

## Ultrasonic Bioeffects: A View of Experimental Studies

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**ABSTRACT:** *Diagnostic ultrasound of the pulse-echo imaging type is used in at least 25 per cent of pregnancies, and Doppler continuous wave ultrasound, as employed in external electronic fetal monitors, is used in nearly all pregnancies. Diagnostic ultrasound energy levels are from 0.1 to 40 mW/cm<sup>2</sup>. These intensity levels depend on the characteristics of the ultrasonic beam and temporal exposure. The American Institute of Ultrasound in Medicine states that . . . "there have been as of October, 1982 no independently confirmed significant biological effects in mammalian tissues exposed to intensities below 100 mW/cm<sup>2</sup>." Some of the animal studies reviewed by the AIUM to reach this conclusion are discussed. (BIRTH 11:3, 1984)*

### Introduction

Ultrasound has had a profound influence upon the practice of medicine, especially in obstetrics. It has been only three decades since some of the first ultrasonic devices were developed to provide an image of the fetus. The early studies with these devices showed a potential to provide high resolution information about the fetus, information which if obtained by other techniques could pose significant risks; ultrasound did not appear to be associated with any known hazards. Diagnostic ultrasound gained acceptance also because it is convenient to use, comfortable for the patient, and not very expensive.

There continues to be a general feeling in the medical community that ultrasound does not

represent a risk to mother or fetus. But academic and government research scientists have continued to investigate and evaluate the risks. Many of these investigators (including this writer) have argued that the appropriate research has not been done to support a reliable assessment of the risks associated with human exposure to ultrasound. But, it could be properly argued that there is always an insufficient data base to "prove" a modality totally safe.

By some estimates, ultrasound use in obstetrics has been increasing at a rate of from 10 to 25 per cent annually for the past decade. Other estimates are that one-half of all pregnancies are being examined with pulse-echo diagnostic ultrasound (in which an image is created) and that virtually every fetus is evaluated with the continuous wave Doppler devices, which may appear to the patient to be electronic stethoscopes. In countries such as the United Kingdom and West Germany, it appears that at least one ultrasonic screening examination is being performed for every pregnancy.

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Such wide acceptance and continued increase of this fetal imaging modality, coupled with a concern for an evaluation of its safety and efficacy, led the National Institutes of Health and the Food and Drug Administration to sponsor a consensus development conference to assess the "Use of Diagnostic Ultrasound Imaging in Pregnancy." A report of this conference was published in the Spring, 1984 issue of *Birth*. As one of the panelists, I concentrated my efforts toward what the experimental (nonhuman) studies provided. What follows are my own views as to outputs (i.e., dose/exposure) from these ultrasound devices and the role that animal studies play in illuminating the risk of ultrasound in humans. For those interested in examining these issues in detail, there is a chronological bibliography available from *Birth*. This includes only review articles and books, not the individual articles from which the reviews were drawn.

### What Is Ultrasound?

Ultrasound is a form of acoustic or mechanical energy. The acoustic spectrum can be divided into three parts, infrasound, audible sound, and ultrasound. These divisions are arbitrarily based upon the frequency range over which humans hear sounds. Infrasound is at frequencies below, and ultrasound is at frequencies above, the audible range. Children may hear sounds from as low as 30 hertz (Hz) to as high as 20,000 Hz (or 20 kHz). As we get older, the lower frequency threshold rises and the upper threshold decreases. For example, in the United States, the buzzing of a television, a tone at 15,750 kHz, is near the frequency boundary between audible sound and ultrasound; the older population generally does not hear this buzzing. The acoustic frequencies used in medical imaging are in the 1 to 10 MHz (megahertz or a million hertz) range, which is about 50 times higher than audible frequency.

Conventional diagnostic ultrasonic systems fall into two classifications: pulse-echo imaging systems and Doppler systems. Pulse-echo imaging systems operate by transmitting a pulse of ultrasound and detecting the received echoes. The direction and range of these echoes are processed into a two-dimensional image which is displayed on a TV-type monitor. Doppler instrumentation produces a continuous wave of ultrasound. The reflected signals, or echoes, are

detected and processed to provide motion information within the body. For example, the fetal Doppler systems transmit ultrasound towards, and receive reflected sound waves from, the moving fetal heart. The received signal is converted into an audible tone which varies with the heart motion.

