Modern ultrasound imaging for diagnostic purposes has a wide range of applications. It is used in obstetrics to monitor the progress of pregnancy, in oncology to visualize tumours and their response to treatment, and, in cardiology, contrast-enhanced studies are used to investigate heart function and physiology. An increasing use of diagnostic ultrasound is to provide the first photograph for baby’s album—in the form of a souvenir or keepsake scan that might be taken as part of a routine investigation, or during a visit to an independent high-street ‘boutique’. It is therefore important to ensure that any benefit accrued from these applications outweighs any accompanying risk, and to evaluate the existing ultrasound bio-effect and epidemiology literature with this in mind. This review considers the existing laboratory and epidemiological evidence about the safety of diagnostic ultrasound and puts it in the context of current clinical usage.

Keywords: diagnostic ultrasound; safety; epidemiology; thermal effects

1. INTRODUCTION

Modern ultrasound imaging for diagnostic purposes has a wide range of applications. For example, it is used in obstetrics to monitor the progress of pregnancy, in oncology to visualize tumours and their response to treatment, and, in cardiology, contrast-enhanced studies are used to investigate heart function and physiology. An increasing use of diagnostic ultrasound is to provide the first photograph for baby’s album—in the form of a souvenir or keepsake scan that might be taken as part of a routine investigation, or during a visit to an independent high-street ‘boutique’.

A fundamental principle of medical ethics is *primum non nocere* (‘first do no harm’), and this is paraphrased in the Hippocratic Oath that contains a promise to ‘abstain from doing harm’. A second principle is that a procedure can be legitimately carried out if the importance of the objective is in proportion to the risk to the subject. Only if the ratio of risk to benefit is beneficial to the subject can it be considered ethical. The assumption hitherto has always been that ultrasound scans are ‘safe’. There are a number of reasons not to be blasé about ultrasound safety. Firstly, it is well known that ultrasound can be used to produce changes in biological tissue—it is this that drives its use as a therapeutic agent, whether at low powers for physiotherapy or drug delivery, or at higher powers for cancer therapy where instantaneous cell killing is sought. Can we really be sure that the ultrasound pulsing regimes used in ultrasound imaging are not also producing biological changes that may be considered deleterious in the context of an imaging application?

Secondly, as will be seen below, while existing human epidemiological studies of the safety of ultrasound are reassuring, it must be remembered that the scans under consideration for these were all carried out using early clinical scanners, before the increase in output levels that has taken place over the last two decades.

It is important, as ultrasound imaging techniques and applications evolve and new devices become available, to be ever vigilant and to provide ongoing assessment of diagnostic ultrasound usage to ensure that its use can continue to be justified on safety grounds. In what follows, the existing knowledge about the interaction of ultrasound with tissue is reviewed in the context of the safety of ultrasound diagnosis for all applications. That of most concern is imaging of the unborn baby, but the discussion is not restricted to this use of ultrasound. The differences between imaging modes (B-mode, pulsed and colour flow Doppler) lie in the lengths of the pulses used, their repetition frequency and the pressure in the pulses [1]. The characteristics of each different mode of ultrasound imaging remain essentially the same, irrespective of the target being imaged. What matters in safety terms is the sensitivity of the tissue
2. INTERACTION OF ULTRASOUND WITH TISSUE

Ultrasound exposure of tissue is often described as being ‘non-invasive’. While this is correct in terms of the definition of a non-invasive procedure (one for which no break in the skin is created and there is no contact with the mucosa or internal body cavity), it must be remembered that the formation of an ultrasound image necessarily requires the exposure of regions of interest to ultrasonic energy.

As an ultrasound beam propagates through tissue, the energy reduces with depth travelled—that is, it is attenuated. Some energy is reflected by tissue structures in the beam path, and some is absorbed. The required ultrasound image is formed from the scattered energy received at the imaging probe, with the time of its arrival being a measure of the depth of the reflecting structure, and its amplitude giving information about the structure itself. The amount of energy absorbed depends on the composition of the tissue and the frequency of the ultrasound beam. Broadly, bone absorbs more ultrasound energy than soft tissue, and also reflects more strongly. Ultrasound absorption in tissue rises with increasing frequency.

In a plane wave, the relationship between the intensity incident on the surface of tissue (I₀) and the intensity at a depth x into tissue (I(x)) may be written as

$$I(x) = I_0 e^{-\mu_x}$$

where $\mu_x$, the intensity attenuation coefficient, is a sum of contributions from absorption ($\mu_a$) and scatter ($\mu_s$) such that $\mu = \mu_a + \mu_s$. The contribution of absorption to attenuation may be 60–80% of the total [2].

The amount of energy reflected by a structure, such as bone, that lies in the ultrasound beam path is determined by the change in acoustic impedance at its surface. The acoustic impedance, Z, is given by $Z = \rho c$, where $\rho$ is the tissue density and c is the speed of sound. The greatest impedance mismatches in clinical ultrasound usage occur at soft tissue–bone and soft tissue–gas interfaces. These are seen as the brightest echoes on an ultrasound image.

The mechanisms of interaction of ultrasound with tissue that may lead to biological effects are often broadly divided into two categories—thermal and non-thermal. In reality, these mechanisms are inter-related since, as will be seen below, tissue heating may facilitate non-thermal effects by reducing the threshold for cavitation, and non-thermal effects such as cavitation may, in turn, affect local tissue heating. For convenience, however, these mechanisms will initially be treated separately in what follows.

