Frequency bands for ultrasound, suitable for the consideration of its health effects

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It is proposed that the ultrasound frequency spectrum should be divided into three bands in order to facilitate a more rational assessment of its health effects. Whilst statement of the frequencies at the borders of these bands facilitates their definition, it is recognized that these observables vary continuously with frequency and consequently these border frequencies should not be used to rule out the possibility of a given effect occurring. The lowest band, US(A), lies between 17.8 and 500 kHz. In this band acoustic cavitation and its associated forces form the dominant process resulting in biological effects in liquids and soft tissues, whereas health effects from airborne ultrasound have been reported but are far less researched. In the middle band, US(B), between 500 kHz and 100 MHz, temperature rise in tissues becomes the most important biological effect of exposure. The highest band, US(C), covers frequencies above 100 MHz, for which the radiation force becomes an increasingly important biophysical mechanism. A justification for the selection of 17.8 kHz in preference to any other threshold for the lower frequency limit for ultrasound is given. © *2018 Acoustical Society of America*. https://doi.org/10.1121/1.5063578

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I. INTRODUCTION

Ultrasound is currently defined by the lack of a property. It is an acoustic wave that cannot be heard by humans. It is a decidedly anthropomorphic definition, even though the same word is used to refer to the acoustic radiation used for echolocation by some bats and toothed whales. Ultrasound is used for acoustic cleaning, for sonochemistry, for shock-wave lithotripsy, for industrial welding, for emulsification of foods, for obstetric scanning, and for acoustic cell positioning. In each case the sole criterion for calling the technique "ultrasonic" is that it is not possible for humans to hear the acoustic wave being generated. This is a strange, negative way of defining a physical phenomenon. As the applications of ultrasound proliferate, operating within a frequency range from about 20 kHz to 1 GHz and above, this definition, based on what ultrasound does not do rather than what it does do, has often resulted in confusion and obfuscation. Is a clearer banding of the ultrasonic regime needed to avoid confusion and conflation of dissimilar technologies (for example, when the manufacturer of a remote battery charger operating at <100 kHz in air, cites FDA regulations for *in utero* exposures at >1 MHz), when both are called "ultrasonic"?[1,2] A report of DNA breakage from 30 kHz ultrasound has been partially justified by reference to medical applications of ultrasound in the MHz frequency range.[3] Even the simple question of the quantification of the lower frequency bound, derived from the physiological response of the human ear, has resulted in several competing alternative definitions.

There is a second way in which ultrasound is defined negatively, and this is as one of the non-ionising radiations. The context for this categorisation is health, and ultrasound lies within the remit of such bodies as the International Commission on Non-Ionizing Radiation Protection (ICNIRP), which concerns itself otherwise with the health effects of non-ionising electromagnetic radiations. Whatever physical or biological responses are caused by ultrasound, they do not result from ionisation.

Therefore the basis of traditional definitions of ultrasound is that it does not cause ionisation and it cannot be heard, two unsatisfactorily negative descriptors when faced with discussions of how ultrasound might affect human health. In this paper, we explore ultrasound from a consideration of what it does, rather than what it does not do. The context is health, and therefore the mechanisms being considered are biophysical, operating either at a neurophysiological level (including hearing and tactile sensations) or at a cellular level (including temperature rise and stress *in vivo*). From these considerations, and especially from the frequency dependencies of each mechanism, it is possible to develop a rationale for the division of the present ultrasonic spectrum into three frequency bands, with the purpose of improving clarity when discussing the biological effects of ultrasound, its safe medical use, and the possible health effects arising from exposure.

It is important to stress that we are focussing attention on the health effects of ultrasound. This approach may or may not result in different conclusions from those that might arise from considerations from industrial or laboratory uses such as sonochemistry or ultrasonic machining.

Numerous, relevant, wide-ranging reviews of have been published, in which the mechanisms and phenomena under

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discussion have been set out in great detail, and for which the arguments have been well rehearsed at national and international levels. These have typically focused on the safe use of ultrasound for medical purposes. It is not the place of this text to reiterate these nuanced discussions, to which the reader is referred for more detail than is appropriate here.[4–7] Questions of any particular health detriment, and whether it may be lethal or temporary, are considered as secondary to the more general underlying question of the dominant biophysical mechanism.

The following is intended briefly to set the context for the banding proposal, which is the purpose of this paper. This purpose is two-fold. It is first to establish three frequency bands within the ultrasonic spectrum in order that future discussions on human exposure to ultrasound might be based on a more rational and scientific basis, with specified values for the boundary frequencies between these bands: and second, to state the frequency of the lower boundary for ultrasound, basing its value practical acoustic metrology.

This paper is not primarily about applications. The examples of the modern uses of ultrasound listed above constitute a very small portion of the ever-expanding list of practical devices for which ultrasound is now employed, many resulting in human exposure in an occupational, medical, or public context. Each device may propagate ultrasound towards or into the body either through air, or through water or by direct coupling. The mode of coupling is of profound importance to the proportion of the acoustic energy that enters the body, and with what structure (e.g., cochlea or foetus) it interacts: the establishment of ultrasonic bands, proposed here, does not replace the need for clarity in expressing these when discussing bioeffects (the remote charger example cited above responds to queries about effects on the cochlea by citing FDA regulations for the foetus). Each device operates over a particular range of frequencies. Under such circumstances, it is not possible to expect every device to operate entirely within any band, and there should be no assumption that this is an objective of this proposal (Leighton[8] shows the spectrum of a device which crosses across bands). Examples of how banding of the ultrasonic spectrum might be applied to particular applications are given in Sec. III.