These diagnostic ultrasonic systems operate within the same ultrasonic frequency range. In terms of ultrasonic exposure types, the imaging monitor uses pulses of ultrasound and the fetal Doppler monitor systems use continuous wave ultrasound, that is, the sound is always on. Both rely upon the received signal, the echo, to provide the appropriate diagnostic information.

There is an engineering trade-off in the design of these systems between the depth from which the echo is received (termed the depth of penetration) and the size of object which can be detected at that depth. As the ultrasonic frequency increases, the resolution improves but the attenuation (loss of signal amplitude with distance) becomes greater. The resolution is a function of the wavelength; as the frequency increases, the wavelength decreases. The smaller the wavelength, the smaller the object that can be imaged. Higher frequencies are desirable so that smaller objects can be imaged, that is, resolution is improved. Ultrasonic attenuation affects the depth of penetration. As the attenuation, or loss of acoustic energy, increases, the depth into the body which the imaging system can reach decreases. This trade-off is important. One always wants to improve resolution. To do so, the frequency is increased but the imaging depth is reduced. This may result in the structures of interest being beyond the imaging depth. It is possible, however, to regain the same depth of penetration by increasing the ultrasonic power, or intensity. How high can the power, or intensity, be increased before biological effects occur? The truth is that no one knows. Because this is not known, it is not possible to establish safety exposure limits with scientific basis.

Over the past decade there has been a gradual increase in the ultrasonic frequency used for obstetrical examinations from 2.25 MHz to present generally employed 3.5 or 5 MHz. It is thought, but not well documented, that the output levels produced by these systems have also gradually increased over this decade.

We know that at sufficiently high ultrasonic energy levels, tissue can be destroyed. For example, high ultrasonic energy levels have been

quite effectively used for many years as a surgical tool. In surgery, this is a beneficial application of ultrasound. For ultrasound therapy in physical medicine, where ultrasound heats tissue to alleviate pain, the biological effect produced is also a beneficial one. But in diagnostic ultrasound, the motivation is to obtain information about the tissue, not to affect it.

For these three ultrasonic uses (diagnostic, therapy, and surgery), the frequency is within the same range. The main difference between these applications is the ultrasonic output. To distinguish among them, three classes of output quantities which quantify the ultrasonic exposure will be discussed. These are energy, power, and intensity.

Energy is work. Energy is required to produce a biological effect, but that does not mean that an effect has occurred when ultrasonic energy is present, because the energy is also required in order to produce an image. The imaging system receives the ultrasonic energy that has been reflected within the body (the echo) and processes the received energy into an image. Energy is the product of *power* and *time*. The unit of power is a *watt* (W). Also used is a thousandth of a watt, or milliwatt (mW). Ultrasonic power is a measure of the rate of work being done by an ultrasonic field; thus, power describes the potential by which the ultrasonic field interacts with the medium in which it is propagating. The ultrasonic power is reported as a temporal averaged quantity. For diagnostic equipment, this is the range of 0.1 to 40 mW. By comparison, the output power of ultrasonic therapeutic equipment, which is used to heat tissue, ranges from 1 to 50 W, and surgery equipment usually exceeds 25 W.

Another physical quantity invoked to quantify the ultrasonic field strength is intensity (Table 1). Intensity describes the spatial concentration of power in the unit of watts per centimeter squared ( $W/cm^2$ ) or milliwatts per centimeter squared ( $mW/cm^2$ ). One can think of intensity by visualizing a flashlight beam shined onto a wall where the center of the beam is brighter (higher intensity) than the rest of the beam. In other words, the intensity varies from point to point across the beam. Two spatial terms are used. The spatial peak (SP) intensity is the highest value intensity in that plane (the wall). The spatial average (SA) intensity is determined by averaging the intensity over some defined area of the beam. The SP intensity is usually

Table 1. Terms Used to Describe Intensity

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<i>Spatial Intensity Variation</i>
Spatial Average (SA)
Spatial Peak (SP)
<i>Temporal Intensity Variation</i>
Temporal Average (TA)
Pulse Average (PA)
Temporal Peak (TP)

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2 to 4 times greater than the SA intensity for unfocused (continuous wave) ultrasonic fields. For focused (pulsed) ultrasonic fields the SP/SA ratio can be as great as 50 or more when the SP intensity is determined at the focus and the SA intensity is determined near the transducer.

