INTERNATIONAL COMMISSION ON NON-IONIZING RADIATION PROTECTION

ICNIRP STATEMENT

VALIDITY OF THE 1984 INTERIM GUIDELINES ON AIRBORNE ULTRASOUND AND GAPS IN THE CURRENT KNOWLEDGE

PRE-PRINT IN: **HEALTH PHYS (0):10.1097/0000000000001800; MAY 20; 2024**

DOI: **10.1097/HP.0000000000001800**

ICNIRP PUBLICATION – 2024

Validity of the 1984 Interim Guidelines on Airborne Ultrasound and Gaps in the Current Knowledge

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Abstract—**Airborne ultrasound is used for various purposes both in industrial and public settings, as well as being produced as a by-product by a range of sources. The International Radiation Protection Association (IRPA) published interim guidelines on limiting human exposure to airborne ultrasound in 1984, based on the limited scientific evidence that was available at that time. In order to investigate whether research since 1984 requires the development of revised exposure guidelines we considered (a) within the context of ultrasound exposure the relevance to health of the biological endpoints/mechanisms listed in the IRPA guidelines, (b) the validity of the exposure limits, and (c) whether there are biological endpoints/mechanisms not covered in the guidelines. The analysis of the available evidence showed that the biological endpoints that form the basis of the guidelines are relevant to health and the guidelines provide limits of exposure based on the evidence that was available at the time. However, the IRPA limits and their associated dosimetry were based on limited evidence, which may not be considered as scientifically substantiated. Further, there is no substantiated evidence of biological endpoints/mechanisms not covered by the IRPA guidelines. These two observations could mean that IRPA's limits are too low or too high. Research since the IRPA guidelines has made some improvements in the knowledge base, but there are still significant data gaps that need to be resolved before a formal revision of the guidelines can be made by ICNIRP, including research needs related to health outcomes and improved dosimetry. This statement makes a number of recommendations for future research on airborne ultrasound.**
Health Phys. 00(0):000–000; 2024

Key words: exposure, occupational; nuclear reactor; radon; safety standards

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(*Manuscript accepted* 4 *December* 2023)

0017-9078/24/0

DOI: 10.1097/HP.0000000000001800

INTRODUCTION

ULTRASOUND CONSISTS of mechanical (acoustic) waves, historically characterized as frequencies above the upper human audible limit (ICNIRP 1985). This limit varies in the human population, and for people with normal hearing there is a steep rise in hearing threshold over the octave of 10-20 kHz, with this rise less pronounced in children (Rodriguez-Valiente et al. 2014), some of whom can hear up to at least 28 kHz (Ueda et al. 2016; Ashihara et al. 2006). Ultrasound always requires at least one medium to propagate and is broadly categorized into ultrasound that travels in the air, termed airborne ultrasound, and ultrasound that travels in condensed media such as solids, liquids, and biological tissue (HPA 2010).

Duck and Leighton (2018) classified ultrasound into three bands:

- US(A), 17.8 to 500 kHz—In this band, acoustic cavitation (i.e., the generation of bubbles) 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;

- US(B), 500 kHz to 100 MHz—This band includes therapeutic and diagnostic biomedical applications, where the bioeffects are dominated by tissue heating; and
- US(C), above 100 MHz—In this band bioeffects are dominated by radiation forces.

The topic of this statement is the effect of airborne ultrasound in the US(A) range. There are currently no applications of airborne ultrasound that we know of in the US (B) and US(C) bands. These frequencies are strongly absorbed in air (Bass et al. 1990) suggesting sources would need to be close to the body to deliver high amplitudes to tissue. Consequently, the effects of US(B) and US(C) will not be considered further here but should be considered in the future if such applications arise.

Airborne ultrasound is produced in industry by various applications, such as cleaning, drilling, welding, and emulsifying, and is used in various commercial products, such as pest repellents, burglar alarms, remote controls, and guidance devices for the blind (Toivo et al. 2017; Pawlaczyk and Dudarewicz 2020). Airborne ultrasound can also be produced as a by-product by various sources, such as compressors, pneumatic tools, high-speed machinery, and jet engines (Pawlaczyk and Dudarewicz 2020). There is a wide variety of devices by which the public is exposed to airborne ultrasound (Leighton 2016; Mapp 2018; Fletcher et al. 2018a; Scholkmann 2019).

The World Health Organization (WHO) reviewed the physical characteristics of airborne ultrasound and the scientific evidence on possible effects on human health in 1982 (WHO 1982). Based on the evidence presented in the 1982 WHO review, the International Non-Ionizing Radiation Committee (INIRC) of the International Radiation Protection Association (IRPA) published in 1984 interim guidelines on limiting exposure to airborne ultrasound for workers and the general public (IRPA 1984). Since then, there has been some national advice on limiting airborne ultrasound (e.g., Health Canada 1991; ACGIH 2004) but no further international guidance on this topic.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) provides scientifically-based advice and guidance on protection against adverse effects of non-ionizing radiation, including ultrasound (ICNIRP 2020a). ICNIRP has published statements specifically on the use of ultrasound for diagnostic and cosmetic purposes (ICNIRP 2017, 2020b). However, these did not consider airborne ultrasound because it is not relevant to these purposes, and ICNIRP has not published statements on ultrasound beyond these purposes. The aim of this paper is to investigate whether the available data on airborne ultrasound requires revision of the IRPA (1984) exposure guidelines and to identify data gaps for further research that will assist in revising the guidelines.

Detailed measurement procedures are beyond the scope of this document and are discussed elsewhere (IEC 2013).

METHODS

In order to investigate whether the available data from research on the effects of airborne ultrasound requires the development of revised exposure guidelines the following topics were considered:

- The relevance to health of effects of airborne ultrasound exposure on biological endpoints and mechanisms that form the basis for the 1984 IRPA guidelines;
- The validity of the exposure limits in the 1984 IRPA guidelines; and
- Whether there are biological endpoints/mechanisms that are not covered by the 1984 IRPA guidelines.

Each of these topics will be discussed in the following sections.

Question 1: Are the effects of airborne ultrasound on biological endpoints/mechanisms that form the basis for the 1984 IRPA guidelines relevant to health?

The first consideration in determining the validity of the 1984 IRPA guidelines is whether there is evidence that the biological endpoints/mechanisms that form the basis of the guidelines may not be relevant to health. In this context, the term "relevant to health" is only used to signify that the biological endpoints or mechanisms have some known association to an adverse health outcome or have been used as a biomarker for a particular disease (ICNIRP 2020b). Therefore, the first consideration is whether there is evidence since the publication of the 1984 IRPA guidelines that the biological endpoints/mechanisms that were used are, in fact, not associated with adverse health outcomes. It is important to note that we are asking whether the endpoints/mechanisms are relevant to health given the "ultrasound exposure" and not just whether the endpoints/mechanisms themselves are relevant to health.

Biological endpoints

The IRPA guidelines are based on the following biological endpoints, which were identified in the 1982 WHO review:

- Skin and tissue heating;
- Adverse auditory effects;
- Non-specific symptoms; and
- Physiological effects.

Skin and tissue heating. Extremely high sound pressures levels (SPLs)[17] of airborne ultrasound (greater than approximately 155 dB) result in excessive body heating that

[17]Unless otherwise stated, the sound pressure level (SPL) in this document is given as the logarithmic measure of the effective sound pressure (P) relative to the reference sound pressure (P_0) of 20 μPa, expressed in dB [$SPL = 20 \log (P/P_0)$].

can cause acute harmful effects, including pain and burns (Health Canada 1991). In humans, exposure at 140-150 dB causes vibration of ear canal/nasal hairs and local warming (Parrack 1966). There has been no research since the IRPA guidelines, which raises doubt about the need to consider adverse effects of excessive heating.

Adverse auditory effects. High-frequency audible components are often present with airborne ultrasound. Prolonged exposure to high-intensity audible sound can cause adverse auditory effects, such as hearing impairment or tinnitus, depending on the duration of exposure (Neitzel and Fligor 2019). Consequently, an SPL of 80 dB(A) for audible sound is chosen as the minimum level of protection in the EU and other countries (ISO 1999 2013; Health and Safety Executive 2005). Adverse auditory effects (including from audible ultrasound) are well documented and can be measured as temporary or permanent threshold shifts (TTS or PTS), i.e., temporary or permanent decrease in hearing sensitivity (Pawlaczyk and Dudarewicz 2020). TTS has also been reported to occur at subharmonic frequencies of pure tone ultrasound at 150 dB (Parrack 1966). There has been no substantiated evidence since the IRPA guidelines that raises doubt about the need to consider adverse effects of ultrasound-induced TTS or PTS.

Non-specific symptoms. The term symptomatic or subjective effects has been used to cover a long and unrestricted list of non-specific symptoms, by definition self-reported, that do not fit into any of the other 3 categories. Symptoms can be non-specific, meaning that they may result from various causes and can sometimes be medically unexplainable, or they can be specific for an underlying disease. Examples of non-specific symptoms are headaches, fatigue, and dizziness, and here we will also regard feelings such as discomfort and annoyance as non-specific symptoms, although pathological processes or ill-health are not always the cause. Severe symptoms are clearly relevant for health. Experiencing slight symptoms for a short time may not be perceived as a severe impairment of health-related quality of life by most people. However, if even slight symptoms are repeatedly experienced or if they persist for a long time, they may result in high level of annoyance. For example, in the environmental noise guidelines of the WHO for the European Region (WHO 2018), high annoyance from audible noise was 1 out of 5 critical outcomes to be considered in the derivation of the guidelines. Based on the results of the WHO noise guidelines, the European Environmental Agency estimated about 22 million disability adjusted life years (DALYs) attributable to high annoyance from transportation noise in Europe every year (EEA 2020). In conclusion, high annoyance is clearly treated as health-relevant by society. However, experiencing subtle symptoms from ultrasound exposure for a limited time or in a rare setting may not directly be considered to be health relevant, unless it is the consequence of an underlying disease triggered by ultrasound exposure.

Non-specific symptoms have been reported as occurring during and persisting (up to hours) after ultrasound exposure and consist of, for example, fatigue, headache, nausea, tinnitus, and vomiting as well as an unpleasant sensation of fullness or pressure in the ears, at a sound pressure level of 110 dB (Acton and Carson 1967). Since a mixture of audible and non-audible ultrasound was applied in this study, it remains unclear whether non-specific symptoms are the direct result of audible or inaudible ultrasound.