II. ALTERNATIVE APPROACHES TO A DEFINITION OF ULTRASOUND FREQUENCY BANDS

In this section we will consider several phenomena that might underpin a definition or definitions of ultrasound appropriate for use when considering health effects and safety. It may be noted that the two phenomena on which the present, excluding, definition of ultrasound is based (human hearing and ionisation) are different in category: one is a purely physiological sensation, and the other a purely physical phenomenon. In consideration of alternative phenomena, links will be made between a physical phenomenon and any associated biological or physiological effect.

Any phenomenon for consideration will convert acoustic energy into another form that can interact with living tissue in some way. It is anticipated that there will be no single phenomenon which is uniquely associated with ultrasound, and which can reasonably be expected to dominate all other phenomena over the full frequency range. This being so, consideration will be given to subdivision, or frequency banding, of the ultrasonic spectrum, so that within each band there is a dominant phenomenon for ultrasound incident on the body from a given medium (air, water, coupling gel, etc.). As will be seen, frequency bands may be conveniently arranged to each cover about 2 decades, broadly centred at about 100 kHz and 10 MHz.

The approach is primarily introduced to replace that of failing to discriminate between fundamentally dissimilar ultrasonic effects when, for example, inappropriately applying regulations from one to another. It enhances a distinction that has been widely used in past discussions, which used a simple division into thermal and non-thermal (predominantly cavitation) mechanisms, with no specific explicit indication whether either was dominant for any specific application or at any frequency.

A. Ultrasound phenomena for health effects

1. Sensory effects arising from ultrasound in air

For the lowest ultrasonic frequencies, for some humans, especially the young, there is a sensation of hearing at frequencies of 17.8 kHz and above,[9–13] particularly if the sound pressure level is high. For decades there have been reports of adverse effects on hearing of low frequency ultrasound in air. Most attention has been paid to temporary and permanent shifts in the hearing threshold for the quietest sound that an individual can hear, and these shifts can be generated by low frequency ultrasound in air.[14] At generally lower sound pressure levels, a range of symptoms such as nausea, headache, fatigue, migraine, dizziness, tinnitus, and “pressure in the ears”[15,16] have been reported, although most of such reports are anecdotal or not in controlled conditions.

In addition to giving rise to auditory sensations, ultrasound can also stimulate other sensory mechanisms, typically through skin tactile receptors, such as Meissner’s corpuscles, Pacinian corpuscles, and Merkel disk receptors.[17] However, details of the sensory routes involved have yet to be elucidated.

The acoustic forces that could give rise to such sensations are described briefly in the following. Radiation force is assumed to be the phenomenon responsible for the tactile sensations when high-amplitude pulsed MHz ultrasound impinges on the skin underwater,[18] or when lower ultrasonic frequencies are used in haptic perception technology to create touch sensations on the hand.[17]

Such sensory responses, whether auditory or tactile, form a necessary part of a complete review of the effects of ultrasound, and the banding structure proposed here might alleviate the difficulty in encompassing the range from such effects to physical effects like cavitation in a single coherent structure for all ultrasound effects.

2. Radiation force at an acoustic interface

A small force is exerted perpendicular to any plane interface between two materials with different specific acoustic impedance Z, across which a progressive acoustic wave passes. The magnitude of the force depends on the change in energy density across the boundary. For a plane wave impinging on a fully smooth infinite plane absorbing interface, the force is $F_{\text{rad}} = W/c_o$ in the direction of wave propagation, where W is the acoustic power and c_o is the sound speed in the propagating medium. Thus, for such a smooth interface there is no dependence on frequency. For example, radiation force is used as a means to measure acoustic power when conditions resemble the above scenario, i.e., when the wavelength is much less than the dimensions of the surface from which it scatters, such that the radiation force is typically frequency independent. Typically, this has been for conditions in liquid, from 0.5 to 25 MHz.[19] However, applications of ultrasound in air (haptic feedback; particle levitation) are tending to deviate from this, and in some cases even approach the so-called "long-wavelength limit." Consequently, in such applications the radiation force becomes frequency dependent.[20–22] Even where the wavelength is much smaller than the target, there can be some dependence on frequency that depends on the scale and structure of the surface[21,23] because smooth acoustic interfaces are rare *in vivo*. Examples that approximate to the ideal are the skin/air interface, and the bone/soft tissue interface, but in both cases surface roughness and scatter modify the situation. Whilst the outer surface of the lung can in some ways be characterised as such an interface between soft tissue and air, there remains uncertainty over the detailed mechanism that gives rise to capillary lung damage in this case, and hence of the appropriate acoustic model.[24]

Because of these complications, and because the ratio of the wavelength to the dimensions of the scattering surface are critically important, then in the absence of some specific standard target (perfectly smooth and of a given size), the radiation force at a smooth planar surface is unlikely to form a useful basis from which to define altered responses over the ultrasonic spectrum.

3. Volumetric radiation force

Sections II A 1 and II A 2 dealt with mechanisms and responses arising at the air/tissue interface. The remaining sections deal with phenomena associated with ultrasound propagating in liquids and soft tissues.