Because diagnostic imaging equipment produces pulses of ultrasound, three additional terms have been developed to describe the temporal nature of the ultrasonic field. Imagine the ringing of a bell. When the clapper strikes, a pulse of sound is transmitted. The intensity of that pulse can be averaged over the duration the sound is heard. This would be the pulse average (PA) intensity. During the pulse, there would be an instant of time at which the sound intensity is at its maximum, the temporal peak (TP) intensity. For the periodic ringing of the bell there is a period of time when no sound from the bell is heard; therefore, the intensity average over time—temporal average (TA) intensity—would be much lower than the PA intensity. For ultrasonic imaging systems, pulses are typically generated every 1 millisecond (1/1000 of a second) and the duration of time which the pulse is on, the pulse width, is about 1 microsecond (1/1000 of a millisecond). Thus, the temporal average (TA) intensity is about 1000 times less than the pulse average (PA) intensity. The temporal peak (TP) intensity ranges from 2 to 10 times greater than the PA intensity.

For pulse-echo diagnostic equipment, three intensity values are commonly reported. Their typical ranges are listed in Table 2 for obstetrical equipment. For the continuous wave fetal Doppler systems, both spatial intensity terms are used but only one temporal intensity term, the TA value, because the sound is on continuously. Most therapy and surgery systems are continuous wave systems. A more detailed accounting of typical intensity values for the various types of

Table 2. Exposure Levels in Medical Applications

Quantity	Diagnostics		Therapy	Surgery
	Pulse-Echo	Continuous Wave		
Power	0.1 - 33 mW	1 - 37 mW	1 - 50 W	>25 W
SATA	0.06 - 60 mW/cm <sup>2</sup>	0.2 - 20 mW/cm <sup>2</sup>	0.5 - 4 W/cm <sup>2</sup>	>10 W/cm <sup>2</sup>
SPTA	0.1 - 200 mW/cm <sup>2</sup>	0.6 - 80 mW/cm <sup>2</sup>	1 - 20 W/cm <sup>2</sup>	>30 W/cm <sup>2</sup>
SPPA	0.2 - 280 W/cm <sup>2</sup>	-	-	-

diagnostic ultrasonic equipment used in obstetrics has been reported in *Birth* (Spring, 1984, page 25). The SATA intensity, the quantity which is most often quoted because of its spatial and temporal averaging, yields the lowest number (ranges from much less than 1 mW/cm<sup>2</sup> to 60 mW/cm<sup>2</sup>) for equipment which would be used in a fetal examination. The SPTA intensity ranges up to 200 mW/cm<sup>2</sup>. Note that the SPTA intensity is greater than 100 mW/cm<sup>2</sup>. Both of these TA intensity parameters provide the basis for estimating the temperature rise in tissue. For therapy and surgical applications, the SATA and SPTA intensities are much greater than for diagnostic equipment.

Much has been made, incorrectly I believe, of the SPTA intensity value of 100 mW/cm<sup>2</sup> published in the American Institute of Ultrasound in Medicine (AIUM) booklet entitled *Who's Afraid of 100 Milliwatts?* as being a safety statement. It is not. Its intent was to be a factual statement about significant and confirmed biological effects. The AIUM Bioeffects Statement (Table 3), is: "... no independently confirmed significant biological effects ..." have been reported below a SPTA intensity of 100 mW/cm<sup>2</sup>. The value is not intended to imply a judgment of safety. This point is raised here because even though some equipment exceeds a SPTA intensity of 100 mW/cm<sup>2</sup>, it does not mean that a safety level has been exceeded.

The SPPA intensity is generally 1000 times greater than the SPTA intensity, and for obstetrical imaging equipment, ranges up to almost 300 W/cm<sup>2</sup>. The SPPA intensity is the spatially maximum value of the pulse average intensity. The SPTP intensity value is not reported because it is still a difficult measurement to make. However, it is greater than the SPPA intensity value by a factor of 2 to 10.

Concerns have been raised about these very high pulsed intensity values. It is simply not

known how high the SPPA intensity must go before biological effects occur. There have been selected experimental studies which have shown a correlation between a biological effect and the SPPA intensity but these studies have been under specialized conditions where micron-sized, stabilized gas bubbles have been present (Child *et al.*, 1981). Because it is believed that these types of bubbles do not exist in human tissues, their applicability to humans is quite remote. However, this continues to be an area of investigation. Also, quite recently, an analysis of studies which involved exposure of animal fetuses to pulsed ultrasound suggested that there is no direct evidence that diagnostic ultrasound produces any effect on the fetus (Carstensen and Gates, 1984).

