Safety of Ultrasound With Selective Emphasis for Obstetrics

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ULTRASOUND EQUIPMENT EXPOSURE CONDITIONS

THE NEED to understand the physical concepts which quantify the output of ultrasound equipment is fundamental. Manufacturers of equipment are beginning to provide these types of data. As clinical ultrasound equipment and its usage increase in sophistication, and the output power levels increase as the frequencies increase in response to the demands for improved resolution, quantitative output data may become essential information to the physician in the diagnostic decision. This section discusses the output exposure quantities of power and intensity in terms of what they mean and what their typical values are for current clinical equipment. During these discussions, the terms "radiation" and "irradiation" are employed. These are physical concepts that describe the nature and process of energy being transmitted as a wave. They do not necessarily mean that the energy is ionizing. Throughout this article, the term radiation, when used by itself, means ultrasound radiation, and the term irradiation describes the wave process of ultrasonic energy.

Ultrasound Power and Intensity

The physical concept which most often is invoked to quantitatively describe the strength of the ultrasonic field is *intensity*. One of the principal reasons for the use of intensity is convenience, since intensity is relatively easy to measure. This does not mean that intensity is the best quantity. In fact, it probably is not best because it is not a measure of absorbed dose (the same problem occurs in measurement of exposure to ionizing energy). Because the vast majority of ultrasonic biological effect and biophysical studies report their findings in terms of the physical quantity intensity and the AIUM/NEMA* Safety Standard for Diagnostic Ultrasound Equipment[1] does likewise, a brief discussion and description of the various types of intensity are in order.

There are measurement techniques which determine intensity directly. But for diagnostic ultrasonic equipment, an easier and more meaningful physical quantity to determine is the temporal average ultrasonic power. It is easier because the measurement techniques employed are generally more sensitive to the temporal average power as compared to the temporal average intensity.[2] It is more meaningful because ultrasonic power is traceable to a standard at the US National Bureau of Standards and thus provides a fundamental basis from which all measurements can be compared.

Ultrasonic power is a measure of the rate of work being done by an ultrasonic field, therefore, power describes the potential by which the ultrasonic field can interact with the medium in which it is propagating. In general, ultrasonic power is reported as a temporal average quantity and has the unit of watt (W) or milliwatt (mW). The ultrasonic power magnitudes of therapeutic equipment are in the range of 1–50 W whereas those of diagnostic imaging and monitoring equipment are in the range of 0.1–100 mW.

Spatial Intensity Considerations

Intensity describes the spatial concentration of power in the unit of watt per centimeter squared (W/cm^2) or milliwatt per centimeter squared (mW/cm^2), the former unit being 1,000 times greater than the latter. If one considers the ultrasonic energy traveling away from the transducer, the space that the energy traverses is referred to as the beam, and the beam axis is a line down the center of the beam. The ultrasonic field distribution at a constant distance from the transducer (on a plane perpendicular to the beam axis) is not spatially uniform, that is, the intensity varies from point to point on this plane. As such, two spatial terms are used to modify intensity, viz., spatial peak (SP) and spatial average (SA). The spatial peak intensity is the highest

*AIUM = American Institute of Ultrasound in Medicine. NEMA = National Electrical Manufacturer's Association.

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valued intensity *in the plane* and is usually at the position in that plane where the beam axis intersects the plane. Another usage of the term spatial peak intensity is the highest valued intensity *in the field,* that is, it is the maximum intensity value when all of the infinite number of points in the infinite number of planes are examined within the ultrasonic beam. The AIUM/NEMA Safety Standard for Diagnostic Ultrasound Equipment[1] employs the latter usage for the spatial peak intensity, viz., at a point in the acoustic field where the maximum exists, and so in reporting the SP intensity, the distance from the transducer must be noted.

The spatial average intensity is that value of intensity which has been spatially averaged over some defined area in the plane perpendicular to the beam axis. This area is usually called the beam cross-sectional area. The ratio of the spatial peak to spatial average (SP/SA) intensity can range from 2 to 4 for unfocused ultrasonic fields and can range up to 50 or more for focused ultrasonic fields at the focus.

Temporal Intensity Considerations

For diagnostic ultrasound equipment, pulses of ultrasonic energy are emitted. Thus, the ultrasonic field is not temporally uniform (temporal uniformity does exist in a continuous wave ultrasonic field), and three temporal terms are used to modify intensity, viz., temporal average (TA), pulse average (PA), and temporal peak (TP). Typically, ultrasonic pulses are generated every 1 millisecond (pulse repetition period = 1 ms; pulse repetition frequency = 1 kHz). The time which the pulse is on, termed the pulse width, is about 1 microsecond (μs). The duty factor is the ratio of the time the pulse is on to the pulse repetition period, or about 1 μs/1 ms = 0.001. Therefore, the ratio of the pulse average intensity to the temporal average intensity is about 1,000, the reciprocal of the duty factor. Considering now the time during which the pulse is on, the pulse average value is the intensity value averaged in time over the pulse width, and the temporal peak value is the maximum value in time, irrespective of the spatial position. Due to nonlinear phenomena[3] the ratio of the temporal peak to the pulse average (TP/PA) intensity can range from 2 to 10.