In summary, there have been a limited number of studies since the IRPA guidelines that have investigated airborne ultrasound and non-specific symptoms, but these do not raise doubt about the need to consider the possibility of ultrasound-induced adverse effects of non-specific symptoms.

Physiological effects. In some animal studies, physiological changes were observed at SPLs ranging from 95 to 130 dB at frequencies from 10 kHz to 54 kHz (compiled in Acton 1974). Limited studies comparing workers with prolonged exposure to airborne ultrasound above 110 dB with workers without ultrasound exposure also reported differences in blood pressure, blood sugar levels, electrolyte imbalance, as well as stress level (WHO 1982). The changes seem to be due to audible sound. Transient physiological effects within the normal range are not relevant for health unless they are the consequences of an underlying disease. There has been no substantiated evidence since the IRPA 1984 guidelines that raises doubt about the need to consider that ultrasound may cause a physiological response that is relevant to health.

Biological mechanisms. The 1982 WHO review and subsequent 1984 IRPA guidelines list two biological mechanisms that may lead to adverse health effects:

- Energy absorption and conversion into thermal energy; and
- Frequency down conversion in the ear.

Energy absorption: When acoustic energy is absorbed into the body it is dissipated as heat in tissue. However, less than 1% of the energy in airborne ultrasound is transmitted into normal skin (excluding sensory organs) and the rest is reflected.

Frequency down conversion: The impedance matching properties of the ear at audio frequencies allows for a very efficient coupling of acoustic energy into the ear. However, hearing of very high frequency sound (VHFS, 11.2 kHz to 17.8 kHz) and ultrasound appears to be restricted by less efficient impedance matching of the middle ear at these higher frequencies (Masterton et al. 1969; Hemilä et al. 1995) and

potential frequency limitations due to the architecture of the cochlea (Ruggero and Temchin 2020). Hearing threshold levels, therefore, increase with increasing frequency above about 4 kHz (Salleh et al. 2013). In addition, the frequency down conversion mechanism can lead to ultrasound-induced audio frequency excitation of the auditory system. This, as well as the energy absorption mechanism, will be discussed further below. There has been no research since the IRPA guidelines that raises doubt about the need to consider the adverse effects of these biological mechanisms.

Question 1 conclusion. The biological endpoints and mechanisms that are used as the basis for limiting airborne ultrasound exposure in the 1984 IRPA guidelines remain relevant to health. We next need to consider the validity of the exposure limits in the guidelines.

Question 2: Are the exposure limits in the 1984 IRPA guidelines valid?

The validity of the exposure limits in the IRPA guidelines was considered by asking the following:

a. Whether there are exposure limits for all the biological endpoints/mechanisms identified in the 1982 WHO review;
b. Whether the limits are valid; and
c. Whether the dosimetric quantities used for the limits are valid.

Question 2(a)—For all the biological endpoints/mechanisms that form the basis of the IRPA guidelines, are exposure limits listed in the guidelines?

The *IRPA guidelines* specify SPL limits for continuous occupational and general public exposure to airborne ultrasound (IRPA 1984). Although not explicitly stated,[18] it appears that a criterion for the prediction of adverse auditory effects and non-specific symptoms due to airborne noise from ultrasonic sources proposed by Acton (1968, 1975) was adapted and adopted by IRPA. This criterion was to limit the one third octave band (TOB)[19] SPL of continuous (8 h shifts) occupational ultrasound exposure in the overall frequency range from approximately 17.6 to 17.8 kHz (lower frequency of TOB centered at 20 kHz) to approximately 126 kHz (highest frequency of TOB centered at 100 kHz). For short-term occupational exposures up to 4 h per day, slightly higher limits are permitted (duration <1 h: +9 dB, 1 h < duration <2 h: +6 dB, 2 h < duration <4 h + 3 dB). For the general public, the limits for continuous exposure include a reduction factor of 5 dB at TOB centered at 20 kHz and 10 dB at higher frequencies. The limits are summarized in Fig. 1. Notes:

1. The markers indicate the permitted RMS SPL in TOB centered at 20, 25, 31.5, 40, 50, 63, 80, and 100 kHz for general public (x) and occupational (o) exposure;
2. For short-term occupational exposure, slight elevations of the SPL are permitted (indicated by grey (o) markers, for details see legend); and
3. The grey vertical lines indicate the approximate frequencies that separate the TOB.

The occupational limits are designed to prevent adverse auditory and non-specific symptoms (Acton 1968, 1975) from exposure to energy in the TOB centered at 20 kHz (75 dB). They correlate with potential (theoretical) damage thresholds for exposure to energy in the TOB centered at 25 kHz and above (where 110 dB is stated) and with a statement in the 1982 WHO review that no adverse effects have been observed in adults at SPL of up to 120 dB. Studies that informed the IRPA guidelines are either discussed in the Appendix or in the quoted references therein.

Other effects are described as speculative statements in the WHO review (such as conjecture about altered blood sugar levels and electrolyte imbalance, effects for which there is little evidence to date). An overview of human studies that were considered when the IRPA guidelines were developed is provided in Table 1.

In the WHO review and IRPA guidelines and the cited references therein, the following mechanisms potentially related to the endpoints listed in Table 1 were addressed.

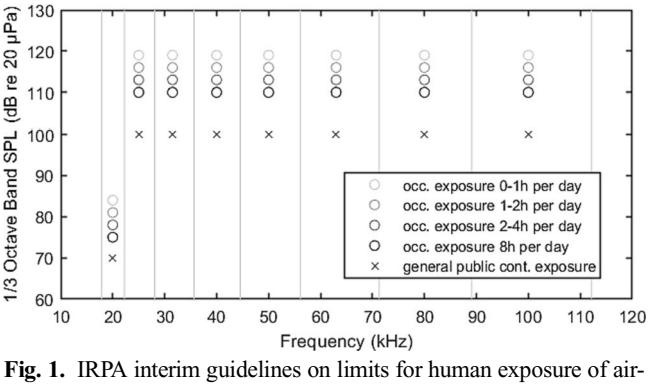

Fig. 1. IRPA interim guidelines on limits for human exposure of airborne ultrasound (IRPA 1984).

[18]The limits for continuous occupational exposure as proposed by the IRPA guidelines and Acton (1975) are identical (in Acton 1975) only the limits up to center frequencies of 40 kHz are specified). In the IRPA guidelines only the following general statement is given: "A recommended occupational exposure limit of 110 dB for frequencies above 20 kHz seems well justified from the available data (WHO 1982). What seems to differ in many standards is $^{t20\ he}$ exposure limit at 20 kHz mid frequency of one-third octave band. Presently available data do not provide a threshold for effects in this frequency band. Acton (1975) recommends an SPL of 75 dB for the one octave band with mid frequency of 20 kHz … The SPL of 75 dB seems appropriate from presently available data." (All dBs in this quote were stated re 20 μPa and refer to occupational exposure.)

[19]TOB specifies the frequency band that includes all frequencies within one third octave. The lower and higher bound of the frequency range of a TOB are separated by a factor of 2^1/3 or 10^1/10, depending on which base is used for defining the TOB. This may lead to some ambiguity.

Table 1. List of human studies that informed the IRPA interim guidelines.

	Type of study	Endpoint/Effect	Participants	Result / Effect threshold	Remarks	Reference
Thermal effects	Experimental (no methodological details available)	Heating of Body surface	Not reported	159 dB	– Symposium abstract, no details available	Parrack (1951)
	Experimental (no methodological details available)	Heating of skin clefts	Not reported	140 dB	– Abstract from report presented at group meeting, no details available – Frequency range 20-150 kHz	Parrack (1962)
Adverse auditory effects	Experimental (no methodological details available)	Subharmonics radiating from eardrum	Not reported	140 dB	– Meeting abstract – "intense sound" exposure (most likely audio frequency)	von Gierke (1950)
	Experimental (sham exposure, no information about randomization and blinding, unclear whether comparisons between or within groups, positive control with before-after design included)	Hearing TTS assessed at frequencies between 250 Hz-10 kHz	"Four or five subjects" (personnel) Age: not reported Sex: not reported	No effect observed at applied narrow band noise (20 kHz) with up to 115 dB	– Exposure to "relatively pure tones" in semi-anechoic chamber, 1-h duration, – Narrative statement that responses to ultrasound were within the range of those from sham exposure; no data given – Positive control with 5 kHz stimulus at 90 dB SPL	Grigor'eva (1966)
	Experimental (no methodological details available)	Hearing TTS	Not reported	Effect observed at subharmonic frequency of incident frequency at SPL of 148-154 dB	– Report of "limited scale" experiments conducted in the 1950s, no details provided – Exposure to single frequencies at 17; 21; 24; 26 and 37 kHz, – 5-minute exposure duration	Parrack (1966)
	Observational (cross-sectional)	Hearing TTS assessed at frequencies between 2-12 kHz	16 industry workers (31 ears) Age: not reported Sex: Male/Female	No effect observed at applied broadband noise with maximum TOB SPL below 120 dB	– Industrial environment, broadband noise containing audible and ultrasonic frequencies, – Audiogram taken before and after a workday (Monday)	Acton and Carson (1967)
	Observational (cross-sectional)	Hearing threshold level (HTL) (assessed by pure tone audiometry 100 Hz- 10 kHz)	18 exposed (ultrasonics industry workers) and 20 controls (hospital staff) Age: not reported Sex: male	Effect observed but no SPL reported.	– Conference paper – Industrial environment broadband noise containing audible and ultrasonic frequencies and other noise sources (gunfire)	Knight (1968)