Table 1. Estimates of rates of temperature rise in soft tissue for different imaging modes made using equation (2.3). These assume average acoustic and thermal parameters for soft tissue of absorption coefficient, $\mu_s$; 0.06 neper cm$^{-1}$ (0.5 dB cm$^{-1}$) at 1 MHz, and heat capacity, C: 4.18 J g$^{-1}$ °C$^{-1}$.

<table>
<thead>
<tr>
<th>Imaging mode</th>
<th>mean $I_{SPTA}$ (W cm$^{-2}$)</th>
<th>C s$^{-1}$</th>
<th>C min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode</td>
<td>0.341</td>
<td>0.048</td>
<td>2.88</td>
</tr>
<tr>
<td>Pulsed Doppler</td>
<td>0.861</td>
<td>0.123</td>
<td>7.38</td>
</tr>
<tr>
<td>Colour flow Doppler</td>
<td>0.466</td>
<td>0.066</td>
<td>3.96</td>
</tr>
</tbody>
</table>

2.1. Thermal effects

The absorption of energy within tissue leads primarily to a rise in temperature. The rate of heat deposition, $\dot{Q}$, is given by the expression $\dot{Q} = \mu I$ per unit volume.

If there is no heat loss out of the volume by conduction, convection or radiation; this may also be written as

$$\dot{Q} = \rho C \frac{dT}{dt}$$

(2.2)

where $\rho$ is the density, $C$ is the heat capacity and $\frac{dT}{dt}$ is the rate of temperature change. By combining these equations, we can get

$$\frac{dT}{dt} = \frac{\mu I}{\rho C}$$

(2.3)

This relationship allows us to estimate the maximum possible rate of temperature rise for different modes of ultrasound imaging. A recent survey has given the mean spatial peak temporal average intensity ($I_{SPTA}$) as 341 mW cm$^{-2}$ for B-mode imaging, as 860 mW cm$^{-2}$ for pulsed Doppler and as 466 mW cm$^{-2}$ for colour flow Doppler [3]. Assuming average acoustic and thermal parameters for soft tissue (\mu_s 0.06 neper cm$^{-1}$ (0.5 dB cm$^{-1}$) at 1 MHz, and C 4.18 J g$^{-1}$ °C$^{-1}$), the temperature rises calculated in this way are given in table 1. Clearly, these are over estimates, as they do not account for thermal conduction, the cooling effects of blood flow, nor for movement of the transducer. Nevertheless, they show the relative heating potential of the different imaging modes. The absorption coefficient of bone is many times that of soft tissues (for example, Duck [2] gives an average value for brain of 0.6 dB cm$^{-1}$ MHz$^{-1}$ and for skull bone of approx. 20 dB cm$^{-1}$ MHz$^{-1}$), and so the rate of heat deposition at the bone surface is much greater. Tissues at most risk from ultrasound exposures are therefore bone and any soft tissues lying adjacent to it, and especially developing bone.

The temperature rise may be limited by the cooling effects of blood flow in the exposed volume. Highly vascular organs, such as the liver and kidney, are thus more difficult to heat than bone, which is less well perfused. However, in narrow, focused beams such as those used in pulsed Doppler examinations, there is a large temperature gradient across the beam, and so thermal conduction out of the heated volume is likely to be
more important than the cooling provided by blood flow [4]. The temperature rise during many diagnostic ultrasound examinations is also limited by the use of scanned beams, with any point in tissue being interrogated for only a very short time. Significantly elevated temperatures are only likely to be found when stationary beams are used, such as in M-mode, spectral Doppler studies and some colour flow imaging techniques.

The biological significance of a temperature rise depends on both its magnitude and its duration, with higher temperatures requiring shorter times to produce comparable effects. The concept of thermal dose was introduced to allow comparison of the bio-effects arising from different thermal histories. Thermal dose is defined in terms of a time that is given by the equation

\[ t_{\text{ref}} = tR^{T_{\text{ref}} - T}, \]

where \( t_{\text{ref}} \) is the thermal dose, is the time at a temperature \( T_{\text{ref}} \) that will produce a thermal effect equivalent to that from a temperature \( T \) maintained for a time \( t \) [5–7]. \( R \) is a constant that has been shown to be 2 for \( T > 43^\circ \text{C} \) and 4 for \( T < 43^\circ \text{C} \). It is well known that temperature rises above normal core levels can be teratogenic, although there is some debate as to whether it is the temperature rise or the absolute temperature that is the most important factor in determining the biological effect [1,8–12]. There have been many laboratory studies of the effects of heat on the embryo or foetus (usually involving whole body heating), and it is the developing central nervous system that is thought to be the most sensitive to heat [1,13,14]. In addition to the rise in temperature and its duration, the stage of development is crucial in determining the severity of effects produced. For example, mild exposures during the pre-implantation period may lead to foetal death, whereas much larger thermal doses can be tolerated after birth. The teratogenic effects of heat at different stages of development in utero have been reviewed [1,10], and include resorption and death during pre-implantation through abortion; neural tube, heart and vertebral defects in the early embryonic stage; and micro-encephaly, abortion and behavioural deficits in the mid-embryonic and foetal stage. However, it must be remembered that these effects have been seen following whole body heating of both the mother and the offspring, in which a slow temperature rise (approx. 0.5°C min\(^{-1}\)) is obtained by warming the skin surface using either hot air or warm water. This differs from ultrasound heating in a number of important ways. In whole body heating, the slow rise in core temperature may trigger a measure of thermotolerance by synthesis of relevant heat shock proteins [15]. Ultrasound heating is very rapid (table 1). In addition, ultrasound exposures in pregnancy only subject a small fraction of the maternal volume to a potential temperature rise, and thus any heating of the embryo is likely to be rapidly dissipated. Exposure of the mineralized bone in the third trimester, however, may result in a more biologically significant temperature rise.