There have been very few experimental studies conducted under the exposure conditions employed by commercial diagnostic imaging equipment. However, this would not be necessary in order to evaluate the risk, provided that the exposure conditions were such that a dose-effect response could be developed and evaluated. Dose-effect studies provide a scientific basis for extrapolating the results of animal studies to humans.

### The Dose-effect Approach

Experimental studies consist of exposing the specimen to ultrasound and evaluating whether there have been any biological changes which can be attributed directly to the ultrasound exposure. The choice of exposure parameters and the type of biological effect are critical elements of the experimental protocol. Exposure parameter variables include, but are not limited to, the following: pulsed or continuous wave conditions, frequency, power, SATA intensity, SPTA intensity, SPPA intensity (if pulsed), unfocused or focused fields, and exposure duration. If a

Table 3. American Institute of Ultrasound in Medicine Statement on Mammalian *in vivo* Ultrasonic Biological Effects

In the low megahertz frequency range there have been as of October, 1982 no independently confirmed significant biological effects in mammalian tissues exposed to intensities\* below 100 mW/cm<sup>2</sup>.

Furthermore, for ultrasonic exposure times\* less than 500 seconds and greater than one second, such effects have not been demonstrated even at higher intensities, when the product of intensity\* and exposure time\*\* is less than 50 joules/cm<sup>2</sup>.

\*Spatial peak, temporal average as measured in a free field in water.

\*\*Total time; this includes off-time as well as on-time for a repeated pulse regime.

Comments by the AIUM Biological Effects Committee relevant to this statement are as follows:

This Statement apparently applies to all existing data on biological changes produced in mammalian tissues by ultrasound in the frequency range of 0.5 to 10 MHz. Included in our literature review leading to this Statement are results obtained with focused as well as unfocused ultrasonic fields, generated continuously or (to a lesser extent) in a series of repeated pulses.

This Statement includes all seemingly reliable data considered in published summaries as well as results of satisfactory quality which have been published more recently. We have consulted a "jury" of informed investigators and have not learned of any exception to the Statement to "safety" decisions. Attention should be given to the following considerations:

1. Most of the data apply to mammals other than man, and it is not clear how to relate them to the human situation.

2. While useful results are now being generated in several research laboratories, the pool of reliable and highly relevant data is only beginning to fill. Most experiments have not been repeated by independent investigators. Especially in short supply are results at low intensities and long exposure times. Little research has been done with repeated short pulses such as would be most relevant to diagnostic ultrasound.

3. Data available at present on intensity levels at which biological effects occur are, in general, not minimum levels (if, indeed, definite minima exist). Further research is urgently needed to determine whether significant biological changes occur at levels lower than those corresponding to the Statement. As more results become available, it is reasonable to expect at least some lowering of the observed "threshold" levels for some biological systems, especially as more sensitive tests are used, and as more critical physical conditions are identified.

4. We believe the Statement will be helpful in arriving at recommendations for wise use of ultrasound in medicine. However, the Statement does not, in itself, imply specific advice on "safe levels" which might be universally valid. Determination of recommended maximum levels will require consideration of such difficult topics as: adequacy of present knowledge of biological effects; expected reliability of equipment specifications; assessment of patient benefits; and others. So far these matters have not been treated systematically.

It is to be noted that the Statement applies to data for mammals only and does not pertain to plants or *in vitro* experiments.

diagnostic machine is the exposure source for the experiment, then generally its outputs do not vary. Only exposure durations would vary since most of the other parameters are fixed within the system. On the other hand, when specially designed exposure systems are employed, virtually every exposure parameter is under the experimenter's control. In my judgment, it is essential to have control over these parameters because only then can dose-effect studies be properly planned and conducted.

What is meant by dose? It is quite difficult

to determine the exposure time that the human fetal heart, for example, is undergoing during an examination, especially when the ultrasonic beam is rapidly scanning from the transducer assembly and the transducer assembly is also being moved. Under such conditions the ultrasonic dose is quite difficult to quantify. Further, it is not known which of the various ultrasonic intensity quantities are relevant in terms of the dose determination. Consider the fact that the very high SPPA intensity acts for only a millionth of a second, and this action repeats itself every

thousandth of a second, whereas the very much lower SATA intensity acts for quite a long period of time; dose for the former could be much lower than that of the latter.