Radiation forces do not simply manifest at reflection from a target: The material supporting an ultrasonic wave also experiences a volumetric force operating in the direction of wave propagation. The force arises from absorption of energy from the wave by the material, by whatever absorption mechanism that may operate.[25] This force has conventionally been represented in the acoustics literature as a force per unit volume, but for the purposes considered here, being concerned about the deposition of energy in living tissue, it is more helpful to consider the force per unit mass F_m, which for a particular frequency is

$$F_m = \frac{2\alpha_a I}{\rho_o c_o}, \tag{1}$$

where α_a is the total absorption coefficient associated with any absorption process, I is the intensity, ρ_0 is the density, and c_0 is the speed of sound. The absorption coefficient has a dependence on frequency, and for a broad-band pulsed ultrasonic beam, the product $\alpha_a(f)I(f)$ may be integrated over all frequencies to give the total force.[26]

This volumetric force is always experienced during the transmission of an ultrasound wave through any lossy medium. If that medium is a liquid and free to move it will do so, resulting in acoustic streaming.[27,28] This may be directly observed during medical scanning in, for example, amniotic fluid or fluid-filled cystic structures, and has been the only directly observable outcome from energy deposition during medical scanning.[5] For tissues that are connected, the force causes strain, an effect exploited in radiation force elastography.[29,30] In both cases, induced streaming or strain, the effects are both established and dissipate within timescales generally measured in milliseconds.

Since an acoustic wave carries momentum and energy, the volumetric radiation force can be thought of as the medium taking up the energy lost from the wave when it is absorbed.[31] In this way, the volumetric radiation force is intimately connected with the next phenomenon to be discussed, the deposition of acoustic energy as heat as the acoustic wave is absorbed. Further discussion will therefore be postponed until the end of Sec. II B.

4. Heat and temperature rise

The dissipation of wave energy as heat in tissue is the dominant consideration for the safe use of diagnostic ultrasound in the MHz band, and has received the most detailed theoretical and experimental attention. Much of this attention has focussed on the prediction of the temperature rise that may be induced *in vivo*, and on those circumstances for which any temperature rise may cause damage. In particular, evidence from thermal teratology has been used to recommend limits for maximum temperature elevations from diagnostic ultrasound investigations. Guidance for operators appears on medical scanners in the form of a numeric index, the Thermal Index (TI), derived from appropriate idealised tissue models, as an indication the maximum worst-case temperature that might be reached with the specific scanning conditions in use at the time.[32]

In a liquid, or liquid-like medium such as tissue, the initial rate at which temperature increases is

$$\frac{dT}{dt} = \frac{2\alpha_a I}{\rho_o C}, \tag{2}$$

where C is the specific heat of the medium.[33] Comparison between equations (1) and (2) demonstrates the intimate relationship between ultrasonically induced heating and ultrasonically induced volumetric force. The quantity $2\alpha_a I/\rho_0$ is common to both expressions. It characterises the rate of transfer of energy from the wave to unit mass of the medium and has units W kg^{-1}. It has been termed acoustic dose rate and is exactly analogous to the specific absorption rate (SAR) used to quantify energy deposition in tissue from microwave and other non-ionising radiations.[34]

The dependence on frequency of volumetric force and of the initial rate of rise of temperature depends identically on the frequency dependence on the acoustic dose-rate, and hence on the acoustic absorption coefficient α_a. For the simple models often used for regulatory purposes, α_a is assumed to have a linear frequency dependence in the low MHz range This assumption is based on a substantial literature of measured frequency dependence of the acoustic attenuation coefficient following a power law, with an exponent typically in the range 1.0 to 1.3.[35] The attenuation coefficient of body fluids such as amniotic fluid, urine and serum albumin exhibit higher values of the exponent,[36] tending towards the square-law dependence of air and water at frequencies well away from resonance. A representative value for the attenuation coefficient of non-fatty soft tissues in the low MHz range of frequencies is 0.4 dB cm^{-1} Mz^{-1}.[37]

Subsequent temperature rise in tissue depends on other factors, including the period of exposure, beam dimensions, and the dissipation of heat by thermal conduction and convection (including perfusion). The time-scales to approach the maximum temperature rise are much longer than the time-scales for radiation force, and the maximum temperature is approached only after several minutes of exposure.

The absorption of energy from the wave will always give rise simultaneously to both heating and volumetric force. When considering potential health effects, it is important to explore whether one is dominant and, if so, is this dominance maintained throughout the ultrasonic spectrum. Ultimately this depends on the cellular sensitivity to the mechanical environment compared with the cellular sensitivity to its thermal environment. Most bio-effects studies have focussed attention on lethal effects, caused either by temperature increases maintained for longer than threshold times for permanent cellular damage[38] or to cause serious but sub-lethal fetal abnormality, or to cause cell rupture resulting from excessive shear. In the MHz range, thermal effects are the dominant cause of lethal outcomes. Sub-lethal cellular responses have been little studied in the context of ultrasound health effects, and operate in both thermal and mechanical domains.[39,40]

Overall, the broadly linear frequency dependence of the ultrasonic absorption coefficient over a wide frequency range suggests that thermal effects would continue to dominate mechanical effects up to the highest frequencies. However, such a view discounts the differing spatial and temporal dependencies of the two effects. Smaller beams associated with higher wavelengths lose heat more readily than larger lower-frequency beams, limiting the temperature rise that can be achieved. Conversely, shear will be higher at the edges of a narrower beam, enhancing the probability of mechanical cellular effects. Overall, as frequency increases beyond 100 MHz, it may be expected that radiation force may progressively become the dominant mechanism.