An analysis of published data by Miller & Ziskin [12] led to the recommendation by many professional bodies that a temperature elevation of 1–1.5°C can be applied indefinitely without concern on safety grounds. This has been revised more recently, with the suggestion that ‘best estimates’ of a threshold for temperature-induced effects give approximately 1.5–2.5°C above normal body temperature held for longer than an hour [1]. For higher temperatures, the threshold for safety was set by the World Federation of Societies for Ultrasound in Medicine and Biology (WFUMB: http://www.wfumb.org/about/statements.aspx) to be the thermal equivalent of 43°C for 75 s (a temperature rise of 4°C for 5 min). However, this first analysis, based on data from a number of different species, did not account for differing core temperatures. Church & Miller [9] have normalized the data to the animals’ normal temperature. This reduced the threshold to lie at a temperature rise of 4°C maintained for 30 s.

Although safety training will exhort the ultrasound user to limit temperature during a scan, it is difficult to assess what this might be during an imaging procedure. In order to aid this assessment, the concept of thermal index (TI) has been developed (see below).

2.2. Non-thermal effects

The passage of an ultrasonic pressure wave through tissue also leads to ‘mechanical’ effects. These include acoustic cavitation and phenomena arising from radiation pressure effects, such as acoustic streaming. It is acoustic streaming that is of most concern on safety grounds.

The negative pressure in an ultrasonic pulse can draw gas out of solution in tissue. These gas bubbles grow from existing nuclei in tissue. Evidence for the existence of such nuclei comes from the development of decompression sickness in deep sea divers [16]. Once a bubble has been formed, it may expand and contract, in what are often termed breathing oscillations, in response to the pressure wave (non-inertial or stable cavitation), or, if at a size that is resonant for the drive frequency of the ultrasound beam, the bubble will expand greatly, followed by rapid contraction (inertial cavitation) and break up. Stable cavitation bubble oscillation may set up microstreaming patterns in fluids in which they form. While this is unlikely to cause significant adverse biological effects, it may alter ionic transport across cell membranes, and may in fact have beneficial therapeutic outcome. Very high temperatures and pressures result from inertial collapse. This can lead to localized tissue damage at the site of the bubble.

The resonant bubble radius \( R_0 \) up to 100 kHz is defined by an equation first derived by Minnaert [17],

\[ R_0 = \frac{1}{\omega_0} \left( \frac{3\gamma P_0}{P_0} \right)^{\frac{1}{2}}, \]

where \( \omega_0 \) is the angular frequency of the ultrasound field, \( P_0 \) is the ambient pressure, \( \rho_0 \) is the liquid density and \( \gamma \) is the ratio of the specific heats of the gas.
within the bubble. Above 100 kHz, surface tension, $\sigma$, becomes

$$R_0 = \frac{1}{\omega_0} \left( \frac{3\gamma P_0}{\rho_0} \left[ 1 + \frac{2\sigma(3\gamma - 1)}{3\gamma R_0 P_0} \right] \right)^{1/3}. \quad (2.5)$$

For frequencies between 1 and 3 MHz, the resonant bubble size is approximately 4–1 $\mu$m.

There is considerable debate as to whether diagnostic ultrasound exposure conditions are able to induce cavitational effects in the absence of exogenous bubbles (such as those that are used as ultrasound contrast agents (UCAs)). The consensus of opinion is that they are unlikely to occur at significant levels, but the possibility of low-level activity cannot be altogether ruled out [1, 18]. Ultrasonically driven cavitational bubbles emit characteristic acoustic signals, which can be detected actively or passively using a piezo-electric sensor (an active sensor ‘pings’ the bubble using an ultrasonic pulse and picks up the returning echo, while a passive sensor solely detects the acoustic emissions that result from bubble oscillations). Considerable effort has gone into determining the threshold acoustic pressure that gives rise to acoustic cavitation in tissue, but, in reality, the validity of published values depends on the sensitivity of the sensor used. Cavitation detection is usually carried out at frequencies above the drive, and the emissions are consequently absorbed strongly in the tissue between the bubble and the detector. In general, the presence of UCAs lowers the threshold for cavitation as they obviate the need to nucleate gas bubbles.

The other often cited non-thermal mechanisms by which ultrasound can produce effects in tissue are those due to radiation pressure and acoustic streaming. The evidence for these mechanisms mediating biological effects is less well established than it is for thermal and cavitational effects.

An ultrasound beam exerts forces on discontinuities in its path. There are two components to these forces: an oscillatory component that time averages to zero and a component with a non-zero time average. The steady component is the radiation force, and arises because of propagation nonlinearities in the sound field. The absorption of energy in liquids in the field leads to a transfer of momentum, and thus fluid movement (acoustic streaming). The velocity gradients near boundaries that are associated with acoustic streaming may be high, and thus the shear stresses that are set up may be significant. Starrritt et al. [19] measured streaming velocities of 14 cm s$^{-1}$ in water during pulsed Doppler exposures, and 1 cm s$^{-1}$ during B-mode.