Continued next page

Table 1. *(Continued)*

	Type of study	Endpoint/Effect	Participants	Result / Effect threshold	Remarks	Reference
Non-specific symptoms	Observational (cross-sectional)	Fatigue, headache, Pain, avoidance (reported by operators)	25 investigated situations, number of subjects not reported. Age: not reported Sex: not reported	Several effects observed, e.g. at – 92 dB SPL in the TOB centered at 20 kHz, – 107 dB SPL in the TOB centered at 25 kHz, – Effect correlates with audible component according to Acton (1974)	– Industrial environment broadband noise containing audible and ultrasonic frequencies.	Skillern (1965)
	Experimental (non–randomized, no control or sham exposure, no positive control, not blinded)	Fullness in the ears followed by headache (reported by operators)	3 Workers Age: not reported Sex: Female	– Effect threshold: 76-78 dB SPL in the TOB centred at 16 kHz, – Effect correlates with audible component – no effect at 100 dB SPL in the TOB centered at 20 kHz and 25 kHz	– Narrow band noise from Galton Whistle – Tested frequencies between 16 and 40 kHz.	Acton and Carson (1967)
	Observational (cross-sectional)	Unpleasant sensation of fullness in the ears, fatigue, headaches, nausea and tinnitus (reported by operators)	About 50 participants, 10 investigated sources (spectra) Age: not reported Sex: male/female	– Effect threshold: 76-78 dB in the TOB centered at 16 kHz – Effect correlates with audible component	– Industrial environment, broadband noise containing audible and ultrasonic frequencies.	Acton and Carson (1967); Acton (1968)
	Case report	Fatigue, unnatural sensation (reported by author)	1 subject (R.B. Crabtree) Age: not reported Sex: male	Effect observed, SPL not reported	– Expert opinion – Industrial environment broadband noise containing audible and ultrasonic frequencies.	Crabtree and Forshaw (1977)
Physiological effects	Experimental (before-after design, no information about randomization and blinding, unclear whether comparisons between groups or within groups, with before-after design included)	Vascular reactions, pulse rate, body temperature, skin temperature (measurement procedure not reported)	"Four or five subjects" (personnel) Age: not reported Sex: not reported	No effect observed with applied narrow band noise (20 kHz) with up to 115 dB	– Exposure to "relatively pure tones" in semi-anechoic chamber, Narrative statement that responses to ultrasound were within the range of those from sham exposure; no data given, 5-min duration – Positive control with 5 kHz stimulus at 90 dB SPL	Grigor'eva (1966)

High frequency hearing ability of population subgroups that extends into the lower end of the ultrasound TOB centered at 20 kHz: Non-specific symptoms were reported by workers exposed to broadband noise containing audible and ultrasonic frequencies emitted by industrial machinery in a wide range of SPLs. Observational studies (Acton and Carson 1967; Acton 1968) found that these effects were only reported if the audible and ultrasonic broadband noise spectrum of the machines contained a SPL exceeding 75–78 dB in the TOB centered at 16 kHz or lower frequencies, which should be audible for most workers with normal hearing (Henry and Fast 1984). Supporting evidence that the effect is related to perceiving the sound stems from laboratory experiments that used a narrow band exposure source (Acton and Carson 1967; Grigor'eva 1966). In order to also prevent non-specific symptoms in the 20 kHz TOB, a limit SPL of 75 dB was proposed by Acton (1975) and was set in the guidelines.

Frequency down conversion by even order subharmonic frequency generation at the tympanic membrane: Hearing damage thresholds in the ultrasonic range have not been identified but hearing TTS at frequencies that are close to the first subharmonic of distinct (single frequency) exposure frequencies at 17; 21; 24; 26 and 37 kHz were observed in unpublished small-scale experiments in the 1950s (as reported by Parrack 1966) at SPLs from 148 to 154 dB. These results have been interpreted in the context of subharmonic frequency generation in the middle ear which was observed in animal experiments on rodents (Dallos and Linnell 1966a and b; Davis et al. 1949) at exposure levels exceeding a threshold SPL of approximately 110 dB. Therefore, occupational SPL limits of 110 dB at TOB centered at 25 kHz and above were suggested to prevent possible hearing damage by this potential frequency down conversion mechanism (Acton 1975). These limits were adopted by the IRPA guidelines.

Energy absorption and conversion into thermal energy: Owing to the high impedance mismatch between air and skin, a conversion of airborne ultrasonic energy into adverse skin and tissue temperature elevations can only occur at very high SPLs that far exceed the limit values of the IRPA guidelines. Therefore, the current limits are considered to be protective against excessive heating. The lowest SPL for slight perceptible heating in humans was observed at 140 dB and higher [slight heating in skin clefts mentioned by Acton (1974) and originally cited by Parrack (1962)]. Far higher SPLs are suggested for mild heating of the human body surface (SPL > = 159) (Parrack 1951). However, these results are poorly documented and experimental conditions (e.g., frequency spectrum of SPL, exposure parameters and duration, etc.) as well as the magnitude of the effects are unknown.

Question 2(a) conclusion. Although no specific set of limits exists for each outcome, the limits cover all relevant endpoints and potential mechanisms listed in the IRPA guidelines and references cited therein.

Question 2(b)—Are the limits in the IRPA guidelines valid?

Both the WHO (1982) and IRPA (1984) acknowledged that the evidence on the effects of airborne ultrasound at the time was limited for all the listed effects and very limited or non-existent for some effects, to such an extent as to preclude making authoritative statements on effect thresholds for the biological endpoints (and even less on the mechanisms). They highlighted the need for more research to fill the knowledge gaps. In 2016, it was noted that, in the intervening 32 years, that call for more research was not met, such that judgements are based on far too little data (Leighton 2016); the limited research has also been identified in a more recent review (Pawlaczyk and Dudarewicz 2020).

The approach currently applied by ICNIRP is to derive exposure limit recommendations from known thresholds for scientifically substantiated adverse health effects induced by the considered non-ionizing radiation exposure (ICNIRP 2020a and b). The few human studies (see Table 1) and animal experimental studies that form the scientific basis of the WHO review and the subsequent IRPA guidelines have a number of limitations, including:

- Co-exposure from industrial environment and audible noise in observational studies (e.g., Acton and Carson 1967; Acton 1968; Crabtree and Forshaw 1977; Skillern 1965; Knight 1968);
- Not being based on ultrasound exposure (e.g., Dallos and Linnell 1966a and b; Davis et al. 1949; von Gierke 1950);
- Incomplete documentation or unpublished work (e.g., Parrack 1966, 1962; von Gierke 1950; Knight 1968);
- Methodological limitations, such as no randomization, no sham exposure in the control group or no blinding in experimental studies or insufficient information on study design, methodology, or results (all studies);
- Restricted population (mostly industry personnel), which does not represent the possible sensitivity distribution of humans to ultrasound and insufficient sample size (all studies); and
- Not being independently replicated (all studies).

Therefore, the limits of the IRPA interim guidelines do not satisfy the ICNIRP principles for guideline development; this, however, does not necessarily mean that the IRPA limits are not protective. In the meantime, a few new human studies on the effect of ultrasound on endpoints considered by IRPA (see Table 2), as well as studies providing indirect evidence at the audible frequencies of VHFS and hearing threshold data have been published. These studies must be considered as well when assessing the validity of the IRPA limits.

Table 2. Additional human studies on the effect of ultrasound not included in IRPA (1984).

	Type of study	Endpoint/Effect	Participants	SPL where effect was observed	Remarks	Reference
Adverse auditory effects	Observational (cross-sectional)	– HTL assessed by conventional audiometry (500-8,000 Hz) and high-frequency pure tone audiometry (10-20 kHz)	55 operators of ultrasonic welders or cleaners; Age and sex not reported vs. 189 unexposed, otologically normal persons (nurses, medical assistants, technicians) Age: 17-49 Sex: M/F	→Differences in HTL at frequencies between 10–20 kHz observed in workers exposed ultrasonic machinery →SPL of cleaners: 100-110 dB (25 kHz or 28 kHz fundamental) and 80-102 dB (first subharmonics in the high-frequency audio range) →SPL of welders 106 dB (20 kHz) and 90 dB (16 kHz)	– Comparative study – Industrial environment with co-exposure to intense noise in the high-frequency audio range – Effects depend on Machinery type, age and time on job	Grzesik and Pluta (1983)
	Observational (prospective cohort)	– HTL assessed by conventional audiometry (500-8000 Hz) and high-frequency pure tone audiometry (10-20 kHz) – Comparison of audiograms taken in an interval of 3 years	26 operators of ultrasonic welders or cleaners Age: not reported Sex: not reported (likely M/F)	– Ageing related HTL shifts across the whole frequency range + additionally noise related HTL shift at frequencies between 14–17 kHz →SPL of cleaners: 100-110 dB (25 kHz or 28 kHz fundamental) and 80-102 dB (first subharmonics in the high-frequency audio range) →SPL of welders 106 dB (20 kHz) and 90 dB (16 kHz)	– Follow-up of exposed subjects of Grzesik and Pluta (1983) – Industrial environment with co-exposure to intense noise in the high-frequency audio range – More than half of the initial cohort (29 workers) not available for follow up	Grzesik and Pluta (1986)
	Observational (cross-sectional)	– HTL Assessed by extended high-frequency pure tone audiometry up to 18 kHz	– 24 ultrasound exposed (industry workers) Age: 25-55 Sex: 2 M/22F – 24 unexposed adults of similar age Age: 25–55 Sex: 8 M/16F	– Statistically significant differences in HTL at frequencies between 10 and 14 kHz →SPL not reported, levels exceeding threshold level value ceiling (TLV-C) of ACGIH	– Industrial environment, – Ultrasound emissions at 20, 25, 31.5 and 40 kHz. Emissions were accompanied by subharmonics produced in the audible high-frequency range, – Audiometry prior to shift, 16 h after the last exposure to noise.	Maccà (2015)