To summarize with a numerical example, the typical ultrasonic power of diagnostic ultrasonic equipment is in the range of 1 mW with a beam cross-sectional area at or near the transducer surface of approximately 1 cm^2. Therefore, the output of a diagnostic system is about 1 mW/1 cm^2(1 mW/cm^2) and this value refers to the spatial average, temporal average (SATA) intensity at the radiating surface (note that the location has been specified). Utilizing this SATA intensity value for both the focused and the unfocused ultrasonic fields, the six intensity parameter values (the three temporal cases for each of the two spatial conditions) have been calculated and are listed in Table 1. For these calculations, the spatial peak to spatial average (SP/SA) ratios have been assumed to be 2 to 4 and 10 to 30 for the unfocused and focused fields, respectively. For a duty factor of 0.001, all of the respective pulse average (PA) intensity values are greater than the temporal average (TA) intensity values by a factor of 1,000. The temporal peak (TP) intensity values range from 2 to 10 times greater than their respective PA intensity values. Note that the SA intensity values are the same for both the unfocused and focused fields. Also note that while the SATA intensity value appears to be a quite small number, the SPTP intensity value for a focused field can be very much greater, by a factor of 10,000 or more in some cases. These values do represent typical numbers for the intensity quantity, and they are not surprising to an individual familiar with imaging system outputs. Manufacturers' descriptions of ultrasound imaging equipment,

Table 1. Calculated Values of the Six Intensities Based Upon a Spatial Average, Temporal Average Intensity.*

Quantity	Unfocused Field (SP/SA 2–4)	Focused Field (SP/SA 10–30)
Power†	1 mW	1 mW
SATA†	1 mW/cm^2	1 mW/cm^2
SAPA	1 W/cm^2	1 W/cm^2
SATP	2–10 W/cm^2	2–10 W/cm^2
SPTA†	2–4 mW/cm^2	10–30 mW/cm^2
SPPA†	2–4 W/cm^2	10–30 W/cm^2
SPTP	4–40 W/cm^2	20–300 W/cm^2

*SATA intensity of 1 mW/cm^2 (ultrasonic power of 1 mW and beam cross-sectional area of 1 cm^2). The calculations are based upon an SP/SA ratio of 2–4 for unfocused ultrasonic field and of 10–30 for focused ultrasonic field. Here, SA is spatial average, SP is spatial peak, TA is temporal average, PA is pulse average, and TP is temporal peak.

†Intensity quantities listed in Table 2.

however, frequently are only the smallest intensity values, thus leaving the uninitiated with an impression that the outputs from ultrasonic imaging systems are rather low.

Table 2 lists values for the ultrasonic power and three of the intensity quantities for various commercial diagnostic and therapeutic ultrasound units (SATA intensity in the plane at the transducer surface and SPTA intensity and SPPA intensity in the plane of the field where the SP intensity value is the greatest).[1,4] Note that the values in Table 1 are based upon an SATA intensity of 1 mW/cm^2. Since the actual SATA intensity values for the diagnostic units in Table 2 range from about 0.1 to 100 mW/cm^2, the listed SPTA and SPPA intensity ranges are quite typical of current equipment and are in general agreement with the calculations of Table 1.

The US Food and Drug Administration recently reported[5] the output for 90 transducers used in fetal imaging systems. The SPTA intensity for these transducers ranged from less than 1 mW/cm^2 to about 180 mW/cm^2. This range is consistent with the ranges listed in Tables 1 and 2. The FDA report further indicated that the SPTP intensity for these transducers ranged from less than 1 W/cm^2 to over 1,000 W/cm^2. This SPTP intensity range is generally consistent with the calculated range in Table 1, considering the fact that for Table 1, a specific SATA intensity value was assumed, and that in actuality it has a considerable range. However, the SPTP intensity (also referred to as the instantaneous peak intensity)[4,6] values which are reported must be viewed with some caution because of technical measurement difficulties and because of nonlinear propagation properties of the medium. There is no agreed-upon procedure to determine this particular quantity, but the calibrated, broad-band polymer hydrophone has been used with some measure of success.[3,6–9]

EXTENT OF USE

An important consideration with respect to the evaluation of risk is an estimate of the extent of ultrasonic exposure which the patient receives. But this may not be a good indicator as to the amount of ultrasonic energy which the patient population or a particular organ system receives because (1) the number of examinations a patient receives is generally unknown, (2) multiple examinations may be performed with different types of equipment, and (3) the amount of ultrasonic energy that a patient receives varies from exam type to exam type and from examiner to examiner. Yet, while no statistically based survey is known to have documented the extent to which ultrasound has been used over the past fifteen years, a number of indicators suggest that its use is increasing and that a large fraction of the human population will eventually be exposed, especially in utero.

In 1971, the US Food and Drug Administration's Bureau of Radiological Health surveyed 301 out of 6306 short-term hospitals in the United States and found that 12% of the hospitals used diagnostic ultrasound.[10] The same Federal agency reported on the conduct of its 1974 hospital survey that 35% of the surveyed hospitals used diagnostic ultrasound.[11] This represented an almost 200% increase in use between the 1971 and 1974 surveys (assuming of course

Table 2. Summary of Ranges of the Ultrasonic Power and the Three Ultrasonic Intensities Determined From Commercial Clinical Ultrasonic Equipment.

System	Ultrasonic Power	SATA on Radiating Surface	SPTA at Maximum SP Value	SPPA at Maximum SP Value
Static Pulse-Echo Scanners	0.5–20 mW	0.4–20 mW/cm^2	10–200 mW/cm^2	0.5–280 W/cm^2
Automatic Sector Scanners	3–20 mW	2.7–60 mW/cm^2	6–200 mW/cm^2	25–100 W/cm^2
Sequenced Linear Arrays	0.1–33 mW	0.06–10 mW/cm^2	0.1–12 mW/cm^2	0.2–100 W/cm^2
CW Doppler (Obstetrical)	1–37 mW	0.2–20 mW/cm^2	0.6–80 mW/cm^2	
Pulsed Doppler (Cardiac)	8–24 mW	3–32 mW/cm^2	50–290 mW/cm^2	3–14 W/cm^2
CW Doppler (Peripheral Vascular)	6–105 mW	38–840 mW/cm^2	0.1–2.5 W/cm^2	
Pulsed Doppler (Peripheral Vascular)	6–10 mW	87–175 mW/cm^2	350–700 mW/cm^2	1–12 W/cm^2
CW Therapy	1–50 W	1–5 W/cm^2	1–10 W/cm^2	

Data obtained from AIUM/NEMA[1] and from NCRP.[4]

that the surveys were essentially identical), for an annualized increase of 43% during this time. The 1974 survey[11] further showed that an estimated 16% of the obstetric services in the United States used diagnostic ultrasound and that about one-third of all US births for 1974 were delivered in these hospitals. Additionally, it was estimated that 470,000 pregnant women were exposed to diagnostic ultrasound in that year with about 35–40% of these women being examined more than once. In the more recent National Council on Radiation Protection and Measurement report,[4] it has been estimated that 40–60% of all ultrasonic imaging examinations are performed for obstetrical purposes.