It is important to assess existing reports of ultrasonic bio-effects and safety research critically. There is a huge canon of literature on the topic, but very little directly addresses the exposure of mammalian tissue using clinically relevant devices. Despite this, there is useful information available. A useful first step in understanding a biological effect is to perform tissue culture experiments using cells grown either as a monolayer or in suspension culture. This offers the possibility of looking at the effects of ultrasound on isolated cell populations and using the sophisticated battery of techniques available for studying such systems. However, the aqueous environment in which cells are maintained is likely to promote effects due to cavitation and streaming, and to minimize thermal effects. Experiments carried out in intact tissues (whether in vivo or ex vivo) provide conditions that are more representative of human exposures, with more relevant tissue heating. Of course, ex vivo tissues, while providing a useful first step (and complying with a researcher’s obligation to respect the 3R’s of live animal experimentation—replacement, reduction and refinement [20]) may maximize thermal effects owing to the lack of blood perfusion. In vitro experimentation has the advantage of facilitating good ultrasound dosimetry. It is generally relatively easy to introduce a hydrophone (for example) into the sample holder in order to perform relevant field calibration. This is far more difficult in intact tissue. The ultrasonic exposure conditions within the tissue volume of interest under these circumstances are usually inferred from free-field measurements in a water bath and a knowledge of the acoustic properties of the tissues involved. An additional caveat to interpreting the bio-effects literature is a consideration of scaling. Most safety studies involve exposure of small rodents, which for most clinically relevant ultrasound beams irradiate a large proportion of their total body volume. This must be taken into account when interpreting the effects seen.

3. MACHINE OUTPUTS

One significant problem encountered in interpreting the ultrasound safety literature lies in understanding the exposure conditions used to induce a given effect, in order to relate them to those used clinically. The output of ultrasound transducers is usually measured in terms of the total acoustic power (using some form of radiation balance) and of acoustic pressure (using a hydrophone probe to map the field). Intensity distributions are usually derived from the measured pressure fields. The best papers in the literature describe the exposure conditions fully, giving the acoustic pressure (or intensity) distribution in the volume of interest, the frequency, the exposure time and the pulsing conditions where appropriate. A recent paper has described best practice in this regard [21]. The aim should be either that the conditions can be reproduced in another laboratory or that they can be related to clinical practice.

Whereas ionizing radiations have well-developed parameters for relating exposure (the amount of ionization produced in air, with units of roentgens) and the dose (the amount of energy deposited per kilogram in the region of interest (units of rads)), medical ultrasound makes no such distinction, with the terms exposure and dose being used (mistakenly) interchangeably. The literature often uses the terms ‘derated’ or ‘in situ’ to describe the intensity or pressure level at the point of interest. It is extremely difficult to measure these values in tissue in vivo and so they are usually inferred from a knowledge (or assumption) of the attenuation coefficients of overlying tissues in the beam path.

In a recent study, Martín [3] conducted a survey of five major ultrasound manufacturers, asking them for
output data from current ultrasound systems. The data provided conformed to either US Food and Drug Administration (FDA) or International Electrotechnical Commission (IEC) reporting formats. The data presented were ‘worst case’ values, that is, maximum values measured under free-field conditions in water. No attempt was made to quote ‘in situ’ values—that is, the values that would be measured (if this were possible) at the point of interest in the organ being examined. Martin [3] reported that median $I_{SPTA}$ values for B-mode scanning had increased from 6 mW cm$^{-2}$ in 1991 to 273 mW cm$^{-2}$ in 2010; for colour flow from 55 mW cm$^{-2}$ to 450 mW cm$^{-2}$, and for pulsed Doppler had dropped from 1070 mW cm$^{-2}$ in 1991 to 749 mW cm$^{-2}$ in 2010. $I_{SPTA}$ values for B-mode rose from 6 mW cm$^{-2}$ in 1991 to 67 mW cm$^{-2}$ in 1995, and from 94 mW cm$^{-2}$ in 1998 to 273 mW cm$^{-2}$ in 2010. The comparison was made with surveys published by Duck & Martin [22], Henderson et al. [23] and Whittingham [24]. The change in values of peak negative pressure ($p_{n}$) shows similar increases, but, in this case, there is also a rise for pulsed Doppler: B-mode (2.1 MPa in 1991, 3.7 MPa in 2010) for pulsed Doppler rose from 1.6 MPa in 1991 to 4.2 MPa in 2010, and for colour flow from 2.3 MPa in 1991 to 4.2 MPa in 2010.

4. ANIMAL STUDIES

The ultrasound safety literature is now considerable and wide ranging. It is not appropriate here to try to review it in its entirety, and the reader is directed to excellent summaries such as that produced by AGNIR [1]. The effects of ultrasound on cells and tissues have been studied at a number of levels—in tissue culture in vitro, in ex vivo tissue preparations and in vivo. Each has its own advantages and disadvantages. In vitro cultures provide a liquid environment for the cells in which thermal effects are likely to be less important than in intact tissues. As pointed out above, in the aqueous media necessary to maintain cell viability, non-thermal mechanisms such as acoustic cavitation and streaming are likely to predominate. Effects that have been studied in cells maintained in culture conditions are lysis, cell division and ultrastructural, chromosomal, cytogenetic and functional changes. While effects have been seen, it is difficult to relate these to clinical diagnostic exposures.