Observational (cross-sectional)	– HTL assessed by standard pure tone audiometry (0.125–8 kHz) and extended high-frequency audiometry (9–16 kHz), – Transient-evoked otoacoustic emissions (TEOAE), – Distortion-product otoacoustic emissions (DPOAE)	– 148 ultrasound + noise exposed industry workers Age: 43.1 ± 10.8 (SD) Sex: 63%M/37%F vs – 168 noise exposed industry workers (matched for age, tenure, sex and A-weighted noise level exposure equivalent to 8 h continuous work shifts) Age: 40.0 ± 6.5 (SD) Sex: 47%M/53%F	– No statistically significant difference in mean HTL at frequencies up to 3 kHz – Statistically significantly higher mean HTL at frequencies from 4 kHz to 12,5 kHz in exposed group – Statistically significantly lower amplitudes of TEOAE at 1; 1,5; 2 and 4 kHz in exposed group, mixed results for SNR – Statistically significantly lower amplitudes of DPOAE in all tested frequencies, similar but less consistent results for SNR. →Main broadband ultrasound contribution to exposed group at f = 20 kHz (up to max 120 dB SPL), but there were also sources with other fundamental frequencies.	– Similar A-weighted noise exposure of control and ultrasound exposed group during 8-h shifts, however unclear if spectral composition of audible noise was similar between groups /e.g., co-exposure to 16 kHz which is strongly attenuated by A-weighting – Exposed group comprised of ultrasound machinery industry workers, control group mainly consists of call-centre employers.	Dudarewicz et al. (2022)
– Experimental (before-after design) Not blinded with respect to ultrasound exposure status	– TTS, HTL assessed by pure tone audiometry (0,5-8 kHz)	16 participants Age: 24-67 Sex: 15 M/1F split into 10 exposed and 6 controls	No effect of TTS exceeding 5 dB (SPL_{eq}: 118 dB, f = 40 kHz)	– Audiometry in soundproof booth – Sound source: haptic array – 40 kHz amplitude-modulated and unmodulated tones (5-s duration) + – SPL assessed in the ear of a head and torso simulator	Di Battista (2019)
– Experimental (before-after design) – Randomized allocation to exposure and parallel control group – Not blinded with respect to ultrasound exposure status	– TTS, HTL assessed by pure tone audiometry in two frequency ranges (0,125-8 kHz and 12-16 kHz) – Subclinical measures for hearing impairment (auditory brainstem response, frequency following response and speech perception in noise)	9 exposed Age: 21 (SD = 1.5) Sex: F 9 controls Age: 21 (SD = 1.7) Sex: F	No effect (max SPL: 120 dB, f = 40 kHz)	– Audiometry in soundproof booth – Sound source: haptic array – 40 kHz amplitude-modulated and unmodulated tones (50-s duration) + masker noise to mask components in the audio frequency range (blinding for detection outcome) – SPL assessed in the ear of a head and torso simulator	Carcagno et al. (2019)

Continued next page

Table 2. *(Continued)*

	Type of study	Endpoint/Effect	Participants	SPL where effect was observed	Remarks	Reference
Non-specific symptoms Ex	Experimental (no control or sham exposure, not blinded)	– Ratings of annoyance and discomfort	9 participants Age: 23–38 (M), 23–44(F) Sex: 4 M/5F	– Significant difference in annoyance ratings occurred between 80 dB(A) / 90 dB(Iin) and 96 dB(A) / 106 dB(Iin). – Significant difference in annoyance ratings occurred between 72 dB(A) / 80 dB(Iin) and 96 dB(A) / 106 dB(Iin). (unclear if statistical significant difference is meant)	– Experiment conducted in sound chamber – Noise source: ultrasonic washer (Ultrasons Annemasse Type 400 T) emitting audible sound (maximum at 12.5 kHz TOB) and ultrasound (maximum at 25 kHz TOB).	Holmberg et al. (1995)
	Observational (cross-sectional), no control group	Questionnaire survey across participants who could perceive ultrasound emitted from rodent repellents	35 (29 college students and 6 additional subjects in their late 20s to 50s). 31 could hear the sound Age: not reported Sex: M/F	Higher ratings for e.g. discomfort, pain in the ear, restlessness SPL between 100-120 dB	– Conference Paper – Repellent device in public spaces operating at 19 kHz and higher harmonics. – Ultrasound was audible – participants have been informed about presence of the device	Ueda et al. (2014)
	Observational (cross-sectional)	Non-specific symptoms assessed using questionnaire: Asthenia, Headache, Nausea, Stomach pain, Vomiting, Tinnitus, Sensation of Fullness, Hypoacusia, Uncertain Gait, Vertigo, Sleep Disorders, Tingling in limbs.	24 ultrasound-exposed (industry workers) Age: 25-55 Sex: 2 M/22F vs. 101 unexposed adults Age: not reported Sex: not reported	– SPL not reported, levels exceeding TLV-C of ACGIH; – Higher ratings of self-reported asthenia and vertigo in exposed group (statistically significant difference compared to control). Re-analysis revealed that this also applies for the self-reported ratings for “tingling in the limbs” (Leighton 2016)	– Industrial environment, – Ultrasound emissions at 20, 25, 31.5 and 40 kHz. Emissions were accompanied by subharmonics produced in the audible high-frequency range, – Number of ultrasound-exposed participants has been corrected (Leighton 2016)	Maccà (2015)
	Experimental (non-blinded provocation trial)	Overall discomfort, nausea, pain, pressure or fullness in one or both ears, headache/ pain or pressure somewhere other than the ears, dizziness or light-headedness, tinnitus, anxiety, annoyance or irritation, fatigue, inability to concentrate during a sustained attention task, galvanic skin response (GSR) (to indicate level of anxiety).	42 (10 self-reported symptomatic Group (3 M/7F, mean age 30 years (19-48 years), 32 asymptomatic (18 M/14F, mean age 23 years (18-34 years).	– SPL between 82 and 92 dB (25 dB above the individual’s hearing threshold). – For both symptomatic and asymptomatic groups, overall discomfort ratings were higher in the VHFS/US condition than the reference (but no difference was seen in performance on the attention task or on average GSR). – In the symptomatic group only, difficulty concentrating and annoyance were also rated higher in the VHFS/US than the reference condition.	VHFS/US tonal signal compared to a 1 kHz reference exposure, each 25 dB above the individual’s hearing threshold. The maximum frequency varied for each participant because it was set to be as high as possible for each individual participant while still being audible at the maximum intensity that the ethics protocols allowed use of. Consequently: – all symptomatic participants exposed to frequencies below 17.8 kHz (the maximum being 17.7 kHz) – only 20% of the asymptomatic participants were exposed to ultrasound frequencies	Fletcher et al. (2018b)

Experimental (double-blind randomized provocation trial)	Nausea, Pain, pressure, or fullness in the ears; Headache/pain or pressure anywhere; dizziness or light-headedness; Tinnitus; Anxiety; Fatigue assessed by rating questionnaire	40 (8 self-reported symptomatic +32 asymptomatic) Age: 18-40 Sex: M/F	No effect at applied (low) SPL	Inaudible single-frequency ultrasound (20 kHz, SPL at least 15 dB under individual hearing level, approx. 84 dB SPL, 20 minutes)	Fletcher et al. (2018c)
Experimental (randomized allocation to exposure or control group, Not blinded with respect to ultrasound exposure status)	Written question after ultrasound tests: dizziness, loss of balance, feeling sick, headaches, or a feeling of pressure/ fullness in the ears	9 exposed Age: 21 (SD = 1.5) Sex: F 9 controls Age: 21 (SD = 1.7) Sex: F	– Feeling "a bit fidgety" and "slight feeling of fullness in the ear" reported by 2 out of 9 exposed individuals – SPL not reported - max. SPL in tests: 120 dB assessed in the ear of a head and torso simulator	– Testing in soundproof booth – sound source was a haptic array – 40 kHz amplitude-modulated (10-minute duration) and unmodulated tones (50-s duration) + masker noise to mask components in the audio frequency range	Carcagno et al. (2019)
Experimental (randomized order of stimuli and sham, single-blinded)	Test subjects were asked to characterize their hearing sensation (in case they had one) after hearing threshold test (qualitatively)	26 Participants Sex: 13F/13 M (not all of them could perceive ultrasound) Age: 19–33	Almost all participants that perceived ultrasound exposure report displeasing perception of ultrasound, Effect threshold correlates with individual hearing threshold	– SPL applied directly in the ear (blinded) hearing threshold determination (variable frequencies up to 24.2 kHz) – SPL limited to 115 dB – Participants were asked to describe their hearing sensation in case they had one	Kühler et al. (2019)
Case Report by teacher	Self-reported headaches	Not reported	Headaches from high-pitched sound; SPL not assessed, SPL above hearing level	– Exposure source: defective motion sensor at 18 kHz (audible to students)	Leighton (2020)
Experimental (single-blind, randomized)	Self-reports of somatic and mental illness symptoms and sleep quality using several standardized questionnaires	21 ultrasound exposed Age: 27.48, SD = 5.53 Sex: 9 M/12F vs. 8 sham exposed Age: 25.57, SD = 5.26 Sex: 7 M/7F	No effect at applied (low) SPL	– 22.4 kHz and higher harmonics, 90 dB SPL measured in laboratory, no in-situ SPL assessment Exposure during night	Ascone et al. (2021)
Experimental Non-randomized self-controlled trial (before-after design with pseudo random sequences of three exposure conditions), blinded order of SPL below and above HTL stimuli	– Self reported ratings of pleasantness/ unpleasantness of perceived ultrasound – Self reported ratings of positive/negative impact of ultrasound on n-back task performance	8 Females, Age: 26.5, SD = 3.42; 7 Males, Age: 24.43, SD = 2.76;	Statistically significantly higher ratings of unpleasant perception upon ultrasound exposure above HTL compared to ultrasound exposure below HTL	In ear exposure to ultrasound (21.5 kHz without subharmonics) 5 dB above vs. 10 dB below HTL Co-exposure of fMRI-Scanner in all exposure conditions	Weichenberger et al. (2022)

Limits for preventing potential adverse auditory effects. In the 1982 WHO review it is noted that "there has been a lack of suitable hearing test equipment and of a standard for describing normal hearing above 8 kHz; thus, threshold shift evaluation above 10 kHz is questionable." The finding that no TTS was observed in a small sample of industry workers after a workday close to ultrasonic machinery with high output powers (Acton and Carson 1967) is, therefore, not considered as sufficiently substantiated to conclude that the investigated SPL do not lead to adverse auditory effects.

In observational studies (not included in IRPA 1984 and more recently) using high-frequency audiometry with frequencies up to 20 kHz, HTL differences at frequencies above 10 kHz have been observed between subjects exposed to ultrasonic machinery and control subjects (Grzesik and Pluta 1983, 1986; Maccà et al. 2015) which tended to increase with increasing exposure duration. In all these studies on industrial workers, significant co-exposure to high frequency sound in the audio range was present. In order to mitigate the potential bias related to noise co-exposure, Dudarewicz et al. (2022) used a control group that was matched to daily noise exposure level (A-weighted SPL equivalent to continuous 8-h shifts), age, sex, as well as tenure (as proxy for industrial noise exposure duration). In their cross-sectional study HTL as well as transient-evoked otoacoustic emissions (TEOAE) and distortion-product otoacoustic emissions (DPOAE) of workers with and without ultrasound exposure during work shifts (but with similar A-weighted audible noise co-exposure SPL) were compared. The authors observed no statistically significant difference in mean HTL at frequencies up to 3 kHz but statistically significantly higher mean HTLs at frequencies from 4 kHz to 12.5 kHz were observed in the exposed group compared to control. Additionally, statistically significantly lower amplitudes of DPOAE and TEOAE were observed in all tested frequencies, indicating a substantially worse hearing ability in the ultrasound exposed group. Altogether, these observational studies provide consistent evidence that prolonged exposure to airborne ultrasonic energy might be associated with reduced high frequency hearing sensitivity, which might be an early indicator for noise induced hearing loss (Mehrpavar et al. 2014). However, co-exposure with sound of certain properties (e.g., VHF audible components that are attenuated when the A-weighting filter is applied) as a confounder cannot yet be definitively ruled out.