An examination of records in one US hospital setting[12] for two different years, 1975 and 1978, indicated that in 1975, 11% of the lowest-risk pregnancy population was examined with ultrasound while 21% of that same risk population was examined in 1978. For the highest-risk pregnancy population, these percentages were 66 and 76 for 1975 and 1978, respectively. An evaluation of these data shows that the use of ultrasound in the lowest-risk pregnancy population is increasing at an annualized rate of about 25%, whereas, for the highest-risk population, it is about 5%. It appears that the rate of increase is greater in the lowest-risk population, which probably does not generally present with clinical problems. In the population which exhibits clinical problems, the use is much greater, but the increase in use is not very high, owing perhaps to the fact that ultrasound is a relatively well established diagnostic tool for this population of patients.

Sales growth information indicates that in 1976, the ultrasonic industry's annual US dollar sales were around $30 million[13] and for the following year about $40 million.[14] In the next four years, estimates of annual sales were $50, $79, $170, and $214 million.[15] An increase from $30 million to $214 million from 1975 to 1980 represents an estimated average annual increase in sales of approximately 48%. In terms of the number of diagnostic devices, it was estimated that 3,500 systems had been sold in 1976 and this number would be around 12,400 in 1982,[16] for an annualized increase of about 24%.

The above data and reports represent the extent of use in the United States. Thus, in summary, if one were to estimate that about one-half of all pregnant women are currently being examined with ultrasound and, additionally, that its usage is increasing at an annual rate of 10–25%, then within a few years, virtually every fetus could be examined with ultrasound.

In countries other than the United States, no surveys or comparable data are available. In the United Kingdom, it has been estimated that in the early 1970s the number of ultrasonic diagnostic examinations was doubling every three years,[17] thus representing an annualized 26% increase. An international mail survey (which included the United States) suggested that between 1963 and 1971, there was an average annual increase in use of clinical ultrasound of approximately 10%.[18] In West Germany, official guidelines adopted in 1980 recommend the use of two ultrasound examinations during pregnancy,[19] and in the United Kingdom, the Royal College of Obstetrics and Gynecology recommends that one screening ultrasonic examination be performed in every pregnancy.[20] In Canada, a survey suggested that between 340,000 and 620,000 patients were examined with diagnostic ultrasound in 1977.[21]

Thus, outside of the United States, there appear to be areas where screening is being recommended for all pregnancies. For the United States, at least one National Institutes of Health (NIH) document[20] recommends against such screening.

SELECTED EXPERIMENTAL STUDIES

Most of the ultrasonically induced developmental-effect studies have been conducted on the fruit fly *Drosophila melanogaster* and on rats and mice. Many of the studies dealing with the effects of ultrasound on fetal abnormalities and on growth and development are conflicting. There have been high-level ultrasonic exposure studies of pregnant mice or rats which have yielded no effects;[22–24] whereas, in other experiments in which pregnant mice or rats were ultrasonically exposed at lower levels (in some cases, diagnostic levels of ultrasonic energy were used), the results have suggested the possibility of structural and/or functional alterations to the fetuses.[25–29] This section selectively examines the experimental observations of fetal growth and development in these three animal systems and

attempts to offer some explanation as to the apparent conflicting observations.

Studies of D. melanogaster

One of the earliest studies to examine ultrasonically induced developmental abnormalities used the *D. melanogaster*. The specimens were irradiated with continuous wave ultrasound (800 kHz; SA intensities of 0.7 to 4.0 W/cm^2; exposure times of 30 sec to 25 min) at different stages of development. The egg, larval, and prepupal stages were more susceptible to damage than the later stages of development. The abnormalities reported were similar to those induced by ionizing radiation but unlike those which are caused by simple heat.[30]

Other fruit fly studies[31] showed that a large fraction of the embryos developed abnormally following ultrasonic exposure (CW, 1 MHz, SA intensities of 0.3 and 0.5 W/cm^2, exposure time of 30 sec) at the syncytial blastoderm stage, that is, 2 hr after laying the eggs. An extension[32] of this study to various exposure conditions (CW, 1 MHz, SA intensities of 0.05, 0.1, 0.23, 0.5, and 1.2 W/cm^2, exposure time of 30 sec) and at various developmental stages at the time of exposure (15, 60, and 120 min after laying) led the authors to suggest that ultrasonic exposures of less than 100 mW/cm^2 (presumably SA) for an exposure time of 30 sec had an insignificant effect upon the normal development of *Drosophila* since a dose–effect response was suggested.