The majority of in vivo studies have used ultrasound exposures more typical of therapy applications than of diagnosis. Very few researchers have used diagnostic ultrasound scanners, or fields representative of those used clinically, to expose tissues. The main difference between these applications lies in the way in which the ultrasound is delivered, with short pulses (1–10 μs duration, pulse repetition frequency approx. 20 kHz) being used for diagnosis, and tone burst (longer than 1 ms) or continuous wave being used for therapy. There is some overlap in pressure amplitudes and intensities used. In what follows, the emphasis will be placed on studies that have used exposures relevant to medical diagnosis. One of the earliest findings was that short exposures of the lungs of rodents, swine and monkeys to ultrasound could lead to peri-alveolar capillary rupture (this is often referred to as lung haemorrhage) [25–45]. The safety implications of these findings are unclear. Similar areas of haemorrhage have been seen where the gas-containing intestine of mouse was exposed [46]. It has also been reported that diagnostic ultrasound might reduce the number of epithelial cells in the crypts of the mouse small intestine undergoing mitosis, and significantly increase the number of apoptotic cells [47]. These effects were reported after exposure to 8 MHz B- and colour flow modes.

In general, there have been very few positive findings following ultrasound exposure of mammalian foetuses to ultrasound. Tarantäl & Hendrickx [48,49] and Tarantal et al. [50] used a commercial real-time sector scanner to expose macaques to pulsed 7.5 MHz ultrasound. They found a short-lasting statistically significant reduction in birth weight, and some short-term changes in behaviour. However, these findings have not been convincingly replicated in human epidemiological studies (see below).

Ang et al. [51] studied the effects of neuronal migration in mice following exposure in utero to diagnostic ultrasound on day 16 of gestation. The brains, removed 10 days after birth, showed no difference in brain size or gross cortical architecture, but there was a statistically significant dose-dependent difference in neuronal dispersion in animals that had been exposed to ultrasound for 30 min or more, with approximately 4 per cent more neurons in the experimental group of animals remaining in the deeper neuronal layers after 60 min of exposure, and not reaching the more superficial layers as had those in the control animals. In extrapolating these results to the human, a number of important factors must be considered. For experimental reasons, the pregnant females required restraint during exposure. This alone influences neuronal migration, as was shown by the increased dispersion in the sham control animals. In considering the ultrasound exposure level itself, it must be remembered that there is very little attenuation in the tissue path overlying the foetal mice, and so the in situ intensity is much higher than might be experienced by the human foetus. In addition, the whole mouse foetus is exposed, whereas only a small proportion of the human foetus would be using these probes. These factors make it difficult to extrapolate to human exposures. It is also not clear whether, in any case, these findings would have any functional significance, as the neurons involved may not persist.

Schneider-Kolsky et al. [52] performed a study on the effects on learning and memory of ultrasound exposure of foetal chick brain. Their findings suggested that B-mode exposure on day 19 of a 21 day incubation period had no effect on learning or memory, whereas 4–5 min of pulsed Doppler ultrasound did. This study suffers from many of the same limitations as the Ang work. The exposure conditions in ovo are impossible to interpret in relation to the human clinical investigations. It seems probable that significant reflections would be seen within the shell. No morphological studies were carried out.

In summary, it seems clear from the laboratory studies that have been reported that, while acoustic cavitation can lead to lysis of cells exposed in culture
conditions because of the low threshold for its induction in this aqueous environment, there is no effect on the reproductive ability of those that survive. This suggests that, unless there is significant cavitation-induced cell lysis in vivo, there should be little concern about damage to cellular DNA. There is evidence from animal studies that where gas bodies are present in tissue, such as in the lung or intestine, some bleeding may occur, although the importance of these findings to clinical safety is not fully understood. Foetal and embryonic studies have generally provided reassuring evidence for safety in the absence of obvious thermal effects. It is clear that the stage of development is an important factor in these studies. One study has demonstrated the potential for alteration of neuronal migration in the mouse brain, and, while the significance of this finding to clinical exposures is not fully understood, there remains the slight possibility that ultrasound may be able to induce subtle effects in the foetal brain [53].

5. HUMAN EPIDEMIOLOGY
As has been made clear above, the area of most concern for the safety of ultrasound lies in exposure of the embryo and foetus. Thus, the vast majority of human epidemiological studies have been on children exposed to ultrasound prenatally. It is certainly true that ultrasound has been used in obstetrics for several decades without any evidence of harm. Any effects that may have been caused by ultrasound examinations in pregnancy have been sufficiently few to preclude their attribution to the effects of acoustic radiation. However, absence of evidence of harm is not evidence of absence of harm, and it is important to conduct well-designed prospective epidemiological studies to establish the facts. The current ubiquitous usage of ultrasound for pregnancy screening purposes makes such studies almost impossible now, but there are existing studies in the literature. This area has been reviewed by a number of people, but most recently there has been a World Health Organization systematic review [54], and a Cochrane review [55]. A number of different endpoints have been studied. These include birth weight, perinatal mortality, neurological development, school performance and handedness. Of these, only handedness has shown any association with ultrasound exposure in utero.

Torloni et al. [54] considered 16 controlled clinical trials (the most rigorous type of epidemiological study), 13 cohort and 12 case-control studies. These were taken from the 6716 titles and abstracts that were screened, of which 61 papers were suitable for review.