Heating arising from exposure to ultrasound, and its resulting biological outcomes can occur under other very specific and less widespread conditions than those described above. For example, ultrasound in air has been demonstrated to be capable of causing heating to the point of discomfort and injury in humans accidentally exposed to 140 dB re 20 μPa in crevices (nasal passages, skin clefts, fingers).[15,41,42] Levels of 169 dB re 20 μPa proved fatal to insects and mice, and generated strong heating associated with hair and fur.[41] Nevertheless, such occurrences result from extreme conditions, and do not undermine the search for dominant mechanisms associated with particular frequency bands.

5. Acoustic cavitation

The occurrence of acoustic cavitation differs in several important ways from the occurrence of heating and radiation force. First, the complexity of possible bubble behaviors, and consequent biophysical outcomes, is considerable, and therefore all analyses use highly simplifying assumptions.

Acoustic cavitation refers to the generation of gaseous bubbles in a liquid by an acoustic wave, and the subsequent acoustically driven behaviour of these and other pre-existing bubbles. Bubbles cyclically expand during rarefaction and contract during compression.

Whilst it is possible to find, or manufacture, exceptions, it is possible to state that acoustic cavitation will become less likely *in vivo* with increasing frequency. In using the term "cavitation," both inertial and non-inertial cavitation are implied, and the complexity of each one of these classifications[43] means that within the space limitations of this paper only an overview can be given. Inertial cavitation involves first an initial explosive bubble growth, followed by a collapse in which the inertial forces of the surrounding liquid dominate over the effect of the increasing gas pressure as the bubble reduces volume. This is a threshold phenomenon, and if the tension in the liquid does not exceed a threshold value, no bubbles of any initial size will undergo inertial cavitation.[44] That threshold pressure increases with increasing frequency,[45,46] which would make inertial cavitation less likely if the bubble population that nucleated inertial cavitation events did not become increasingly favorable, and it will now be shown that, whilst this is a complicated issue, in general it does not. If the liquid tension exceeds the threshold during the rarefaction of the incident ultrasonic field, then there exists a range of bubble sizes (that range increasing with the size of the tension, and reducing to just one bubble size at the threshold tension) that will nucleate inertial cavitation. Bubble smaller than the lower limit of this range will not grow sufficiently because of surface tension, whilst bubbles larger than the upper size limit of this range will not grow sufficiently large because the duration of the tension is not sufficiently long (the larger the bubble, the lower its natural frequency, and the slower its response time).[31] With increasing frequency, that range becomes more narrow for a given tension in the liquid (mostly because the larger bubble size limit reduces). The center of the range is, very approximately, close to the resonance bubble size,[47] and so moves to smaller bubble sizes as frequency increases.

Whilst all but one of the facts in the preceding paragraph would suggest that inertial cavitation becomes less likely with increasing frequency, the last fact appears at first sight to run counter to that: whilst one might not imagine many gas nuclei resonant at 20 kHz (i.e., radii around 150 μm radius) *in vivo*, one might imagine it more likely to find a micron-sized bubble naturally *in vivo* (resonant at closer to 1 MHz). The argument might indeed be put that, since the practically achievable tensile strength of water is much less than its theoretical value, this must reflect the presence of small gas bodies, or the breakage of the forces of cohesion between the liquid and other bodies (solids, fats, etc.).[43] Any such gas bodies must be small (contrast agents injected into the body,[48] short-lived gas nucleated by cosmic rays, gas bodies stabilized by solids or hydrophobic chemicals, etc.[43]). However, the ease with which we generate cavitation in water at, say, 20 kHz comes from the fact that, as the frequency decreases, the threshold pressure required to make a pre-existing bubble of a given size undergo inertial cavitation decreases, and there is greater tolerance on the range of pre-existing bubble sizes that can nucleate inertial cavitation[43,49] and rectified diffusion can be more effective at bringing bubbles into this range of tolerance.[50] Cavitation in water at low ultrasonic frequencies tends to be easier than at high, and conditions *in vivo* tend to be far less prone to support cavitation than they are in water.[51] Very large tensions, such as those generated by lithotripsy, can generate the acoustic signals that suggest cavitation *in vivo* from tensions sustained for energy in the 0.5–1 MHz range,[52,53] and in laboratory experiments contrast agents might be introduced to generate cavitation from ∼MHz fields, but in general the trend is that inertial cavitation becomes less likely with increasing frequency.

