefly in Sec. I, are also subject to the limits derived here, unless the total exposure duration falls below 10 s in which case a different analysis will apply (Table I).

Before the technique is used more extensively, it would be advisable to establish MPEs specifically for the wavelengths and pulse durations used in terahertz imaging. This is because there may be additional damage mechanisms for picosecond pulses and there is a possibility of increased absorption at the water resonances in the terahertz band.

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