In experimental studies, only the effects of short-term exposure were investigated. In one experimental study on a limited number of volunteers exposed to amplitude modulated and unmodulated 40 kHz ultrasound emitted by a haptic device (the SPL at the subjects' ears was not measured, and 120 dB was assessed in the ear of a head and torso simulator, max. 41 minutes total exposure duration distributed across different exposure conditions and tests), no statistically significant shifts in hearing threshold level or subclinical measures for hearing impairment (auditory brainstem response, frequency following response and speech perception in noise) were observed (Carcagno et al. 2019). The only experimental indication of a hearing damage threshold of purely ultrasonic exposure was reported by Parrack[20] who referred to "small scale" investigations with distinct frequencies performed in the 1950s. Apart from the investigated ultrasound frequencies (17; 21; 24; 26 and 37 kHz), SPLs of approximately 150 dB, exposure duration of 5 minutes and the fact that the induced TTS of less than 30 dB at subharmonic frequencies recovered quickly, no experimental details or information about the investigated population (number, age, sex) is provided. Therefore, the reported finding of a potentially adverse effect of ultrasound exposure is based on a study that is not methodologically sound. To our knowledge there have not been any attempts to reproduce these results.

However, there is mechanistic evidence that supports these findings. In experiments on rodents such as guinea pigs and chinchillas first conducted by Davis et al. (1949) even-order subharmonic generation with fundamental frequencies up to 18 kHz was observed if a threshold SPL of approximately 110 – 120 dB in the ear canal was exceeded. By subsequent destruction of the cochlea and removal of the stapes and from the finding that subharmonics are radiated from the eardrum, the origin of even order subharmonic generation could convincingly be delimited to the middle ear, more precisely the tympanic membrane together with the attached malleus (Dallos and Linnell 1966a and b). A more recent investigation of this phenomenon in gerbils extends the applied fundamental frequency range to ultrasonic frequencies up to 40 kHz (40 kHz is still audible to gerbils) and provides additional confidence in the finding that the middle ear of certain rodents generates even order subharmonic frequencies upon exceeding a threshold SPL in the order of 110 dB (Huang et al. 2012). However, this extensive study also quantified that the efficiency of transferring the subharmonic frequency generated in the middle ear into the cochlea is similar to, or slightly higher than, the one of a pure tone with the same frequency applied at the ear canal.

The mechanistic evidence from animal experiments is consistent but it is unclear whether the quantifications can be transferred to humans experiencing high SPL in the ultrasonic frequency range. Early work from the 1950s using audio frequencies suggests that the effect also appears in human ears, as subharmonic emissions could be detected if a higher threshold SPL of approximately 140 dB was exceeded (von Gierke 1950). A nonlinear response of the

[20]Parrack HO. Physiological and psychological effects of noise. In: Proceedings 2nd Annual National Noise Abatement symposium (abstract listed in Cordell, 1968); 1951.

human eardrum, which is a prerequisite for subharmonic frequency generation at that site, appears to be in line with early theoretical considerations (Kobrak 1948; Pong and Marcaccio 1963). A study on four cadaveric human ears suggests the onset of compressive nonlinearity at the tympanic membrane (measured by laser-doppler vibrometry at the umbo) at 130 dB SPL (10 kHz) with falling tendency at higher frequencies (Cheng et al. 2021). However, no subharmonic frequency generation could be detected in that study, possibly due to too low SPL in the ear canal. As no ultrasonic frequencies were used in these limited human studies, the results do not necessarily apply to ultrasound. This would require new experiments on humans to confirm or refute the mechanistic evidence and to provide actual threshold data of effect appearance in the ultrasonic frequency range. Work on determining the mechanism for generation of subharmonics and ultraharmonics in humans and their importance relative to other possible mechanisms in generating adverse effects would be useful. However, conducting human studies in which potentially hazardous SPLs are applied is not compliant with modern ethical standards.

Limits for preventing non-specific symptoms. The results from early observational and experimental studies were used to determine the IRPA (1984) exposure limits (see Table 1). The exposure sources in the observational studies (Acton and Carson 1967; Acton 1968; Crabtree and Forshaw 1977; Skillern 1965; Knight 1968) were part of an industrial environment, where co-exposure to chemicals and other environmental factors cannot be excluded. The investigated industrial ultrasound exposure sources also emitted a significant amount of noise in the audio frequency range, which represents an important confounder. Indeed, the onset of non-specific symptoms observed in Acton and Carson (1967) and Acton (1968) correlates with the presence of audible components in the lower frequency range, since these effects were only reported if the audible and ultrasonic broadband noise spectrum of the machines contained a SPL of more than 75–78 dB in the TOB centered at 16 kHz or lower frequencies. This finding is supported by evidence from laboratory human experiments using more controlled narrow band exposure sources: In experiments on three women exposed to the sound of a Galton whistle, health complaints were only reported by two subjects who were able to perceive a 16 kHz pure tone only if the ultrasound spectrum of the whistle contained a SPL greater than 75 dB in the TOB centered at 16 kHz (Acton and Carson 1967).

After the publication of the IRPA 1984 guidelines, mainly experimental studies but also some observational studies have been published that are relevant for the endpoint of non-specific symptoms (see Table 2). Statistically significantly higher self-reported ratings of asthenia, vertigo, and tingling of the limbs between the exposed and unexposed group were reported in an observational (cross-sectional) study on industry workers (Maccà 2015). In another cross-sectional study (reported as a conference paper by Ueda et al. 2014) on 35 participants (age between 20 and 50 years) in the vicinity of a pest repellent system with a SPL between 100 and 120 dB and purely ultrasonic emission at 19 kHz and higher harmonics, it was reported by all participants that the emitted ultrasound could be heard and more than half of them felt discomfort from the perceived sound (evaluation based on a questionnaire). After relocation of the device accompanied by a reduction of the SPL of at least 12 dB, the sound could not be perceived anymore.

In a laboratory experiment, using an ultrasonic washer as exposure source (maximum emission at 25 kHz and audio frequency subharmonics at 12.5 kHz), even at the lowest applied levels [broadband SPL of 80 dB(lin)] the test subjects reported considerable annoyance and discomfort ratings which increased with increasing SPL (Holmberg et al. 1995). An experimental investigation on 38 young, otologically normal adults exposed to VHFS in the audio-frequency range (randomized order of stimuli presentation), suggests that the usable dynamic range (the SPL difference between adverse effect threshold and the hearing threshold level at a specific frequency) for comfortable hearing decreases with increasing frequency (Kurakata et al. 2013). This is supported by the results of an experiment on adults that previously experienced effects self-attributed to VHFS (symptomatic group, n = 10) and asymptomatic adults (n = 32) (Fletcher et al. 2018b). The subjects of both groups were exposed to 82-92 dB SPL VHF audible sound applied by circumaural headphones. For each individual a stimulus frequency that corresponds to a hearing threshold level of approximately 63 dB SPL was chosen and the stimulus intensity was set 25 dB above the individual hearing threshold level. As reference, the authors used a 1 kHz tone with a SPL also 25 dB above the individual hearing threshold level. The overall discomfort ratings (assessed by using a rating questionnaire) of both groups were slightly, but statistically significantly higher than in the audible 1-kHz reference condition. For the symptomatic group only, statistically significant elevated scores were obtained for both annoyance and inability to concentrate, when compared to the reference stimulus.

Similar experimental data on the frequency dependence of the usable dynamic range for non-specific symptoms have not been identified for the ultrasound frequencies in the 20 kHz TOB and above and only little narrative or observational data is currently available. Some publications report that hearing perceptions in the ultrasound range are more or less unpleasant (as soon as the sound is perceived) and that the dynamic range of comfortable hearing is quite narrow in the low frequency ultrasound range (Leighton

2016; Kühler et al. 2019). In a single-blinded human experiment on ultrasound-induced brain-activation, Kühler et al. (2019) determined hearing thresholds of single frequency ultrasonic signals (up to 24.2 kHz) with up to 115 dB SPL applied monaurally in the ear canal of the left ear. No quantitative evaluation of non-specific symptoms was performed, but almost all of the test subjects that heard the applied ultrasound, described the hearing sensation as displeasing. In a more recent single-blinded experimental study that applied a sequence of sham-exposure, ultrasound exposure 5 dB above the individual hearing threshold level (HTL) and ultrasound exposure 10 dB below the individual HTL (both at 21.5 kHz, the order of ultrasound exposure levels being randomized), statistically significant higher ratings of unpleasant perception upon ultrasound exposure above individual HTL compared to ultrasound exposure below HTL were reported (Weichenberger et al. 2022).

In the studies reported above, the appearance of non-specific symptoms was closely related with the hearing perception itself. Therefore, a nocebo effect cannot be excluded, which means that self-reported effects as well as potentially-related objectively measurable effects may occur simply because those exposed expect or fear that the detected exposure may be unpleasant or harmful. If the exposure is clearly audible, blinding will be impossible, but when the exposure is not, or may not be, audible, the gold standard is randomized double-blind experiments. Double blind means that the participant and the experimenter in contact with the participant do not know when the participants are exposed at different exposure levels or to sham, and ideally after exposure they should report whether they perceived any signal. Fletcher et al. (2018c), using a double-blind randomized provocation design, investigated whether exposure to inaudible ultrasound (20 kHz, SPL 84 dB) or sham provoked non-specific symptoms in volunteers that self-identified as experiencing symptoms from ultrasound (symptomatic group) and asymptomatic volunteers. The study provides no evidence that inaudible ultrasound provoked non-specific symptoms, noting that the exposure was limited to 84 dB SPL. However, the authors did report evidence of a small nocebo effect (linked to the expectation of being exposed) in a separate experiment without actual ultrasound exposure. The nocebo effect size appears to be small compared to some of the self-reported effects in observational studies, although the transfer from an experimental setting with a short exposure time to a long-term exposure setting of observational studies is clearly limited. In a single-blind randomized study, Ascone et al. (2021) investigated whether exposure to inaudible ultrasound from commercial devices for 28 nights (22.4 kHz, target level below 90 dB SPL) or sham exposure is associated with self-reported behavioral effects, including non-specific symptoms and sleep quality. The authors reported no consistent evidence of ultrasound effects on self-reported behavior but there were instances of symptoms in the sham condition pointing to a possible nocebo effect driven by the expectation of being exposed.