Dose-effect studies are still important for two reasons: they provide the capability to extrapolate the amount or kind of effect at the doses used experimentally to the dose generated (note that it is easier to determine what is generated than what a tissue receives) by diagnostic systems, and they provide the fundamental basis from which the biophysical mechanisms causing the effect can be evaluated (i.e., was it due to heating, cavitation, or some other cause). To obtain measurable and highly repeatable biological effects in experimental studies, the dose conditions are higher than those used diagnostically. The dose is varied over this higher range and the effect is evaluated. In this way extrapolation to diagnostic dose levels is placed upon a scientific basis. Let us consider two examples. In one case, the effect might be proportional in such a way that, when extrapolated, it does not go to zero (or to a normal level) until the dose goes to zero. This would be considered a no-threshold effect. On the other hand, the experimental study could yield an effect which goes to zero (or a normal level) at some no-zero dose. This would be an example of a threshold effect. Thus, in the former case, the degree of the effect would have to be evaluated when extrapolated to diagnostic levels. For the latter, the evaluation would depend upon where the threshold occurred. This and the effect variables which are much more extensive than the exposure variables, will be discussed further in the next section.

#### Experimental Studies of Ultrasound Bioeffects: Some General Observations

Experimental studies of ultrasonic biological effects can be classified into morphological or functional alterations. Morphological or tissue damage is usually permanent or irreversible. Such studies have been essential to the understanding of the mechanisms responsible for ultrasonically-induced alterations to biological materials. Ultrasound at high levels can cause damage to tissue by heating or by a phenomenon called cavitation, a general term used to describe the growth and subsequent dynamic behavior of gas bubbles produced in tissue by ultrasound. The action by ultrasound on these bubbles

causes them to respond by producing large shearing forces within the bubble vicinity. These forces, in turn, can disrupt and destroy biological tissues. Morphological changes caused by both heating and cavitation have been identified and studied with very high ultrasonic intensities.

Biological changes such as biochemical values, pH, function, activity, weight, etc., are termed functional alterations. These changes are not necessarily permanent. An example of a functional alteration is fetal weight change. There have been a large number of experimental studies that have evaluated the effect of ultrasonic exposure upon the pregnant mouse. Some of the reports have shown the fetuses which were exposed *in utero* to be smaller at the time of birth than if they were not exposed (O'Brien, 1983).

In general, much greater ultrasonic intensity levels are required to produce morphological alterations as compared to functional alterations. The SPTA and SATA intensity levels used in the fetal weight studies were much less than those used for studying morphological alterations. Had these higher intensity levels been used to expose the mouse fetuses *in utero*, irreversible damage to the fetuses, and perhaps death, would have been the result.

Scientists tend to question research findings of others whether they agree or disagree with them. It is interesting, however, that the content of scientific conflict changes as the level of ultrasound diminishes. Morphological alterations are produced by quite high levels of ultrasonic energy. There is no conflict over whether the morphologic effect has occurred, but rather what caused the alteration. Was the effect caused by heating, cavitation, or some other mechanism? These are the levels employed in the surgical application of ultrasound for which consistently well-defined, permanent biological alterations can be produced. For example, three laboratories have independently confirmed that a highly focused ultrasonic beam can produce a lesion in mammalian (cat and rat) brain tissue (Fry *et al.*, 1970; Pond, 1970; Robinson and Lele, 1972). Further, there is agreement that the effect has a threshold, and these investigators all agree as to the threshold. However, there is disagreement as to what degree the effect is caused by a thermal mechanism or by cavitation.

At lower ultrasonic levels, usually within the therapeutic range, there are conflicting viewpoints as to whether and to what degree mor-

phological alterations have occurred. Most of the mouse fetal weight studies have been conducted at intensities in the therapeutic range (SATA intensities: 0.5-6 W/cm<sup>2</sup>). There have been some 28 studies which have examined the effect of *in utero* ultrasonic exposure on fetal weight in either rats or mice (O'Brien, 1984). Within these studies, there are a number of perplexing and conflicting observations. For example, under the identical exposure and experimental conditions, in one strain of mouse, statistically significant fetal weight reduction was determined, whereas, in another strain of mouse, there was no change in the fetal weight. Further, both of these observations have been confirmed in independent laboratories. Thus, under biological conditions which are not understood, consistent and confirmed observations have been obtained for both a positive effect and a negative effect. Additional comments about fetal weight studies will be made.