In contrast, non-inertial bubble pulsation is not a threshold event, so at first sight would appear to scale in likelihood with the prevalence of bubbles, if one makes the reasonable assumption that we only consider bubble pulsation close to resonance, since this is the highest amplitude and so most significant. However, the question of significance raises other issues: if large bubbles were to occur, even though they are far from pulsation resonance and so do not pulsation significantly, they could scatter strongly,[54] as could collections of bubbles.[55] These are unlikely to be factors *in vivo* because the occurrence of such bubbles is unlikely, outside of the use of contrast agents[48] or ultrasound for therapy.[52,55,56]

However, bubble pulsation is not the only form of non-inertial cavitation: if the pulsation amplitude exceeds a threshold value, surface waves can form on the bubble wall.[57,58] As with inertial cavitation, at threshold this excites the surface waves on one bubble size only, but the more the driving pressure exceeds threshold, the greater the range of bubble size that can exhibit surface waves, and the greater the number of modes that can be excited.[59] These make the effect less likely with increasing frequency. Whilst such surface waves can produce bioeffects,[60] the applications would suggest use on the outer surfaces (e.g., skin[61]), or within anatomical (e.g., oral) cavities,[62] rather within soft tissue.

For most body tissues, in the absence of pre-existing bubble nuclei, ultrasonic cavitation occurs only for frequencies considerably lower than 1 MHz, and arises at nucleation sites at which bonding forces are low, such as at lipid/aqueous interfaces. Spontaneous acoustic cavitation *in vivo* is improbable at ultrasonic frequencies in the MHz range.[63] Under these circumstances, cavitation may be discounted unless special conditions exist. Examples of such special conditions are when bubbles are introduced during the use of gas-filled contrast agents for medical diagnosis and therapy. Alternatively, the rarefactional pressure may be sufficiently large, and the rarefaction phase sufficiently long, for nucleation bubbles to be generated within tissues. Conversely the presence of nucleation sites in crevices at solid/soft-tissue boundaries or at lipid/aqueous tissue boundaries implies the potential for stable ultrasonic cavitation to occur *in vivo*, especially for low ultrasonic frequencies.[64]

B. Frequency bands for ultrasound health effects

Sections II A 1–II A 5 have presented, in brief outline, the main phenomena that are relevant to any discussion of the potential health effects of ultrasound. Past discussions, especially those associated with medical applications of ultrasound, have placed emphasis on heating and the biological response to any associated temperature rise, and on acoustic cavitation and the biological response to any associated forces, especially shear. In the foregoing discussion it has been noted that other phenomena, both physiological and physical, occur within the full range of the ultrasonic frequency spectrum. Hearing may occur in humans,[12,65] and does occur in other animals, at lower ultrasonic frequencies. Radiation forces occur at acoustic interfaces and within a tissue volume. Such forces may be responsible for a range of sensory responses.[66] With the exception of the force exerted on a smooth infinite planar interface, the magnitude of all the phenomena depends on the frequency of the ultrasonic wave.

Given the overall frequency dependence of the various physical and physiological phenomena listed, it is unsurprising that difficulties arise when attempting to generalise discussions on ultrasonic health effects, safety considerations, and regulatory structures using a single nomenclature covering all acoustic frequencies from about 20 kHz upwards. A comparable problem was addressed some time ago when considering the biological effects of ultraviolet radiation. It was recognised that there was a wide range of skin penetration depth for the full spectrum of UV, and that the exposure necessary to create erythema varied considerably over this range. As a result, a decision was made to divide the UV spectrum into three bands. In a similar manner, therefore, it is proposed that the ultrasonic spectrum should be formally divided into three bands. All the listed phenomena (with the exception of the effect of ultrasound on the ear) must be considered within each band, but in each band one of the phenomena may be considered to be dominant.

The proposed bands and associated frequencies and phenomena are shown in Table I. Three ultrasonic bands US(A), US(B), and US(C) are proposed, defined by the frequency

TABLE I. Ultrasonic frequency bands.

Band name	Frequency range	Main physical interaction	Main biophysical response	Minor responses
Sound	<17.8 kHz	Vibration	Hearing	
US(A)	17.8–500 kHz	Acoustic cavitation	Mechanical strain and shear	Hearing and sensation
US(B)	500 kHz–100 MHz	Visco-thermal absorption	Temperature rise	Cavitation and radiation force
US(C)	>100 MHz	Visco-thermal absorption	Radiation force and strain	Temperature rise

ranges 17.8 kHz (see the Appendix) to 500 kHz, 500 kHz to 100 MHz, and above 100 MHz, respectively.

It is recognised that the selected boundaries cannot represent conditions of abrupt change from one bio-physical regime to another, the boundaries between UVA and UVB, and between UVB and UVC, being no more than indicative thresholds as one set of bio-effects conditions changes to another. The selection of the lowest boundary frequency, 17.8 kHz, is based upon the considerations of acoustic metrology that are set out in the Appendix. Ideally the boundaries between US(A) and US(B) at 500 kHz, and between US(B) and US(C) at 100 MHz should be set on a similarly rational basis. One approach might emerge, for example, from an analysis of the variation with acoustic frequency of the likelihood of lethal damage from temperature rise and from cavitation in a target tissue, selecting a frequency at which there is an equal likelihood of each occurring for any exposure conditions. It is not difficult to see how profoundly unsatisfactory such an approach would be, with its additional dependencies on target tissue, pulsing conditions and biological endpoint. Instead, a pragmatic selection of boundary frequencies has been made, broadly derived from the known formulations underpinning each bio-effects mechanism.

Broadly, the three bands may be described as follows:

Band A—for which most biological effects result from local forces at gas-liquid interfaces, including cavitation effects.
Band B—for which most biological effects result from temperature rise from volume absorption.
Band C—for which most biological effects result from surface and volume forces.