The most widely studied adverse event has been birth weight. However, it seems clear that, for almost all except one study published between 1950 and 2007 (involving approx. 37,000 women), ultrasound exposure in vivo had no significant influence on mean birth weight [56–67]; only one study has given cause for concern [63]. In this Australian randomized controlled trial, half of the 2843 women studied were offered continuous wave Doppler ultrasound examinations five times in the third trimester. The controls received one diagnostic imaging ultrasound scan at 18 weeks. A statistically significant increase in the number of babies in the Doppler group with a birth weight below the 10th percentile (relative risk 1.35, 95% confidence interval 1.09–1.67) was reported but the difference in mean birth weight between the groups was not significant (25 g). Birth weight difference was not a formal hypothesis in this trial. A subsequent report from this group found no significant difference in mean weight, height, head circumference or other physical measurements at any age (measured separately for girls and boys) in the same group of children [68].

One of the goals of ultrasound screening in pregnancy is to reduce the rate of perinatal mortality. In this context, it is arguably more important that mortality is not increased by these investigations. Controlled trials and a cohort study involving approximately 250,000 women have demonstrated a non-significant reduction in perinatal mortality [69]. Similarly, no association has been found between ultrasound exposure and incidence of pre-term births, admission to neonatal intensive care, and low Apgar scores at 5 min [54].

Eight studies of childhood malignancies have provided data on more than 14,000 children, with no association being found, even when sub-groups for leukaemia [70–74] and central nervous tissue tumours were considered [70,75,76]. There have been four published studies addressing potential harm to the developing foetal brain, as manifested by dyslexia, delayed speech development, impaired vision and hearing and a number of other outcomes. These involved approximately 6000 children in total [77–81]. Although two of these studies, one a case-control study and the other a cohort study, found a possible association between ultrasound exposure and dyslexia, the much larger controlled trials [79–81] found no statistically significant associations. It thus seems unlikely that the foetal brain is damaged by ultrasound exposure in utero [54].

Salvesen et al. [82] could find no association between school performance in 8–9 year olds (arithmetic, spelling and reading scores) and in utero ultrasound. A more recent study [83] found no statistical significance for children aged 15–16 years; although boys tended to have lower grades, this was not statistically significant.

Kiefer et al. [84] found an increased risk of subnormal intellectual performance in 18 year old men who had been exposed to ultrasound prenatally. However, they concluded that confounding socio-geographical factors meant that the ‘study failed to demonstrate a clear association between ultrasound and intellectual performance’. A different study was unable to find an association between ultrasound and schizophrenia [83].

The only finding that has been consistent over several surveys and epidemiological analyses is that of an increase in non-right handedness in boys exposed to ultrasound in utero. This was first reported by Salvesen et al. [55,85] in 8–9 year olds. These findings were replicated by Kiefer et al. [87]. Meta-analysis of these studies has been conducted [54,55,88,89]. The Cochrane review did not present gender-specific data, and failed to demonstrate this association; however, the other two papers were
able to confirm that one in 20 exposed male foetuses is likely to be non-right handed. The relevance of these findings is hard to gauge. Of course, being left-handed is not problematical, or abnormal in any way. However, it is an interesting question as to what has caused this, if it is indeed a real ultrasonically induced effect. This is an area that clearly would benefit from more investigation.

While the over-riding epidemiological evidence about prenatal exposures to ultrasound is reassuring from a safety viewpoint, it must be remembered that the ultrasound examinations to which these children were subjected involved ultrasound scanners that have long since been superceded. None of these were colour flow or pulsed Doppler examinations, and B-mode outputs have increased by more than an order of magnitude over the intervening years [3]. We therefore cannot be complacent, and must make sure that good practice is continued to maintain ultrasound imaging’s, to date, excellent safety record.

6. REGULATIONS AND GUIDELINES

Most professional bodies concerned with diagnostic ultrasound have safety committees which have issued clinical safety statements on topics of relevance to the ultrasound user, and in some cases also guidelines for good practice and safe use (British Medical Ultrasound Society (BMUS), http://www.bmus.org/policies-guides/pg-safety-statements.asp; American Institute of Ultrasound in Medicine (AIUM), http://www.aium.org/publications/statements.aspx; European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), www.efsumb.org; Australian Society for Ultrasound in Medicine (ASUM), http://www.asum.com.au/site/policies.php; International Society for ultrasound in Obstetrics and Gynaecology (ISUOG), http://www.isuog.org/ClinicalResources/Statements+and+Guidelines/Safety+Statements/; and WFUMB above others).

In Europe, ultrasound imaging manufacturers are required to meet the essential requirements for safety and effectiveness of the Medical Devices Directive, if their devices are to be sold in the European Union. This entails demonstrating acoustic safety by conforming to IEC standards for declaring output values (IEC 61157, 606-2-37 [90,91]). The situation in the USA is different in that the acoustic output levels are limited by the FDA. The maximum permitted $p_{PTA}$ is 720 mW cm$^{-2}$ for all applications other than ophthalmology, in which it is restricted to 50 mW cm$^{-2}$. This is known as track 3 for approval, and was introduced in 1992. With the exception of ophthalmology, this maximum level is application independent, and, at that time, the onus for safety was put back onto the user. On-screen labels of two indices, thermal and mechanical, were provided to help judgments about safety to be made. The mechanical index (MI), which is an indicator of the potential for cavitation activity in the absence of UCAs, is defined as

$$\text{MI} = \frac{p}{\sqrt{f}},$$

where $f$ is the frequency and $p$ here is the rarefractional pressure reduced to account for any attenuation that would occur in the tissue path to the measurement point using an attenuation coefficient of 0.3 dB cm$^{-1}$ MHz$^{-1}$. The model used to derive this formula predicts that cavitation is unlikely for MI < 0.7. The FDA track 3 limits MI to a maximum of 1.9.