For a third general category, at ultrasonic levels lower than those in the therapeutic range, and sometimes into the diagnostic range, that is, within the SATA intensity range of 0.1-100 mW/cm<sup>2</sup>, there are conflicting data as to whether a functional alteration occurred. This is aptly demonstrated in the numerous experimental studies which examined the effect of ultrasound on sister chromatid exchange (SCE) frequency, an indication of chromosome damage the biological significance of which is unclear. Some of these studies have shown an effect when a diagnostic ultrasound device was used. However, others have reported no change in SCE frequency, some at diagnostic levels and some at levels much higher than therapy. Liebeskind's study (1979a) appears to have received the greatest attention since it indicated an increase in human lymphocyte SCEs (a positive effect) from a diagnostic system. But in another study by Liebeskind (1979b), also with a diagnostic system, no change in SCEs was reported (a negative effect). Here, two different types of cells were used. There have been two other positive observations (Haupt *et al.*, 1981; Ehlinger *et al.*, 1981) of increased SCEs, both with diagnostic levels of ultrasound. But, there have been at least ten other studies, some at diagnostic levels (both pulsed and continuous wave exposure conditions) and some at levels within, or even higher than, therapeutic levels which have reported no increase in SCEs. These fourteen studies have been carefully and thor-

oughly reviewed by the AIUM Bioeffects Committee (Goss, 1984). Their conclusion is that these studies do not suggest a hazard in diagnostic ultrasound.

One of the few *in utero* studies of exposure of rats with diagnostic levels of pulsed ultrasound which showed fetal weight reduction (Pizzarello *et al.*, 1978) was not replicated by another group (Carstensen and Gates, 1983). The original positive finding was performed under a single exposure condition. The attempt to replicate the study duplicated all experimental and animal protocols and, additionally, utilized ultrasonic exposure conditions equal to and higher than the original study.

One of the more controversial studies of prenatal ultrasonic exposure of pregnant mice was conducted with a commercial fetal Doppler device (Shoji *et al.*, 1971, 1972). While fetal abnormalities were observed in both the exposed and control groups, the differences were not significant. However, the rate of fetal death was increased significantly in the exposed group. The same researchers (Shoji *et al.*, 1972; Shimizu and Shoji, 1973; Shoji *et al.*, 1975) found a statistically significant increase in fetal abnormalities in a different mouse strain. In both of these studies, pregnant mice were given an initial dose of sodium nembutal which was effective for about 1 hour, after which the animals struggled for 4 hours; the ultrasound exposure duration was 5 hours. Edmonds (1980) drew attention to errors in the statistical analyses, the conclusions drawn, and the effective ultrasound power (about 280 mW) and concluded that the reported effects were related to a combination of prolonged binding of the mice and ultrasonic hyperthermia.

A significant reduction in the frequency of mitotic cells in surgically stimulated rat liver from diagnostic level, continuous wave ultrasound (SATA intensity: 60 mW/cm<sup>2</sup>) was reported (Kremkau and Witkofski, 1974). However, this observation was not able to be confirmed under virtually the identical research protocol, even when the SATA ultrasonic intensity ranged from 60 mW/cm<sup>2</sup> up to 16 W/cm<sup>2</sup> (Miller *et al.*, 1976).

These are a few of the many studies reporting ultrasonically induced biological effects at intensity levels below 100 mW/cm<sup>2</sup>, for which attempts at replication failed. There are also many studies for which no attempt has been made to replicate the original finding, because, in general, research funding does not support this type of activity.

## Conclusion

The significance of an ultrasonically induced biological alteration is usually viewed with respect to risk to humans. 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 has been used for many experiments, and any resulting biological alteration cannot be extrapolated from the experimental animal to humans. Only dose-effect observations provide for understanding the mechanisms of interaction of ultrasound in biological systems, and a firm scientific basis for extrapolation to humans.

## Acknowledgments

This work was supported in part by grants from the National Institutes of Health, National Institutes of General Medical Sciences (GM 30481) and National Cancer Institute (CA 36029).

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