Within the low ultrasonic band, US(A), 17.8 to 500 kHz, acoustic cavitation dominates in liquids and soft tissues. At the low end of this band, some humans and many animals can hear, especially loud sounds, and there are anecdotal reports of a range of human effects.[14,15] Some heating of gasses and solids will occur. In air, public and occupational exposures occur, and in tissue practical medical applications associated with this band include thrombolysis, extracorporeal lithotripsy, dental scaling, and ultrasonic cutting. Lithotripsy is an application which uses a pulse containing a strong tension that falls into band A and generates cavitation, and a compressive shock wave that falls in band B, which interacts with the stone via other mechanisms (e.g., spallation, the generation of internal and shear waves in the stone, the inhomogeneous compression of the stone, etc.).[67]

In the middle ultrasonic band, US(B), 500 kHz to 100 MHz, temperature rise from absorbed energy dominates. Cavitation in this band retains biological importance only in association with high-power heating and in the presence of introduced micro-bubbles in the form of contrast agents, both at the lower frequencies in this band. Radiation volume force may become important towards the upper end of the band. Practical medical applications include diagnostic imaging, physiotherapy, and focussed ultrasonic surgery.

The upper band, US(C), above 100 MHz, has been distinguished from US(B) because beam-widths at these frequencies are sufficiently narrow to limit heating, whilst retaining local forces. This allows applications at very high frequencies to be appropriately separated from practical medical applications in the lower MHz range of frequencies.

III. DISCUSSION

Discussions of the health effects of ultrasound can become confused because of the wide range of acoustic frequencies potentially under consideration, and the consequent range of mechanisms that may cause biological effects, each with its own dependence on frequency. It has been found helpful for another radiation, ultraviolet radiation, to divide the spectrum into bands in order to structure the discussion of its biological effects. Such divisions must by their nature be arbitrary. There are no fixed frequencies below which an effect always occurs and above which it never occurs. The current definition of ultrasound is no exception: the upper threshold for human hearing can never be used without qualification as a definition of the boundary frequency between sound and ultrasound. The value of approximately 20 kHz that has been used as a broad definition of the threshold is unsatisfactory, because it lacks a firm rationale. The lower frequency bound for Band A ultrasound of 17.8 kHz, proposed here, is based on a more rational development from the legacy of having existing MPLs based on third octave bands.[8] Defining the lower limit of ultrasound more precisely brings with it an important corollary, that it removes any uncertainty as to whether low frequency ultrasonic emissions lie within the range of hearing for some humans. This is an important conclusion when evaluating the full range of possible health effects.

Furthermore, second-order effects may bridge such frequency boundaries, further blurring any precision in response. For example, subharmonics may be heard when the ear is exposed to ultrasonic frequencies. Low-frequency shear waves are generated from exposure to MHz ultrasound during shear-wave imaging. Such considerations need to be recognised to avoid inappropriate application of any banding structure at frequencies close to a band boundary.

The main rationale underpinning the selection of threshold frequencies has been bio-physical, and it is also worth noting the associated values of two physical quantities in a human physiological context. The wavelength in soft tissue is approximately 84 mm at the lower end of US(A), 3 mm at 0.5 MHz, and 0.015 mm at 100 MHz, values that may be scaled against the range of sizes of body structures, from large organs to cells. Ultrasound absorption in soft tissue follows an approximately linear frequency dependence with a typical absorption coefficient of about 0.5 dB $\mathrm{cm}^{-1}\,\mathrm{MHz}^{-1}$. Thus, the half-power thickness at 0.5 MHz is about 12 cm, comparable with the dimensions of a large organ such as the liver or the brain. By contrast the half power thickness at 100 MHz is only 0.06 cm comparable with tissue structural dimensions. Such considerations serve to reinforce the differences in biophysical responses that are to be expected within the whole ultrasonic spectrum.

One important purpose of the proposed banding definitions has been to enable an easier separation of discussions of safety in a medical context from considerations of health effects that may result from industrial and domestic exposure, which usually operate at lower ultrasonic frequencies. Of course, there is also another criterion separating these two uses. The lower ultrasound frequencies that interact with the human body are typically, though not always, airborne. The higher frequencies typically used for medical applications are normally coupled directly to the body without any intervening propagation path in air. Nevertheless, such a distinction does not invalidate the underlying basis on which the proposed banding may be defined. This is because the considerations on which the banding is based assume that the sound has already reached its biological target tissue, and any statement of exposure should contain enough information to assess how the propagation medium, and interfaces between these, are involved in the mapping from stated or measured levels, to those at the site of biological interest, to those laid out in guidelines. It is certainly necessary to quantify the transmission across any coupling interface into the body, whether that is from air, liquid or solid, but that is a separate issue.

The selected frequency boundaries between US(A) and US(B) bands at 500 kHz, and between US(B) and US(C) bands at 100 MHz, are partly rational and partly pragmatic. As the frequency increases, acoustic cavitation events become progressively less likely to occur, and the acoustic absorption coefficient rises. Taken together, these two facts support a separation into two frequency bands for which acoustic cavitation tends to dominate within the lower frequency band, and heating tends to dominate in the higher frequency band. The acoustic absorption coefficient of air also increases with frequency and above about 200 kHz the penetration of ultrasound through air is less than about 1 mm. Consideration of the effects of airborne ultrasound can therefore be restricted to the US(A) band. Amongst medical devices, those for which cavitation plays a part, extracorporeal lithotripters and dental scalers, also fall within the US(A) band. On the other hand, all medical scanning and ultrasound physiotherapy equipment works within US(B), where thermal considerations dominate therapeutic and safety discussions. Cavitation and similar considerations arise only under unusual conditions, associated with the injection of gas-body contrast agents, and bubble formation secondary to heating in focussed ultrasound surgery.