The results from these newer controlled and blinded experimental studies are in line with the older studies, suggesting that effects on non-specific symptoms only occur when the ultrasound is being perceived at least for SPLs below around 100 dB. Consequently, studies on hearing thresholds for ultrasound are of interest. Already before 1982/1984 there was evidence from a double-blind study that young individuals can hear 18-kHz tones at 60-70 dB quasi free-field SPL (Henry and Fast 1984), which is within the 20 kHz TOB but considerably below the limits of 75 dB SPL (for occupational exposures) or 70 dB SPL (for the general public). Recent hearing threshold data that were obtained in free field settings (only free field data is considered here, because the exposure limit is also a free field quantity) suggest that some very sensitive adult individuals are able to perceive amplitude modulated pure tone ultrasound in the order of 28 dB SPL at 18 kHz and 66 dB SPL at 20 kHz (Ashihara 2007) which is far below IRPA's 20 kHz TOB limits of 75 dB SPL (occupational) or 70 dB SPL (general public). It has also been shown that the hearing range of some individuals extends into TOB with center frequencies higher than 20 kHz. Ashihara et al. (2006) reported minimum hearing thresholds at 88 dB SPL or higher for 24 kHz tones and Ashihara (2007) found that 3 out of 32 ears which were individually tested had measurable hearing thresholds below 100 dB SPL at 28 kHz.

No hearing thresholds at 30 kHz could be measured, but it remained unclear if the maximum applied SPL of 100 dB was insufficient to induce auditory perceptions. Ueda et al. (2016) investigated the hearing thresholds in children and found hearing threshold levels lower than 100 dB SPL at 26 kHz for 40% of the subjects, and examples of very sensitive children that can even hear frequencies of 30 kHz and above (Ueda et al. 2014). In a blinded experiment using a haptic array as narrow band exposure source, one of the nine subjects that took part in the study could correctly detect the exposure status even at 40 kHz frequency at an SPL of 120 dB (Carcagno et al. 2019); whether ultrasound detection or other cues were responsible for this result is not entirely clear. The experimental data provided in Ashihara et al. (2006) suggests that the hearing threshold at ultrasound frequencies can be at least slightly influenced by the presence of ambient noise in the audio frequency range and it is likely that especially the minimum values are most affected. It is unclear whether this might also have an impact on the threshold for causing non-specific symptoms.

The IRPA limit at 75 dB SPL in the 20 kHz TOB is a simple extension of the criterion originally proposed for the 16 kHz TOB and aims at preventing the perception of ultrasound, in order to avoid non-specific symptoms. To further justify the originally proposed criterion, the ISO noise rating curve NR85 was extrapolated to 16 kHz (Acton

1968). Whereas NR85 might have been applicable to very noisy industrial environments for voice-frequency and often broadband noise, application to signals above 17.8 kHz (especially tonal signals) in quiet spaces of the general public such as libraries and schools (where problems have been observed in a case report; Leighton et al. 2020) goes even beyond the extrapolation into the 16 kHz TOB, and its application may not be valid. The studies on which the IRPA limit at the 20 kHz TOB are based on were restricted to a small sample of industry workers, which is further problematic because the observed non-specific symptom threshold level in the order of 75–78 dB SPL in the 16 kHz TOB (which is the basis of the 75 dB SPL limit in the 20-kHz TOB) cannot necessarily be generalized to the general public. Results from newer studies provide supporting evidence that the onset of non-specific symptoms is related to the hearing threshold which varies substantially between individuals and can be lower than the IRPA limits. Data from a broader portion of the population suggest that a segment of it has a lower hearing threshold than industry workers that were investigated in the studies considered in the IRPA guidelines, although no ultrasound hearing threshold data are available for direct comparison. Consequently, the IRPA (1984) limits for preventing non-specific symptoms (such as fatigue, headaches that may be related to annoyance and discomfort) might be non-protective for a part of the population with a lower ultrasound hearing threshold. Further, data specific to children would be required to generate guidelines for public exposure. A few studies have indicated that the symptoms may be due to a nocebo effect, which is in line with general knowledge about nocebo effects. However, evidence for a nocebo effect does not exclude other mechanisms. A provoking nature of the ultrasound may also be an explanation, i.e., ultrasound might also provoke the reaction by a mechanism other than the nocebo effect (for instance because the sound might be perceived as very unpleasant, which ultimately might cause such effects under prolonged exposure by another mechanism). The few observations published to date consistently report that ultrasound is often perceived as displeasing or unpleasant as soon as the sound is heard, which suggests (but does not necessarily prove) that potentially adverse non-specific symptoms will only manifest if the sound is heard. This is supported by the few well-controlled blinded studies with inaudible ultrasound, in which no ultrasound-induced effects were reported at low SPLs (Fletcher et al. 2018b; Ascone et al. 2021).

If ultrasound hearing thresholds are measurable, they might be a reasonable proxy for the lower boundary of the possible onset of non-specific symptoms due to ultrasound exposure. To date, there has been only one investigation on how the appearance of self-reported effects (in this study pleasantness/unpleasantness and perceived impact on cognitive tasks) is related to the HTL (Weichenberger et al. 2022) and there are no investigations on the impact of psychoacoustic parameters like loudness, sharpness and fluctuation strength, and related sound field properties. In order to validate the working hypothesis that the individual hearing threshold can indeed be used as a proxy for the lowest possible threshold for developing non-specific symptoms, more psychoacoustic research with audible ultrasound is needed, although the lack of blinding will always remain an issue. To confirm that this proxy is conservative, the very limited database requires further blinded randomized provocation trials that investigate non-specific symptoms in the inaudible ultrasonic range. Studies should compare symptomatic and asymptomatic individuals and include adequate numbers of subjects that reflect properties of the whole population, including children.

Physiological effects. In laboratory experiments on four to five subjects using narrow band exposure sources with center frequencies of 20 kHz and mainly inaudible 110–115 dB SPL, no auditory or physiological changes (compared to unexposed control) could be elicited, whereas auditory and physiological reactions were observed if audible signals at frequencies of 5 kHz were used as positive control (Grigor'eva 1966). In more recent studies on audible VHFS (Fletcher et al. 2018b) and inaudible ultrasound (Fletcher et al. 2018c), the galvanic skin response of each subject was assessed as a measure of the level of anxiety. There were statistically significant galvanic skin responses reported only in the symptomatic group during the VHFS exposure, whereas no statistically significant difference in the galvanic skin response between symptomatic and asymptomatic subjects was found for inaudible ultrasound, which was applied at low levels (84 dB SPL). From these few studies it appears there is no direct evidence that the limits are not protective against physiological effects, but the very limited database requires further research.

Elevation of limits for short term exposure. As discussed above and shown in Fig. 1, slight elevations of the SPLs are permitted for short-term occupational exposure. There is no data justifying the IRPA guidelines recommendation to use a relaxation of 3 dB per doubling of exposure time for occupational exposure. Apparently, this trade-off practice is transposed from recommendations for workday exposures to lower frequency occupational noise (typically below 8 kHz). In order to prevent hearing impairment, in 1977 the ILO recommended using a warning limit of 85 dB(A) and a danger limit of 90 dB(A), both assessed as A-weighted SPL energy equivalent to continuous 8-h exposure as well as special provisions for more intense (and short time) exposures (ILO 1977). The elevations in ILO (1977) do not address the endpoint of non-specific symptoms where psychoacoustic parameters might be relevant (Fastl 2005) and it is also not clear if an inherently linear

argument will apply for ultrasonic frequencies at all. There is also not enough evidence of any dose-response relationship which would support this relaxation. In fact, these elevated limits potentially exceed the threshold SPL for subharmonic frequency generation observed in rodents at fundamental frequencies below 18 kHz (Dallos and Linnell 1966b). For the general public, no such exceptions are allowed and the limits for continuous exposure include a reduction factor of 5 dB at TOB centered at 20 kHz and 10 dB at higher frequencies. No scientific rationale was provided by IRPA on how the size of this reduction was calculated.

Question 2(b) conclusion. As the exposure limits are mainly based on small-scale investigations on workers in industrial environments, the results cannot be extrapolated for the whole population, especially in light of the permitted elevations of 3 dB per halving of exposure time for which no justification is provided.

Available observational studies consistently report that prolonged occupational exposure to intense ultrasonic noise is associated with high frequency hearing loss but it remains unclear if audible VHF and ultrasound, inaudible ultrasound or confounding factors are responsible. Since in these studies the SPL exceeded the limit of 75 dB in the 20 kHz TOB for most workers, this cannot be regarded as evidence that this limit does not protect from adverse auditory effects. Whether or not the limits at the 25 kHz TOB or higher are protective against adverse auditory effects cannot be judged owing to the limited database.

The results from the few available scientific studies of varying quality indicate that non-specific symptoms will only manifest if ultrasound is perceived. Although it cannot be excluded that possible health effect thresholds have been overlooked in studies because of limited sample sizes, demographics, or limited exposure conditions (SPL, duration, repetition, pulsing, etc.), it should be considered as a preliminary working hypothesis that at frequencies where a hearing threshold can be measured, the hearing threshold represents a lower boundary for the possible range of non-specific symptom thresholds. Consequently, non-specific symptoms might also be induced at TOBs with center frequencies higher than 20 kHz (which were considered not to be audible by IRPA in 1984), and in general the limits might be too high to protect all individuals of the population. All hearing threshold data available to date show that individual hearing threshold levels at very high and ultrasonic frequencies generally increase with increasing frequency and a large part of the population cannot hear ultrasound at all. However, the preliminary working hypothesis is not sufficient to generally exclude all kinds of adverse effects because it is likely that inaudible ultrasound at very high SPLs can cause harm, for example by heating or other yet unidentified mechanisms.