In these early *Drosophila* studies, the dosimetry must be suspect since few details were provided. However, these studies did represent a quest for obtaining such data some 30 yr ago and to that extent suggest the possibility that prenatal exposure of ultrasonic energy was examined in terms of inducing abnormal growth and/or development. Also, it should be noted that the current ionizing radiation protection guidelines are, to a large extent, based upon ionizing radiation studies of *Drosophila*.[33]

These early CW ultrasonic biological effect studies with *Drosophila* have been more recently confirmed under much better dosimetric conditions.[34,35] The interesting feature of this class of work is that the investigators can essentially reproduce and confirm the earlier findings; therefore, the contemporary work can aim at an assessment of the mechanisms responsible for the biological alterations. Without a fundamental understanding of the causes for specific biological effects in experimental animal systems, our ability to extrapolate these or any other findings to the human, for purposes of radiation protection, is severely limited. The reason that the *Drosophila* studies were so useful in assessing ionizing radiation protection guidelines was that a basic understanding existed about the interaction mechanisms of ionizing radiation. Herein lies the basic importance of animal experimental studies.

Returning to the *Drosophila* studies, their larvae contain stabilized, reproducible populations of gas. They thus have become rather attractive animals for studying the role of cavitation and its influence in producing biological alterations. While it is not known whether humans naturally contain these types of gas populations, it might be possible to produce similar types of gas populations artificially through injections of certain types of contrast materials. Thus, by studying *Drosophila,* one may be able to gain some insight into whether, perhaps, ultrasonic contrast materials will represent a biological risk by providing the "seeds" for specific types of cavitation. This is, of course, a hypothetical argument but the general approach is still valid, viz., understanding the fundamental mechanism greatly enhances the chances of knowing what diagnostic ultrasound will do in humans.

Studies of Biomolecules and Cells

Ultrasonic biological effect studies on biomolecules have mainly increased our understanding of the cavitation type of mechanism.[4,20,36–38] Such studies on cells[4,15,20,37,39,40] have done likewise but, additionally, have created great concern in the diagnostic ultrasonic community. This concern arose because of the results from two related classes of ultrasonically induced biological effects, viz., genetic effects and sister chromatid exchange effects.

There does not appear to be any strong evidence which links ultrasonic exposure to genetic effects at either therapeutic or diagnostic ultrasonic energy levels. What is known is that isolated deoxyribonucleic acid (DNA) macromolecules can be degraded by ultrasound as can

almost any other biological molecule when it is subjected to cavitation. Classical chromosome aberrations did not appear to be induced by ultrasound although other types of chromosome alterations have been observed,[41,42] but at relatively high energy levels. What has permitted us to develop a reasonable experience in this area dates back to 1970 when Macintosh and Davey[43] reported a significant increase in the number of chromosomal aberrations after in vitro irradiation of cultured human lymphocytes to CW (Doppler) ultrasound. This report caused great concern because a commercial fetal heart detector was used, raising the distinct possibility of risk to patients and fetuses; therefore, numerous researchers attempted to determine the validity of the findings (reviewed by Thacker).[44] A second report by Macintosh and Davey[45] not only attempted to verify their original findings that ultrasound induced chromosome damage but also extended the study to show a "threshold intensity" of 8.2 mW/cm^2 for a 1-hr exposure. However, an additional followup study showed that the high incidence of aberrations previously reported could not be reproduced by the same principal author.[46] It was suggested furthermore, that the earlier positive findings may have been due to some yet unidentified artifact unrelated to the ultrasonic irradiation.

It is possible to learn from this particular situation that a single isolated report must be carefully reproduced. The foundation of science is the confirmation of work. When a large number of investigators bring their resources to bear onto a specific problem area, a reasonable understanding results.

More recently, the examination of ultrasound effects on genetic material has focused upon sister chromatid exchange (SCE) frequency, an indicator of chromosome damage. SCEs are used to screen for potential mutagenic agents, but it must be noted that the biological significance of SCEs is not well understood.[47] Liebeskind's study[48] has received perhaps the greatest attention, since the study indicated that exposure to a diagnostic ultrasound device caused an increase in SCEs in human lymphocytes and in a human lymphoblast cell line. In another study from the same laboratory,[49] no change was reported in SCEs in a different cell type. Thus, from the same group of researchers, there have been both positive and negative observations with respect to ultrasonically induced SCEs. There have been two other positive observations of increased SCEs in which human lymphocytes were exposed at diagnostic levels[50,51]; hence, a total of all three positive findings[48,50,51] of increased SCE frequency have resulted from diagnostic levels of ultrasonic energy. On the other hand, there have been at least 8 other studies, some at diagnostic levels, some at much higher levels, which have reported no increase in SCE frequency.[52–59a] The reasons for these differences are not known, but differences in experimental technique should be considered since none of these experiments were conducted under identical conditions. Additionally, only three of the studies[48,49,59,59a] included positive controls, a serious omission particularly when reporting negative findings.

Caution must be exercised in assessing the significance of biological alterations such as increased SCEs as discussed above, or other such observations to be discussed subsequently. Biological alterations are simply observations, and whether or not ultrasound will be shown to represent a significant risk in humans will depend upon the types of effects observed, the exposure levels at which these effects occur, their dose–effect responses and the assessment of the mechanism from dose–effect data. These studies are useful, however, in pointing both to potentially hazardous and potentially therapeutic interactions of ultrasound.

Rodent Embryo and Fetus Studies

Over the last few years, experimental observations have been made which suggest that subtle effects occur in rodent embryos and fetuses when exposed to ultrasound in utero. The balance of this section selectively examines ultrasonically induced fetal effects in experimental animals with emphasis upon one specific observation, viz., ultrasonically induced fetal-weight change. In choosing this observation, an attempt has been made to approach the assessment of risk from ultrasound for this single biological endpoint. In a chemical and physical sense, it is not known whether the products of conception are very sensitive to ultrasonic energy, but clearly they are sensitive from an emotional and, perhaps, political point of view.

The two fetal parameters of greatest potential

value in assessing ultrasonic effects are weight and the incidence of anomalous development. The literature for both of these parameters is quite large, with teratological reports numbering around 40 and fetal weight reports around 32. There is no complete review of either subject and this report will not do so either. However, the size of this literature should suggest that we know quite a lot about how ultrasound interacts with the fetus, but in fact, we still know very little because most of these reports are incomplete in one way or another, and dose–effect observations are difficult to deduce.