A final decision was associated with the need for a high-frequency band US(C). There would appear to be very few, if any, health considerations at frequencies above 100 MHz, since the attenuation of tissue mitigates against any *in vivo* applications. Nevertheless, cell positioning using radiation force, and acoustic microscopy, may operate at such frequencies, and may appropriately be considered in a separate category from more common medical applications.

It was pointed out in the introduction that this paper is not about specific applications. Nevertheless, the test for a new framework for ultrasound health effects is its application to the assessment of possible new devices, and clarification of the applicability of new experimental evidence. We may consider how the existence of an accepted banding structure would impact on the problems noted in the introduction. The use of airborne ultrasound for remote battery charging lies clearly in Band A. This is because the attenuation coefficient of air above 500 kHz poses additional challenges to an already inefficient method of energy transfer. Considerations underpinning the FDA regulations are based on a review of health effects of US(B) with no considerations applied for frequencies below 100 kHz or above 100 MHz. It is entirely inappropriate to justify the safety of a means to propagate power in US(A) using a regulatory regime designed exclusively for exposure within US(B). Having used the banding to identify this discrepancy, it can further be noted that the ultrasonic levels stated by the manufacturer refer to levels in air, but are compared by the manufacturer to *in utero* levels stated in the FDA: the different impedances and reference pressures in each introduce a discrepancy of 61.5 dB, even if no other mistakes are made in the comparison.[31,84]

The second example alluded to in the introduction was that of a study into DNA breakage at 30 kHz. Here the error of the authors was to imply an associative link between their results, observed at frequencies well within the US(A) band, and uses of ultrasound for medical applications that almost exclusively are carried out within the US(B) band.

New applications of ultrasound appear regularly, and the consideration of one novel application will serve to explore how the banding might be applied. An ultrasound method has been proposed as a fingerprint detector,[68] which operates at 20 MHz, within ultrasound band B. This allows a clear statement that cavitation events *in vivo* are very unlikely indeed, that heating is the most likely bio-effects mechanism, and that radiation force may play a part. The outcome is that those responsible for assessing its potential health effects are guided to consider specific mechanisms when assessing safety.

There is nothing within the banding scheme that acts to prevent the development of a new device operating at a frequency that lies close to a band boundary. In such a case, it would only be necessary to state "This device operates at the boundary of US(B) and US(C)," for example. In this case the dominant bio-effects mechanism would depend as much on the pulsing regime as on the band or frequency.

IV. CONCLUSION

It is recommended that the ultrasonic spectrum be divided into three frequency bands to facilitate considerations of health effects. These should be US(A) 17.8 kHz $< f <$ 500 kHz, US(B) 500 kHz $< f <$ 100 MHz and US(C) $f >$ 100 MHz.

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APPENDIX: THE LOWER FREQUENCY BOUND FOR ULTRASOUND

At present, the upper frequency bound for audible sound, and so the lower frequency bound for ultrasound, is ill-defined. The IEC states that the boundary is "about 20 kHz." Such imprecision is unsatisfactory for our purpose.

There have been various competing definitions for the lower limit of ultrasound:[2] 10 kHz,[69] 15 kHz,[70] 16 kHz,[71,72] or 18 kHz[73] and of course 20 kHz.[74] The most common reason for setting the limit is that this is stated to be the accepted boundary between the frequencies humans can hear, and those they cannot. The concept is nonsensical unless some additional signal characteristics (particularly amplitude-related ones) are constrained: if we are indeed at such a boundary, then at least for the low ultrasonic frequencies, for many people increasing the amplitude of a signal will take it from the imperceptible to the perceptible.[8] Furthermore the variation between individuals, even within the same age group and life experiences, is so large that no single frequency can be said to be representative of the boundary, and when considers the general trend of increasing sensitivity to high frequencies with decreasing age, setting a representative frequency based on adult data makes no sense. Why should we consider children in setting this limit? Because in the 1970s and 1980s (when there was more interest in the issue of ultrasound in air) the sources in question tended to be occupational devices that exposed adults (e.g., ultrasonic cleaning baths or welding tools). However, recent years have seen the proliferation of sources that expose the public, which mean that the sensitivity of children cannot be ignored. Analysis of the recent data suggested "that 5% of the people tested by Rodríguez Valiente *et al.*[9] who were between the ages of 40 and 49 years old, had hearing at 20 kHz that was at least 20 dB more sensitive than the median for the 30–39 year olds tested…. At 20 kHz, 5% of the 5–19 year age group had a threshold 60 dB more sensitive than the median for the 30–39 year age group."[2]