In conclusion, the exposure limits suggested by the 1984 IRPA guidelines are not completely justified by the currently available scientific evidence, at least for protection of the whole population from developing exposure-induced non-specific effects. In order to validate the working hypothesis and to narrow down the range of the possible health effect thresholds, further controlled randomized human experiments on audible and inaudible ultrasound are necessary. Thereby, application of a double-blind protocol for inaudible exposures is crucial. Further, all experiments should include hearing threshold assessment at high and ultrasonic frequencies, systematic assessment of non-specific symptoms as well as complementary assessment of hearing threshold shifts, possibly induced by the experimental exposure. The impact of different sound field properties and psychoacoustic parameters as well as different populations, particularly children, should be systematically explored. It is important to test whether the nature of ultrasound, and not only the fact that the ultrasound is being heard, is influencing effects like annoyance.

Question 2(c)—Are the dosimetric quantities used for the limits in the IRPA guidelines valid?

The concluding remarks of the IRPA guidelines state that the document will be subject to periodic revisions as more information becomes available; that is, the authors understood the limited justification for what they were able to provide, and therefore provided a strong argument for the need for more data. In similar vein, the WHO review (pp. 18-19) mentions the need to develop a system of dosimetric variables.

ICNIRP defines dosimetry as a procedure that aims at quantification of an exposure to radiation. Quantitative descriptions of an exposure to radiation, for the purpose of formulating protection standards and exposure limits, require the use of adequate quantities (ICNIRP 1985). "Adequate" means that the quantities should represent those physical processes which are closely linked to the biological effects of radiation (ICNIRP 1985). However, this requires profound knowledge about the underlying biophysical mechanisms. Mechanisms by which ultrasound may cause some adverse auditory effects in humans are not well investigated (subharmonics were adopted, but never proven as a mechanism for TTS and PTS). For non-specific symptoms (annoyance, headaches, migraine, tinnitus, a feeling of pain or pressure in the ears, nausea, etc.) a possible causal pathway might include ultrasound hearing perception, which has been consistently described as feeling unpleasant (here, a nocebo effect cannot be ruled out due to methodological reasons), but beyond that the mechanism is unknown.

Dosimetry in the guidelines. Except for heating, all adverse effects that are covered by IRPA (1984) directly involve the ear. A valid limit for these endpoints can therefore

only be protective if they are not exceeded at the position where the individual ear can be present. The sensitivity of the eye for non-thermal adverse effects has also been suggested (Lenhardt 2007), but not substantiated.

As outlined above, there is some evidence that a possible threshold for ultrasound-induced non-specific symptoms is related to the individual hearing threshold level. This also appears to be the logic behind the 1984 IRPA limit of the 20 kHz TOB, but it remains unclear what other sound field or psychoacoustic properties (e.g., duration, modulation, tonality, loudness) are needed to induce non-specific symptoms. Without a mechanism, it is not possible to identify what parameters of the ultrasonic field are important to quantify in calculating the dose, and, therefore, it is impossible to define valid dosimetry. This might explain why essential information for assessing the SPL (e.g., permissible averaging times for assessing RMS values) is missing in the IRPA guidelines.

If one assumes that the frequency down conversion mechanism is indeed a relevant mode of action in humans and the IRPA free field SPL exposure limits reliably protect against adverse effects of exposures in each TOB, it remains questionable that these limits protect against effects of simultaneous multi-frequency exposure. In that case, each TOB SPL contributes to a total broadband SPL at the tympanic membrane. A rationale for why the possibility of cumulative multiband exposures is not considered for a proposed nonlinear mechanism that includes an instantaneous pressure threshold effect is not provided. Other amplitude threshold effects of non-ionizing radiation exposure (such as low frequency electromagnetic fields, see ICNIRP 2010) require an instantaneous amplitude dependent multi-frequency exposure metric which considers that signal components potentially add up in phase. In contrast, the SPL is an RMS metric that correlates with the square root of the power of the overall signal. In an extreme case (N spectral components with identical amplitude and zero phase difference), the maximum instantaneous pressure level is up to 10*log10(2*N) dB higher than the RMS SPL of such a signal. A clear understanding of any potential mechanism would be helpful in deriving appropriate exposure metrics. Also, basing exposure limits on RMS values in TOBs may be inadequate, given that most ultrasonic sources used now in public places are tonal in nature (Leighton 2016; Scholkman 2019).

The TOB centre frequencies of the SPL limits in the IRPA guidelines are rounded values and the exact values depend on whether log base 10 or log base 2 is used for the computation (Leighton 2017). This potentially results in an ambiguity regarding the corresponding frequency limits. If one computes the TOB frequency limits from the rounded frequency values, both an overlap of TOB as well as unregulated frequency gaps between the TOB appear (Leighton 2017). This is of special importance at the boundaries of the TOB centered at 20 kHz because of the abrupt change in permitted SPL. Acton (1975) states that the nominal frequency limits of the TOB centered on 20 kHz are 17.6 kHz and 22.5 kHz, but this information is not specified in either the IRPA guidelines, or in the WHO review. However, even with specified TOB boundaries a potential ambiguity remains: the energy of any spectral component with finite bandwidth and a center frequency exactly at the boundary of two adjacent TOB will be split into these bands, which can result in compliance with the guidelines even if the SPL is higher than the permitted level in each of the two adjacent TOB. To prevent this, a quasi-continuous metric would be necessary. Additionally, if the steep rise of the hearing threshold in the lower end of the 20 kHz TOB is indeed associated with a similar steep rise in the non-specific symptom threshold, the low frequency resolution of the 20 kHz TOB would be inappropriate and narrower bandwidths would be required in this frequency range.

Dosimetry in the studies that informed the IRPA guidelines. From the limitations of the experimental studies on humans, it becomes apparent that dosimetry, in the studies that provide the evidence, is also undermined, in part, because no exposure details are reported. Of the studies that form the scientific basis of the IRPA guidelines, Acton and Carson (1967) provided the study with the most comprehensive description of exposure assessment. In that study a calibrated free field microphone (frequency response up to 100 kHz) was used to assess the SPL at the places where the heads of the operators were located and TOB SPL spectra were obtained using an audio frequency spectrometer with maximum frequency at 40 kHz. Owing to physical phenomena such as reflection, diffraction and interference, the SPL may vary strongly in space and time. Spatially resolved measurements have not been reported, which leaves the possibility of under- or overestimation of the SPL at the relevant position (Radosz and Pleban 2018; Schöneweiß et al. 2020).

In the animal studies providing mechanistic evidence, the SPL in the ear canal at distinct frequencies is reported. This single frequency SPL in the ear canal might be a more relevant exposure metric that can be potentially directly linked to the induction of hazardous effects. However, the relation of this value to a free field SPL measured at the position of an ear (as done in the studies in industrial environments; Acton and Carson 1967; Grigor'eva 1966) is unclear for ultrasound frequencies. To establish a relationship between internal body (assessed in the ear canal) and free field exposure quantities, further research is necessary. However, a high intrinsic uncertainty in such a relationship can be expected, owing to effects such as scattering at the pinna (Leighton 2016). If possible at all, this would facilitate the comparison of

hearing threshold data obtained with different methods of sound presentation (free field vs. insert ear phones).

Question 2(c) conclusion. In summary, the dosimetry that is used in the IRPA guidelines and the publications that the guidelines are based on were not mature at that time, which has also been acknowledged by the authors of the guidelines. Appropriate dosimetric quantities still have to be established. However, a prerequisite for defining such quantities is understanding the mechanism for potentially adverse effects, which requires more research.

Question 3: Are there biological endpoints that are not covered by the 1984 IRPA guidelines

The third consideration is whether there is evidence of biological endpoints (within the scope of ICNIRP) that are not covered by the 1984 IRPA guidelines; that is, biological endpoints other than heating, adverse auditory effects, non-specific symptoms or physiological effects as identified in the 1982 WHO review.

Brain physiology and function. There is only limited new research on brain physiology and function that is not covered by the 1984 IRPA guidelines. The study by Fletcher et al. (2018b) on human volunteers investigated whether exposure to VHFS and ultrasound (frequencies between 13.5 and 20 kHz and SPLs between 82 and 92 dB) affects attention. In the study, performance in an attention task after exposure to VHFS/ultrasound and a reference 1 kHz stimulus was compared between volunteers that self-identified as experiencing non-specific symptoms from VHFS/ultrasound (symptomatic group) and asymptomatic volunteers. There was no difference in performance on the attention task between exposure to VHFS or ultrasound and the reference stimulus for either group of volunteers. In their second study, Fletcher et al. (2018c) used a double-blind randomized provocation design to investigate whether exposure to inaudible ultrasound (20 kHz, SPL 84 dB) or sham affects attention. Similarly to their first study, Fletcher et al. (2018c) compared performance in an attention task after inaudible ultrasound exposure or sham between symptomatic and asymptomatic subjects. The double-blind randomized study also showed no effect on attention for either group. It is noted that in both studies by Fletcher et al. there was a very low number of symptomatic subjects compared to asymptomatic subjects. A further limitation of these studies is the low exposure levels, which were used because of ethical considerations.

In their single-blind randomized study, Ascone et al. (2021) investigated whether inaudible exposure to ultrasound from commercial devices for 28 nights (22.4 kHz, target level < 90 dB SPL) affects cognitive performance. There was no effect on most of the cognitive domains tested; a positive effect was found for two of the cognitive tests but these results could have been due to multiple testing. The study by Ascone et al. also investigated brain structure parameters, which were measured via structural magnetic resonance imaging (MRI). The authors reported both increases and decreases in regional grey matter volume pre-to-post ultrasound exposure but were unable to relate these brain structural changes to behavioral changes.

There have been other studies that have investigated exposure to ultrasound and brain activity. Fujioka et al. (2002) overlaid MRI images of the brain on equivalent current dipole sources detected by magnetoencephalography (MEG); averaging MEG waveforms evoked in response to auditory stimulation allows mapping of the auditory evoked magnetic field (AEF). The authors found no cortical response to inaudible 60 dB SPL ultrasound stimulation at frequencies of 20 kHz or above. Another study by Kühler et al. (2019) examined the fMRI and MEG response to acoustic stimulation and found no evidence of auditory cortex activation for airborne ultrasound below and above the hearing threshold. It remains unclear if this finding is due to limited sensitivity of the applied methods. In a follow up to Kühler et al. (2019), Weichenberger et al. (2022) used fMRI to investigate brain activity during resting-state as well as during cognitive processing in subjects with normal hearing exposed to a 21.5 kHz tone. This study also found no evidence of auditory cortex activation for airborne ultrasound below and above the hearing threshold, but found a higher n-back-task-related activation of the inferior frontal gyrus (IFG) in the below threshold condition compared to the above-threshold condition, as well as an association between higher IFG activation and faster reaction times during the below threshold exposure condition. The health relevance of these, yet unreplicated, findings is currently unclear. In their study on young women using a haptic device as ultrasound exposure source (for details see Table 2), Carcagno et al. (2019) also performed electroencephalography measurements and observed no statistically significant phase-locked activity at the modulation frequency or at low-frequency subharmonics of the ultrasound tone.