Of the approximately 32 studies which reported the effect of in utero ultrasonic irradiation on fetal and/or neonatal weight, 10 of the studies used rats as the experimental animal and 22 used mice. Listings of these studies are provided in Tables 3 and 4. The two tables separate reports that do (Table 3) or do not (Table 4) provide data that would support the comments and conclusions. Essentially, all of the exposure conditions used in these studies fell outside of the levels of exposure employed in diagnostic ultrasound. This observation does not, in and of itself, weaken the importance of the studies but helps to place them in perspective.

All of the studies that used rats as the experimental animal were essentially negative; that is, the reports concluded that ultrasound did not influence fetal or neonatal weight, with the exception of one positive study[25] that utilized diagnostic-level pulsed ultrasound. A very recent attempt[60,61] to duplicate the experimental conditions of this single positive study failed to confirm the previously observed adverse effects on fetal weight. Based on these studies, it is reasonable to conclude that ultrasonic irradiation does not adversely affect fetal or neonatal growth of rats. However, these experiments do not appear to add much to our understanding of risk assessment, for it is not known whether or not the rat is the correct experimental model for this particular biological alteration. The rat fetus simply may

Table 3. Reports That Provide Data on Fetal Weight and/or Neonatal Weight Under Experimental Conditions in Which In Utero Ultrasonic Exposure of the Pregnant Rat or Mouse was Performed.

Animal/Strain	Ultrasonic Delivery	Weight Results		Stats	Reference
		Fetal	Neonatal		
Rat/Wistar	3.2 (CW)	N	—	Yes	24
Rat/Sprague Dawley	2.25 (PW)	P	—	No	25
Mouse/CF_1	1.0 (CW)	N	P	Yes	26
Rat/Sprague Dawley	2.25 (PW)	N	—	Yes	60
Mouse/DHS	2.25 (CW)	N	—	Yes	62
Mouse/DHS	2.25 (CW)	N	—	Yes	66
Mouse/HeMk	2.25 (CW)	P	—	Yes	66
Mouse/LAF_1/J	1.0 (CW)	N	N	Yes	67
Rat/Charles River	2.5 (CW)	N	—	Yes	69
Mouse/CF_1	1.0 (CW)	P	—	Yes	70, 71
Mouse/LAF_1/J	1.0 (PW)	P	—	Yes	72, 73
Mouse/CFW	2.0 (CW)	P	—	Yes	74
Mouse/CFW	2.0 (PW)	P	—	Yes	74
Mouse/ICR	1.0 (CW)	N	—	Yes	76
Mouse/LAF_1/J	1.0 (CW)	N	—	Yes	77
Rat/not given	2.25 (CW)	N	—	No	110
Mouse/dd	2.3 (CW)	P	—	Yes	111
Rat/Wistar	2.3 (CW)	—	N	Yes	112
Mouse/CFW	2.0 (CW)	—	P	Yes	113
Rat/Charles River	0.8 (CW)	N	—	Yes	114
Rat/Wistar	0.8 (CW)	N	—	Yes	115

The notation (P) indicates that some aspect of the data showed a statistically significant effect with respect to the sham and/or the authors of the report provided the conclusion that the effect was positive. The notation (N) indicates that the data did not show a statistically significant effect and/or the authors of the paper provided the conclusion that the effect was negative. The dash (—) indicates that the report did not include that aspect of the study for the conditions listed. The indication of whether statistical analyses were performed refers only to the specifically indicated weight results; it does not indicate necessarily that the negative effect is statistically significant, only that a statistically significant difference was not obtained. The ultrasonic delivery indicates the ultrasonic frequency in MHz and whether the exposure was continuous wave (CW) or pulsed (PW).

Table 4. Reports That Provide a Conclusion About but No Data Within Report on Fetal Weight and/or Neonatal Weight Under Experimental Conditions in Which In Utero Ultrasonic Exposure of the Pregnant Rat or Mouse was Performed.

Animal/Strain	Ultrasonic Delivery	Weight Results		Stats	References
		Fetal	Neonatal		
Mouse/SASICI	1, 2, 3 (PW)	N	—	No	22, 23
Mouse/ICR	1.0 (CW)	P	P	Yes	27
Mouse/ICR	1.0 (CW)	P	P	Yes	28, 29
Mouse/ICR/IL-Wei	2.28 (CW)	N	N	No	68
Mouse/CF_1	1.0 (CW)	—	P	Yes	75
Mouse/ICR	2.0 (CW)	N	—	Yes	116
Rat/Wistar	0.7, 3.2 (CW)	N	—	No	117, 118
Rat/Wistar	2.5 (PW)	N	—	No	117, 118
Rat/Wistar	0.93 (CW)	—	N	No	118, 119

The notation (P) indicates that the authors of the report provided the conclusion that the effect was positive. The notation (N) indicates that the authors of the report provided the conclusion that the effect was negative. The dash (—) indicates that the report did not include that aspect of the study for the conditions listed. The indication of whether statistical analyses were performed refers only to the specifically indicated weight results; it does not indicate necessarily that the negative effect is statistically significant, only that a statistically significant difference was not obtained. The ultrasonic delivery indicates the ultrasonic frequency in MHz and whether the exposure was continuous wave (CW) or pulsed (PW).

not be susceptible to weight alteration from ultrasound. As Carstensen and Gates[61] so eloquently stated the case of negative findings:

> Negative screening studies have relatively little scientific value. If experiments are not guided by rational postulates and the results are negative, it simply means that the investigator was looking for the wrong endpoint under the wrong exposure conditions or perhaps that the methods were not sensitive enough to detect subtle effects which actually were present.