Given the lack of logic in the selection based on a boundary between acoustic waves that are perceptible, and those that are not, then is there an alternative boundary that is based on logic? The concern expressed above from the 1970s onwards on the health effects of ultrasound in air, led to guidelines for the maximum permissible limits (MPL) to which people can be exposed. Whether these guidelines are appropriate or based on a sufficient research base is open to question,[2] but they exist and are based on third octave band levels sound pressure levels (dB re 20 μPa). Only one (which was explicitly labelled as "interim" when it was published in 1984[75] was for public exposures, and whilst it is expressed in third octave bands, overwhelmingly the interpretation is to associated the MPL with the centre frequency of the band. To take a typical example, Holme[76] states that: "the US limits are the most lenient ones with the maximum level being 105 dB at 20 kHz[77] vs 115 (possibly + 30) dB at 40 kHz. The occupational limit[42,75] has been reduced from 110 dB to 75 dB and the public limit of Ref. 75 is 70 dB rather than 100 dB. Thus in the worst case, the limits may be 30–35 dB lower at 20 kHz than at 40 kHz" (where we note that each dB level here has a reference level of 20 μPa).

However by stating an MPL "at 20 kHz," one is actually stating the MPL for a tone at 17.9 kHz, since the guidelines are set for the third octave bands.[2,8] Whether the use of third octave band MPLs for tonal exposures (as many public exposures increasingly are) is a debate for elsewhere.[2,8] However, the practice of setting MPL's in third octave bands is well established for the audiofrequency range. Given that this approach has been extended to higher frequencies, we must dovetail across the frequency bands to ensure that there are not particular exposures that all bodies setting guidelines considers to be out-of-remit.[8] There is a danger of this, given that the agencies responsible for noise exposure at voice frequencies tend to pay less attention to noise as frequencies increase above, say 8 kHz. If this were coupled with a statement, for example, that the strong tones detected in public at 19.2 kHz were "not ultrasonic,"[2] and therefore out-of-remit for bodies (such as ICNIRP) that are restricted to considering only ultrasonic frequencies, then the question would be, "who sets the guidelines for high frequencies less than 20 kHz"? The Charter of ICNIRP covers radiation protection for "acoustic fields with frequencies above 20 kHz (ultrasound) and with frequencies below 20 Hz (infrasound),"[78] which would at first sight appear not to allow it to issue guidelines for energy below 20 kHz.[8]

The dilemma is resolved by the acknowledgement that all the MPLs set by the various bodies for signals "at 20 kHz" in fact extend across the third octave band centred on 20 kHz. As Leighton[8] discusses, the value of the frequency at the boundary between third octave bands varies depending on the method used to calculate them, but most usefully for the purpose of identifying the lower limit of the band centred on 20 kHs, is 17.8 kHz. If a body setting MPLs for ultrasound is dominated by non-acousticians, they may indeed not even be aware that the "20 kHz" center frequency is a convenient accommodation to replace the 19.95262 kHz that results from calculating the centre frequency from the formula in Standards.[79,80] Commonly, the center frequencies should be calculated from 1 kHz based on $f_c = (1000\,\mathrm{kHz}) * 10^{n/10}$ which, when $n = 13$ places the "center" frequency of the 20 kHz band at 19.95262 kHz and its lower frequency at $(1000\,\mathrm{kHz}) * 10^{(n-0.5)/10}$, gives 17.78279 kHz (to the nearest 0.01 Hz). This might seem more satisfactory approach as the lower limit of one third octave band will always coincide with the upper limit of the band below it [when $n = 12$ is substituted into $(1000\,\mathrm{kHz}) * 10^{(n+0.5)/10}$ it also gives 17.78279 kHz]. The use of more memorable center frequencies creates ~1% discrepancies on the calculated limits of a given third octave band. Such uncertainties highlight the tension between charters[78] and regulations that require a precisely defined frequency at the boundary between bands, and the protective operations that those entities were instituted to facilitate. Leighton[8] gives the example of a source (in a public place) that emits in roughly equal measure between the third octave bands centred at 16 and 20 kHz: it is unhelpful if no organization is allowed to consider its output as a whole because, say, the ICNIRP remit is limited to the band centred at 20 kHz.

It is therefore recognized that, even if organizations must abide by frequency limits, it is wise if researchers, policymakers, journalists and journals are circumspect in the use of a single frequency to define whether an acoustic wave is ultrasonic or not.

In this appendix, levels have been expressed in decibels (dB), and the reader needs to bear in mind that a level so reported is a logarithmic measure not of absolute power but of power ratio,[81] and as such it cannot be more accurate than the accuracy with which the author records, and the reader understands, the reference power to which the ratio is compared.[82] In particular, the common practice of stating reference rms sound pressures when reporting a level in dB (the minimum requirement, given that the reference pressures in air and in fresh water—a proxy often used for soft tissue—are different) needs to be accompanied by recognition that to convert from rms pressures to the powers that are at the heart of the dB ratio, the waveform is assumed to be plane or spherical, have a time history that has been meaningfully converted into an rms value,[83] and that the density and longitudinal sound speed of the medium are involved in the conversion. Because of this, when comparing dB levels in air and water, at the very least one should take into account that a sound wave of given intensity in water will have a sound pressure level relative to 1 μPa (the international standard reference sound pressure for sound in water) that is 61.5 dB greater than that relative to 20 μPa (the corresponding reference sound pressure in air) of a wave of the same intensity in air.[84] Additional considerations (such as that the mechanism by which biophysical or psychological effects, and the effects themselves, are likely to be different in air and water/tissue) may also be germane.

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