The TI is defined as the ratio of the acoustic power for the conditions being displayed ($W$) to the power required to raise the temperature by 1°C ($W_{\text{deg}}$).

$$\text{TI} = \frac{W}{W_{\text{deg}}}.$$

Three different TIs have been defined, TIS, which is appropriate for soft tissues only; TIB, which is for use when bone lies at the focus; and TIC, for situations where bone lies near the skin surface, such as during neonatal brain scanning. The formulae used to calculate the thermal indices differ with scanned and non-scanned modes, and with different beam apertures (Output Display Standard, ODS [92]). The FDA track 3 limits TI to a maximum of 1.0 for ophthalmic applications, and 0.6 for all others.

The quid pro quo for this arrangement was that users would be educated in the importance of these indices. However, almost 20 years later, it is disappointing to see that this has not been very successful, with a number of surveys showing that less than 50 per cent of users could answer questions about these indices correctly [93–95]. In a recent survey of obstetric scans conducted within National Health Service (NHS) departments in the UK [96], maximum TIs observed during scanning were reported as ranging between 0.1 and 2.5 with a mean (± standard deviation) of 0.98 ± 0.69. The maximum TI (2.5) was found during a pulsed Doppler scan. In the same study, MI ranged from 0.2 to 1.6, with a mean of 0.74 ± 0.45. For trans-vaginal scans, TI ranged from 0.1 to 0.4 (mean 0.23 ± 0.15) and MI from 0.4 to 1.0 (mean 0.7 ± 0.22). In a similar survey carried out in an independent ultrasound clinic performing four-dimensional scans, the MI ranged from 0.4 to 1.3 (mean 0.99 ± 0.22) and the TI from 0.1 to 0.5 (mean 0.17 ± 0.08).

The BMUS has published guidelines for the safe use of diagnostic ultrasound. These guidelines tabulate recommended maximum scanning times for obstetric, neonatal and other applications (BMUS website and [97]). These times are based loosely on the thermal dose, while applying a safety margin, and identify different exposures in terms of the TI displayed. For obstetric scanning these times are

- $0.7 < \text{TIs} \leq 1.0$: 60 min
- $1.0 < \text{TIs} \leq 1.5$: 30 min
- $1.5 < \text{TIs} \leq 2.0$: 15 min
- $2.0 < \text{TIs} \leq 2.5$: 4 min
- $2.5 < \text{TIs} \leq 3.0$: 1 min

Scans involving TIs > 3.0 are not recommended. For scans up to 10 weeks after the last menstrual period TIS should be monitored, whereas, for later scans, it is TIB that is important.

Safety statements from all the professional bodies convey similar messages, namely that there is no reason to withhold diagnostic ultrasound during
pregnancy, provided it is performed by fully trained operators. The exception to this is the routine use of Doppler in the first trimester of pregnancy. This is discussed below.

The 2010 Clinical Safety statement from EFSUMB is typical of other such statements and is:

**Clinical Safety Statement for Diagnostic Ultrasound (2010)**

Diagnostic ultrasound has been widely used in clinical medicine for many years with no proven deleterious effects. However, if used imprudently, diagnostic ultrasound is capable of producing harmful effects. The range of clinical applications is becoming wider, the number of patients undergoing ultrasound examinations is increasing and new techniques with higher acoustic output levels are being introduced. It is therefore essential to maintain vigilance to ensure the continued safe use of ultrasound.

Ultrasound examinations should only be performed by competent personnel who are trained and updated in safety matters. It is also important that ultrasound devices are appropriately maintained.

Ultrasound produces heating, pressure changes and mechanical disturbances in tissue. Diagnostic levels of ultrasound can produce temperature rises that are hazardous to sensitive organs and the embryo/foetus. Biological effects of non-thermal origin have been reported in animals but, to date, no such effects have been demonstrated in humans, except when a microbubble contrast agent is present.

The thermal index (TI) is an on-screen guide to the user of the potential for tissue heating. The mechanical index (MI) is an on-screen guide of the likelihood and magnitude of nonthermal effects. Users should regularly check both indices while scanning and should adjust the machine controls to keep them as low as reasonably achievable (ALARA principle) without compromising the diagnostic value of the examination. Where low values cannot be achieved, examination times should be kept as short as possible. Guidelines issued by several ultrasound societies are available.

Some modes are more likely than others to produce significant acoustic outputs and, when using these modes, particular care should be taken to regularly check the TI and MI indices. Spectral pulse wave Doppler and Doppler imaging modes (colour flow imaging and power Doppler imaging) in particular can produce more tissue heating and hence higher TI values, as can B-mode techniques involving coded transmissions. Tissue harmonic imaging mode can sometimes involve higher MI values. 3D (three dimensional) imaging does not introduce any additional safety considerations, particularly if there are significant pauses during scanning to study or manipulate the reconstructed images. However, 4D scanning (real-time 3D) involves continuous exposure and users should guard against the temptation to prolong examination times unduly in an effort to improve the recorded image sequence beyond that which is necessary for diagnostic purposes.