Among mice studies that have been reported,[22,23] one group exposed pregnant mice to pulsed ultrasound under 13 different exposure conditions† at various ages of gestation‡ and subsequently examined the fetuses at either the 18th or 19th day of gestation. Statistical analyses were performed and it was concluded that there was no effect on litter size, resorption rate, or abnormality rate. Although each fetus was weighed, there was no mention in the report of any statistical analysis or any specific conclusion as to whether fetal weight was affected. The authors generally concluded that the study was negative.

One of the more controversial studies reported the effects from prenatal ultrasonic exposure of pregnant mice (strain: DHS) in which the ultrasound source was a commercial fetal Doppler device.[62,63] Irradiations (CW, 2.25 MHz, SA intensity of 40 mW/cm^2, exposure time of 5 hr) occurred on the 9th day of gestation. Fetal abnormalities were observed in both the irradiated and the control groups but these differences were not significant. However, the rate of fetal death was increased significantly in the irradiated group. These same researchers also reported[62,64] a statistically significant increase in fetal abnormalities in a different mouse strain (A/He) and reported a significant effect on fetal mortality. It appears that prolonged induction of a moderate temperature rise may have been responsible for these observations.[65] In a more complete presentation and discussion in which the two mouse strains (DHS and A/HeMk) were tested for fetal malformations,[66] mean fetal weight and fetal mortality following in utero ultrasonic exposure (CW, 2.25 MHz, SA intensity of 40 mW/cm^2, exposure time of 5 hr). The conclusions from this study were, (1) malformations were increased at a statistically significant rate in the A/HeMk strain only, (2) a statistically significant decrease in mean weight occurred in the A/HeMk strain only, and (3) a statistically significant increase in late prenatal mortality was observed in both strains. The suggestion from this study that there may be a strain-specific effect or effects is interesting in comparison to a similar suggestion more recently made that a strain-specific effect may be respon-

†1.0, 2.0, and 3.0 MHz: SATP intensities from 0.75 to 27 W/cm^2; SPTP intensities from 20 to 490 W/cm^2; exposure times were typically 300 sec.

‡5 groups at gestational age (GA) 8; 3 at GA 5; 1 at GA 5, and 8; 1 at GA 8, and 9; 1 at GA 1, 7, 10, and 12; 1 at GA 3, 5, 6, and 8; and 1 control.

sible for ultrasonically induced weight reduction in some strains of mice and not in others under similar exposure conditions.[67]

The report of another mouse study,[68] supposedly negative, contains contradictions about the effects of in utero ultrasonic exposure. In this work, pregnant mice were exposed to ultrasound (CW, 2.28 MHz; SA intensities of 0.16, 0.27, 0.49, and 1 W/cm; exposure times of 5 and 10 min) at various gestational ages (8 to 16 days). The authors reported ". . . the fetuses were small and shrunken, with oligoamnion . . ." for the 1 W/cm^2 exposure conditions. In the article's conclusion, however, it was stated that "This relatively high intensity was tolerated by the animals, and there were no deleterious behavior or structural effects in the mother, their fetuses, or the neonates. . . ." In other words, the authors' conclusions were essentially negative but their results do not appear to support this conclusion.

An examination[69] of the effects of multiple prenatal exposure (gestational ages of either 8, 9, and 10 or 11, 12, and 13 days) from a commercial prototype of a fetal Doppler device (CW, 2.5 MHz, SA intensity of 9.1 mW/cm^2, exposure times of 30 min or 2 hr) showed that the rat fetuses examined at day 20 of gestation had no significant differences in fetal and maternal weight, viability, death, litter size, implants, and external and soft tissue abnormalities. Incomplete or absent ossification of strenebrae was present in 50% of the irradiated and 36% of the controls but it was suggested that there was no biological significance since the effect was predominantly in the 30-min-exposure group, not the 2-hr-exposure group. It is also interesting to observe that, in the 2-hr-exposure group, the animals exposed on days 8, 9, and 10 of gestation showed a 12% increase in fetal weight at day 20 of gestation compared to the sham and those animals exposed on days 11, 12, and 13 of gestation showed a 15% reduction. With such large percentage changes of mean fetal weight between sham and exposed groups, it is surprising that the statistical analysis did not yield significance unless the number of animals used for the study were too small.

One of the more comprehensive classes of studies which investigated fetal weight reduction in mice from in utero ultrasound exposure has resulted in a dose–effect observation which can be applied to making an assessment of risk relative to dose. Continuous wave exposure conditions were applied on the 8th day of gestation and the fetuses were examined on the 18th day of gestation. The studies suggested that in utero ultrasonic irradiation affected prenatal growth and development because a statistically significant fetal weight reduction (from 6–18% relative to the sham) was observed.[70,71] There were seven exposure groups (CW, 1 MHz, SA intensities from 0.5 to 5.5 W/cm^2, exposure times from 10 to 300 sec) and a dose–effect dependence of exposure condition versus average fetal weight was identified. Even though the actual exposure conditions of this study did not overlap diagnostic exposure conditions, the extrapolation of the dose–effect response from this study back to diagnostic exposure conditions showed that the fetal weight reduction would be quite small, perhaps even biologically insignificant (for a CF_1 mouse).[71]

The observation that in utero ultrasonic exposure can cause weight reduction in mouse fetuses compared with the sham has been confirmed by two other research groups using two different strains of mice. In one study (Fry et al.),[72] very high level, pulsed ultrasound conditions were employed (1 MHz, SPTA intensity of 50 W/cm^2, SPTP intensity of 2,936 W/cm^2, exposure time of 20 sec) and a significant reduction in fetal weight was reported. The mice were exposed to ultrasound on the 8th day of gestation and the fetuses were examined on the 18th day of gestation. The later report[73] indicated that the highest exposure conditions (1 MHz, SPTA intensity of 51 W/cm^2, SPTP intensity of 1,936 W/cm^2, exposure time of 20 sec) produced a statistically significant 18.8% fetal weight reduction relative to the sham whereas at a SPTA intensity of 45 W/cm^2 (SPTP intensity of 1,936 W/cm^2) for the same exposure time there was no change in the fetal weight relative to the sham. The other research group reported[74] fetal weight reductions ranging up to 25% relative to the sham when the mice were exposed (CW, 2 MHz, SA intensity of 1 W/cm^2, exposure times from 80 to 400 sec) at 0, 7, and 12 days of gestational age, and the fetuses were examined on the 17th day of gestation.