Question 3 conclusion. The existing evidence on cognitive ability and brain activity do not indicate that airborne ultrasound affects brain physiology and function in an adverse way. Nevertheless, the research to date is limited and further randomized provocation trials, including sham exposure or exposures at different exposure levels, are required, paying particular attention to sufficiently sensitive testing methods and adequate numbers of subjects. When the signals applied are not obviously audible for all participants, exposure conditions should also be blinded and it should be checked whether any participant was able to detect the ultrasound exposures better than by chance. Studies should further consider self-reported sensitivity to ultrasound by separating "symptomatic" and "asymptomatic" subjects.

OUTLOOK

Most of the data used for deriving the 1984 IRPA guidelines does not fulfill the requirements stated in ICNIRP's principles for non-ionizing radiation protection for guideline development (ICNIRP 2020). Further, according to the ICNIRP principles, exposure should be limited to either below the level with an accepted risk for adverse effects (no such accepted risk has been established for airborne ultrasound), taking into account any beneficial effects for health (it is not feasible to assess this for airborne ultrasound exposure), or below the threshold level for adverse health effects (the threshold level has been defined by a very poor data basis, as outlined above).

No substantial scientific advances have been made since 1984 regarding the endpoint of ear damage mediated by the putative frequency down conversion mechanism. However, more data on the distribution of hearing thresholds in the population (up to the 30 kHz TOB) and some data on non-specific symptoms have become available over the years (Henry and Fast 1984; Ashihara et al. 2006; Ashihara 2007; Kurakata et al. 2013; Rodríguez Valiente et al. 2014; Kühler et al. 2019; Weichenberger et al. 2022). As outlined above, there is some evidence that non-specific symptoms can occur in sensitive individuals upon exposure to ultrasound in the 20 kHz TOB at SPLs below the exposure limit designed to protect from such effects. Using hearing threshold data as a proxy for the non-specific symptoms threshold (at frequencies where such thresholds can be measured), updated interim limits for the general public, based on hearing thresholds in the ultrasound range, could be proposed as a conservative approach. These should be based on experiments that use free field exposures, because the limits have to also be free field quantities as no reliable relationship between body-internal (assessed in the ear canal) and free field exposure quantities has been established. Because we should use hearing threshold data across the population to cover individuals with very low hearing thresholds to ultrasound, age-specific percentiles rather than averages should be used to derive exposure limits. Such limits would be most applicable for quiet environments, such as libraries and schools. A potential masking effect by additional noise in less quiet environments would possibly allow less strict limits for situations where audible noise is present (e.g., traffic or industry). However, it remains to be shown if and to what extent a masking by audio frequency noise affects the threshold for ultrasound induced non-specific symptoms.

Exposure limits do not necessarily need to be formulated in TOBs, which potentially allows one to define a metric that is free from the ambiguities addressed in question 2(c) earlier and has a higher frequency resolution. However, similar to the IRPA limits, any proposed new metric will suffer from the fact that the mechanism that facilitates non-specific symptoms upon ultrasound exposure is not known; this requires further research on mechanisms.

A stepwise 3-dB elevation of occupational limits for halving of exposure periods is not applicable for preventing exposure-threshold dependent non-specific symptoms, without evidence for a clear dose component (dose = exposure intensity × time). It therefore appears to be reasonable to refrain from the possibility of elevating the limits for shorter time periods of occupational exposure unless there is new evidence supporting the elevation. This would be in line with the exposure limit proposed by Health Canada (1991), which mentions "The SPLs, for 1/3-octave bands, are independent of time of exposure as subjective effects can occur immediately." Health Canada also introduced an additional limit for occupational exposure (total SPL of 137 dB) that aims at protection from tissue heating (e.g., in skin clefts) in case ear protection is worn and the limits for preventing non-specific symptoms and adverse auditory effects are exceeded. However, the relationship between SPL and potential adverse temperature elevations is so poorly investigated that further research is necessary to provide an appropriate SPL limit.

Measurement technology and procedures for the assessment of airborne ultrasound fields have advanced significantly in the last few years (e.g., Kling et al. 2017; Ullisch-Nelken 2017; Radosz and Pleban 2018). However, owing to the lack of a substantiated biophysical mechanism, there has not been any scientific progress in defining the properties of a suitable exposure metric that represents those physical processes which are closely linked to the biological effect. Further, as previously mentioned, no universal relationship between the undisturbed body external airborne ultrasound field parameters and body-internal pressure distributions in the ear canal and at the tympanic membrane exists because the presence of the head can disturb the sound field and ear canal geometry varies significantly between individuals.

CONCLUSION

The current analysis on the validity of the 1984 IRPA guidelines has shown that the biological endpoints that form the basis of the guidelines are relevant to health and the guidelines provide limits of exposure based on the evidence that was available at the time. However, the IRPA limits and their associated dosimetry were based on limited evidence, which may not be considered as scientifically substantiated. Research since the IRPA guidelines has made some improvements in the knowledge base but there are still significant data gaps that need to be resolved before a formal revision of the guidelines can be made by ICNIRP (listed in the Appendix).

Acknowledgments—Collaborators: Ken Karipidis, ICNIRP and Australian Radiation Protection and Nuclear Safety Agency (ARPANSA); Jacques Abramowicz, Department of Obstetrics and Gynecology at the University of Chicago, Illinois, USA; Akimasa Hirata, ICNIRP and Nagoya Institute of Technology, Japan; Jens Kuhne, German Federal Office for Radiation Protection; Timothy Leighton, University of Southampton, United Kingdom; Gunnhild Oftedal, ICNIRP

and Norwegian University of Science and Technology (NTNU); Jan Radosz, Central Institute for Labour Protection—National Research Institute in Poland; Martin Röösli, ICNIRP and Swiss Tropical and Public Health Institute; Rodney Croft, ICNIRP and Australian Centre for Electromagnetic Bioeffects Research, Illawarra Health & Medical Research Institute, University of Wollongong, Australia; Eric van Rongen, ICNIRP and Health Council, The Netherlands; Nigel Cridland, ICNIRP and Public Health England; Anke Huss, ICNIRP and Institute for Risk Assessment Sciences (IRAS) at Utrecht University, The Netherlands; Guglielmo d'Inzeo, ICNIRP and "La Sapienza" University of Rome, Italy; Carmela Marino, ICNIRP and Agency for New Technologies, Energy and Sustainable Economic Development (ENEA), Italy; Soichi Watanabe, ICNIRP and National Institute of Information and Communications Technology (NICT), Japan.

The support received by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV), the European Union,[20] the International Radiation Protection Association (IRPA), the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), and the New Zealand Ministry of Health is gratefully acknowledged. All information concerning the support received by ICNIRP is available at www.icnirp.org. The views and opinions expressed in this publication are those of the author(s) only and do not necessarily reflect those of the organizations they are professionally affiliated with nor those of the donors or the granting authorities which can't be held responsible for them.

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■■

APPENDIX

Data gaps in knowledge related to the effects of airborne ultrasound on health

For all the endpoints listed in the table below, general data gaps remain. These concern the following aspects:

- Effect thresholds;
- Impact of sound field properties (i.e., SPL, spectral shape, modulation) and related psychoacoustic parameters (i.e., loudness, tonality, sharpness, fluctuation, roughness) on thresholds;
- Threshold distribution across the population (this requires sufficient sample size including children as well as self-identified symptomatic and asymptomatic individuals); and
- Mechanistic understanding and exposure metrics.

Further research should aim to fill these data gaps. Because of the huge variety of hearing thresholds across the population, analysis should be stratified by age and individual reported sensitivity to VHFS and ultrasound. Since it appears feasible that ultrasound-induced non-specific symptoms, physiological and stress-related effects and effects on cognition and behavior might be linked by a common mechanism of action, it is recommended to test some of the endpoints within one study rather than performing several separate studies.

For example, data on non-specific symptoms should be always collected as part of an investigation on the other endpoints, given that this procedure does not impact the validity of the study (e.g., by creating expectations of the participant). Further, the actual HTL of the participants should be assessed before and after each study in order to investigate whether the experimental exposure has an impact on hearing level. Further, the influence of audio-frequency noise on ultrasound hearing thresholds should be explored in order to allow blinding in experiments that apply ultrasound which otherwise would be audible for the participant (blinding by appropriate masking). The general impact of ambient audio-frequency noise on thresholds for effects and effect sizes of non-specific symptoms, physiological and stress-related effects cognition and behavior should also be investigated. See Table A1.

Table A1. Research needs.

Endpoint	Research needs
Hearing thresholds at ultrasonic frequencies	Human experimental studies on the distribution of hearing thresholds in the ultrasonic range including in very young children.
	Testing the working hypothesis that the hearing threshold can be used as proxy for the non-specific symptom threshold (at frequencies where a hearing threshold can be measured).
Non-specific symptoms	Human experimental studies on the frequency dependence of the usable dynamic range (the span between hearing threshold SPL and effect threshold SPL) of audible ultrasound.
	Blinded randomized provocation trials at sufficiently high SPL of inaudible ultrasound.
Physiological and stress-related effects	Human experimental studies applying an objective assessment to map physiological effects of audible ultrasound (e.g., galvanic skin responses, brain imaging with high sensitivity).
	Blinded randomized provocation trials at sufficiently high SPL of inaudible ultrasound (same endpoints).
Cognition and behavior	Human experimental studies applying an objective assessment of effects of audible ultrasound on cognition and behavior.
	Blinded randomized provocation trials at sufficiently high SPL of inaudible ultrasound (same endpoints).
Hearing damage	Assessing TTS using standard and extended high-frequency audiometry as complementary assessment before and after of each human experiment on non-specific symptoms, physiological and stress-related effects and effects on cognition and behavior.
	Experimental studies on humans to confirm or disprove the mechanistic evidence for subharmonic generation and to provide threshold data of effect appearance in the ultrasonic frequency range (in compliance with ethical standards).
	Prospective cohort studies investigating hearing threshold level.
Dosimetry	Research on the relationship between threshold SPL in the ear canal and free field SPL measured at the position of the ear, relevant parameters of anatomy and acoustic field properties.