**Ultrasound exposure during pregnancy**

The embryo/foetus in early pregnancy is known to be particularly sensitive. In view of this and the fact that there is very little information currently available regarding possible subtle biological effects of diagnostic levels of ultrasound on the developing human embryo or foetus, care should be taken to limit the exposure time and the Thermal and Mechanical Indices to the minimum commensurate with an acceptable clinical assessment.

Temperature rises are likely to be greatest at bone surfaces and adjacent soft tissues. With increasing mineralisation of foetal bones, the possibility of heating sensitive tissues such as brain and spinal cord increases. Extra vigilance is advised when scanning such critical foetal structures, at any stage in pregnancy. Based on scientific evidence of ultrasound-induced biological effects to date, there is no reason to withhold diagnostic scanning during pregnancy, provided it is medically indicated and is used prudently by fully trained operators. This includes routine scanning of pregnant women. However, Doppler ultrasound examinations should not be used routinely in the first trimester of pregnancy. The power levels used for foetal heart rate monitoring (cardiotocography – CTG) are sufficiently low that the use of this modality is not contra-indicated on safety grounds, even when it is to be used for extended periods.

**Safety considerations for other sensitive organs**

Particular care should be taken to reduce the risk of thermal and non-thermal effects during investigations of the eye and when carrying out neonatal cardiac and cranial investigations.

**Ultrasound contrast agents (UCA)**

These usually take the form of stable gas filled microbubbles, which can potentially produce cavitation or microstreaming, the risk of which increases with MI value. Data from small animal models suggest that microvascular damage or rupture is possible. Caution should be considered for the use of UCA in tissues where damage to microvasculature could have serious clinical implications, such as in the brain, the eye, and the neonate. As in all diagnostic ultrasound procedures, the MI and TI values should be continually checked and kept as low as possible. It is possible to induce premature ventricular contractions in contrast enhance.

7. CONTENTIOUS ISSUES

7.1. Pulsed Doppler during first trimester

Recent papers have advocated the use of routine pulsed Doppler measurement of the cardiac and infra-cardiac
regions of every first trimester foetus (11–13 + 6 weeks) [98]. It has become a contentious issue as to whether this practice should be condoned, and, perhaps more importantly, whether it is, in any case, needed. Although Kagan et al. [98] have argued for first stage testing in trisomy 21 screening based on maternal age and Doppler ultrasound, equally good results have been obtained using a two-stage nuchal translucency and biochemistry screening programme that does not require the use of pulsed Doppler [99].

While there is no evidence that pulsed Doppler in early gestation can cause harm, we cannot be completely certain that it is 100 per cent safe; if it were to have an adverse effect, this might be most likely to occur in the most vulnerable stage of foetal life, namely in the first trimester. Good practice would, therefore, suggest advocating restricted, or at least very cautious (rather than routine), use of pulsed Doppler at this time.

### 7.2. Souvenir scanning

Many professional ultrasound bodies have issued statements to the effect that the use of ultrasound solely for the production of souvenir scans (also known as keepsake or bonding scans) cannot be recommended, citing safety grounds as the basis for this (WFUMB, AIUM, ISUOG and BMUS). At first sight this may seem to contradict the ‘clinical’ safety statements from these same organizations in which routine scans during pregnancy are said to be safe. Of course, an ultrasound scan conducted in a souvenir scanning centre is not inherently more harmful than the same scan conducted for clinical reasons if carried out by a qualified practitioner. The difference between these scanning scenarios lies in the perceived benefit obtained versus any potential risk. A ‘routine’ obstetric ultrasound scan is conducted with the expectation that it will beneficially inform the management of the pregnancy, whereas a souvenir scan is solely for ‘recreational’ purposes. Thus, the clinically indicated scan should confer significant benefit, whereas the souvenir scan should not. A compromise is reached by conceding that providing a ‘souvenir’ image at the end of a clinically indicated scan does not add significantly to any potential risk, and may dissuade the pregnant mother from resorting to a high-street ‘boutique’ with unknown skills and qualifications to obtain such a scan [100,101].

### 8. SUMMARY AND CONCLUSIONS

The first mention that ultrasound could be used to produce images of the foetal head was probably in a lecture given by Ian Donald in 1959. Since that time, the use of ultrasound in obstetrics has grown rapidly, and has a generally accepted excellent safety record. However, it is impossible to prove zero risk, and the absence of evidence of harm should not be taken as evidence of absence of harm. The epidemiological evidence that exists is reassuring as to the safety of routine ultrasound scanning, but of necessity it only includes subjects who were imaged with devices that were state of the art at the time (mostly early 1980s). No pulsed Doppler or colour flow examinations are included, and the output from modern ultrasound scanners is considerably higher today than it was at that time. It is, therefore, essential to remain vigilant, and to assess new technologies and applications from a safety aspect as they arise.

Above all, ultrasound scans should only be carried out when there is a clinical need, and only by fully trained professionals who understand the modality and its safe use. This is especially vital for obstetric scanning.

### REFERENCES


78 Campbell, J. D., Elford, R. W. & Brant, R. F. 1993 Case-control study of prenatal ultrasonography exposure in