The question of whether fetal weight reduction is sustained postweaning has also been ad-

dressed. In a preliminary study,[75] conducted at lower ultrasonic intensity, time-mated CF_1 mice were irradiated on the 13th day of gestation (CW, 1.0 MHz, SA intensities of 0.25 and 0.80 W/cm^2, exposure time of 2 min) and examined at 55 days postconception (about 2 wk postweaning). Statistically significant weight reductions of 8.7 and 14.8%, respectively, relative to the sham were reported. However, a followup study[26] did not confirm this earlier finding of sustained postweaning weight reduction. Rather, a weight gain compared to the sham was reported. Utilizing a different mouse strain (ICR), this same research group[27–29] ultrasonically exposed pregnant mice (CW, 1.0 MHz, SA intensities of 0.075 and 0.75 W/cm^2, exposure time of 2 min) at various ages of gestation (4, 10, and 14 days) and analyzed the fetuses at day 18 of gestation and the offspring at 21 and 200 days postconception (DPC). Body weight, mortality and, in the 200 DPC group, selected organ weights were recorded. The general conclusion provided in their abstracts[28,29] was that "... statistically significant differences across exposure groups were found in several of the measures, although there was not always a consistent trend in weight with increasing exposure." In another of their abstracts,[27] the same laboratory reported a statistically significant difference across exposure groups in fetal weight on the mice exposed on day 4 of gestation, with the exposed group weighing less than the nonexposed.

This group also has reported that no statistically significant difference was observed in the rate of visceral or skeletal defects, as compared with a control group, in ICR mice exposed in utero on day 8 of gestation (CW, 1.0 MHz, SA intensities of 0.05, 0.5, and 1.0 W/cm^2, exposure time of 2 min) and examined on day 17 of gestation.[76] Neither were there statistically significant differences in mean fetal weight or in maternal body weight gain in this study, but these fetal weight results do not agree with other reports from the same researchers discussed above.[27–29] The only apparent difference in experimental technique is the gestational ages of exposure (day 8 for the negative findings and days 4, 10, or 14 for the positive findings). The mice came from the same colony and the exposure technique was the same for both experimental observations.

Fetal weight reduction was also not observed in two separate studies in which LAF_1/J mice were exposed on the 8th day of gestation (CW, 1.0 MHz, SP intensity of 2.5 W/cm^2, exposure time of 20 sec) and examined on the 18th day of gestation,[67,77] and in one of these studies, there was also an absence of weight change in the mice pups examined at days 21, 29, and 42 postconception.[67]

EPIDEMIOLOGIC STUDIES

The epidemiologic studies can be categorized into three groups, viz., those in which infants were exposed and examined,[78] those in which fetuses were exposed in utero and the children were examined following birth,[79–82] and those in which fetuses were exposed in utero and fetal outcome was assessed.[83,84] Severe limitations in each of these studies have been identified and a general conclusion of these studies is that they provide little, if any, data or properly derived conclusions to assess the safety of ultrasound.

Perhaps the most critical evaluation of the epidemiologic studies which aimed at assessing the safety of ultrasonic usage was reported in the Consensus Development Conference on Diagnostic Ultrasound Imaging in Pregnancy document.[20] In this document, the reports of Kohorn et al.,[78] Falus et al.,[79] Scheidt et al.,[80] Moore et al.,[81] Stark et al.,[82] Bernstine,[83] and Hellman et al.[84] have been critically discussed in detail. There have been other reviews[4,15,37,39,85] of this literature but they have not been as critical, complete, or detailed.

Further comment is in order about the Denver[81,82] and the Winnipeg study.[86–88] The Winnipeg study was not critically examined in the National Institute of Child Health and Human Development (NICHD) report[20] because the study details were not available. Both of these studies have suggested that in utero ultrasound produces an effect upon the weight of the children. Moore et al.[81] reported a significantly higher percentage of low birth weight infants while Stark et al.[82] found no such effect. It is of interest that both of these reports resulted from the same US Food and Drug Administration-funded study in Denver. The divergence of their conclusions appeared to result from data base differences. The NICHD report[20] analyzed both reports from the Denver study and concluded:

> . . . that a significant association of ultrasound with low birthweight was present in the study. However, the procedure for matching exposed and unexposed infants was probably not sufficient to have made them comparable in terms of complications that affect birthweight, and the association cannot be assumed to be causal.

Developmental, neurological, and psychological examinations of the children were part of the Denver study protocol and virtually no differences between the exposed and unexposed children (examined at ages between 7 and 12) were found. One exception was dyslexia, in which children exposed in utero to ultrasound had a higher percentage of dyslexia than the unexposed. This finding was true for all three hospitals in the Denver study although the differences were not statistically significant.[20]

The Winnipeg study has been reported only through meeting presentations[88] and abstracts.[86,87] There is a very large study currently under way that will consist of at least 10,000 pregnancies exposed to ultrasound. In a recent presentation,[88] it was suggested that decreased weight in children 4 yr old who were exposed to ultrasound in utero was significant when compared to the unexposed sibling. This suggestion, however, has not been subjected to peer review and thus should be viewed appropriately.

None of the epidemiologic studies reported herein were randomized. In order to gain a perspective of epidemiologic studies in general, and perhaps a better appreciation of the ultrasound epidemiologic studies reported above, the following discussion will be used to emphasize the importance of randomization. Without randomization, bias of the study results is possible. For example, consider a study in which the effect of ultrasound of human fetal weight is to be evaluated. A randomized design would call for equal numbers in the exposed and unexposed groups and the decision as to which group the individual is assigned would be random. But, if the study were not completely random, those patients in which a clinical problem was suspected or known to exist might be more commonly assigned to the exposed rather than the unexposed group. After all, when a clinical problem presents, the physician needs the diagnostic information from the ultrasound exam. Thus, in the unexposed group, all of the patients would be essentially normal, that is, there would have been no suspected clinical problem. And in the exposed group, essentially all of the patients with a suspected clinical problem along with all others who were assigned would be included. Now, if one of the endpoints tested for was birth weight, the analysis of the birth weight data might show that the average weight was lower in the exposed group as compared with the unexposed group. Does this now mean that ultrasound causes lower birth weight? No. This result would be quite logical, for the example created, because a fairly typical suspected clinical problem in pregnancy might have manifested itself as interuterine growth retardation. Thus, the biased selection process could have yielded a statistically significant but invalid finding.

In contrast to this example, four randomized clinical (not necessarily safety) studies[89–92] were reported within the last 4 yr. None of these studies showed any differences between in utero exposed and unexposed populations for mean birth weight.

GENERAL OBSERVATIONS

The use of ultrasound as a diagnostic tool in clinical medicine has possibly increased exponentially during the past decade or more. A very large literature describes the multiplicity of purposes for which ultrasound is either superior to, or is a valuable adjunct to conventional radiographic techniques. There is a belief, which appears to be common among physicians, that exposure to ultrasound is without any harmful effects in humans, at least as compared to x-ray. This belief is certainly true to the extent that ultrasound is a non-ionizing form of radiation, and it may be a true belief in general, as the biological effects of ultrasound appear to occur at levels normally considered to be well in excess of those of clinical diagnostic exposures. Nonetheless, this viewpoint may be changing, at least in terms of what the literature is reporting. Recent reviews[4,15,20,37,39,40,93–104] of the ultrasonic bioeffect literature appear to suggest that as more sensitive biological endpoints are studied, the values of the ultrasonic exposure parameters required to produce measurable effects are decreasing. There is some support to this suggestion from the published work[25,48,50,51,63,64,66,105–109] which describes ultrasonically induced biological effects from ultrasonic diagnostic equipment,

that is, ultrasonic energy from a commercial diagnostic device has been observed to alter a biological system in experimental studies.

One can think of ultrasonically induced biological effects as being classified into one of two general categories, viz., morphological alterations or functional alterations. A change in biological material which is determined through histological means is considered a morphological or structural alteration; therefore, most ultrasonically induced morphological alterations have been assessed by light microscopy. Biological changes which are assessed by a change in some biochemical level, pH, function, activity, etc., are considered to be a functional alteration. In general, much greater ultrasonic intensity levels have been required to produce a morphological alteration as compared to only a functional alteration.

In the context of a morphological or functional alteration, there are various degrees to which the experimental data are conflicting. One category of observations deals mainly with morphological alterations (usually termed lesions in the ultrasonic literature) of biological tissues produced by quite high levels of ultrasonic energy. Here, there is virtually no conflict in terms of whether or not a specific effect has occurred (or whether the effect is reproducible). But there are conflicting viewpoints in terms of the fundamental mechanism or mechanisms responsible for the alterations.

At lower ultrasonic energy levels, usually within the therapeutic range, there are conflicting viewpoints as to whether or not and, if so, to what degree a morphological alteration has occurred. For a third general category, at ultrasonic energy levels lower than those of the therapeutic range, and sometimes within the diagnostic range, there are very conflicting data as to whether a functional alteration occurred.

Another observation deals with the question of the significance of an ultrasonically induced biological alteration. The significance of a biological alteration is usually viewed with respect to its risk, but very little effort has gone into the assessment of specific biological alterations. This is true, in part, because appropriate dose–effect responses of these alterations have not been developed. Rather, a single dosimetric condition (one ultrasonic intensity condition at one exposure time) has been utilized for the experiments and this has precluded our ability to investigate the role of particular biological alterations in terms of extrapolating from the experimental animal to humans. Herein lies the greatest importance of investigating ultrasonically induced biological alterations in experimental animals. Such biological observations can provide insight into the risk, if any, to which humans might be subjected. Too often, however, a report appears in which a biological effect is reported under a single ultrasonic exposure condition. When the exposure condition arises from a diagnostic device, we tend to question whether the reported observation is real, or whether the experimental set-up procedure produced extraordinary conditions to elicit the effect. Nonetheless, there is a tendency to suggest that diagnostic exposure conditions represent a risk to the patient. While the results of exposure condition are at levels much in excess of diagnostic conditions, they are discounted as not being applicable to the clinical situation. The overall problem is that non-dose–effect studies are quite difficult to apply to assessing risk. They do, however, identify biological endpoints to which dose–effect experimental regimens should then be applied.

SUMMARY

Based upon experimental animal studies, the available information suggests that the risk associated with clinical use of ultrasound is quite low. However, our knowledge regarding ultrasonic bioeffects and biophysical interaction is rather incomplete at this time. It is essential, therefore, for the clinicians to be provided with up-to-date information of potential risks so that they can continue to render an informed benefit–risk judgment. The principal source of such data is from animal experiments, but it is difficult to evaluate any of these studies in isolation, especially when there are conflicting observations. And there *will* be conflicting observations, especially in studies employing relatively low levels of ultrasonic exposure. This is a given and it must be understood.

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