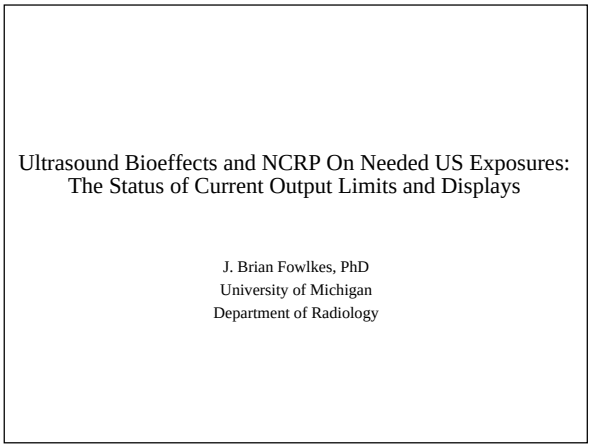
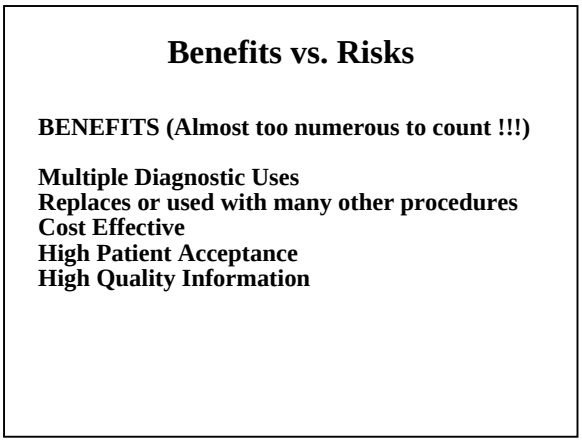
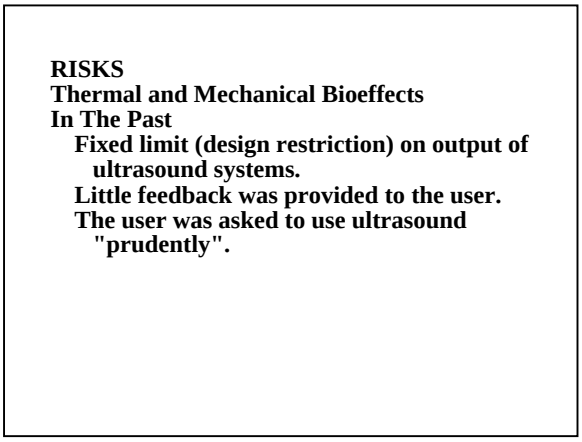


This presentation will provide an overview of the bioeffects issues associated with ultrasound imaging. It is important to realize the potential risks since current ultrasound systems can have higher outputs under certain imaging situations than in the past. The goal here is to provide the essential information for understanding the MI and TI and how these display indices can be used to limit ultrasound exposure and thus reduce the potential for bioeffects.



Although there is the potential for bioeffects from ultrasound, there is insufficient data to establish any causal relationship between ultrasound as used in medical imaging and any specific biological effect. At the same time, it is essential to balance the potential risks against the clear benefits of ultrasound imaging. There are numerous benefits for ultrasound particularly in terms of cost and patient compliance. There is little doubt of the impact ultrasound has had in clinical practice and it is the most rapidly expanding among imaging modalities.



Many users are unaware of recent changes in acoustic outputs associated with a relatively new market approval method. In the past, the FDA regulated ultrasound scanners by placing specific limits on the output based on the levels output by systems available as of 1976. The operator was provided little information by systems concerning the output (perhaps only a relative scale). It was expected, as it is to this day, that ultrasound would be used in a prudent fashion.

RISKS Cont'

In The Future (Now)
- **Indices to help understand potential bioeffects.**
- **Output restrictions are reduced.**
- **However, diagnostic information content is also increased.**

Another Risk To Consider
Can you afford not to get the information?

More recently another approval method requires the output to be displayed in some fashion (described later and in AIUM/NEMA 1998) for new systems capable of increased acoustic output. Systems approved in this fashion can have higher output limits, some of which are to the benefit of increased diagnostic capabilities. It should be remembered, however, that one of the critical risks would be withholding a well established procedure where there is little risk to the patient.

FDA's Pre-amendments Levels

	Derated Intensity Values		
	I_{SPTA} (mW/cm^2)	I_{SPPA} (W/cm^2)	I_m (W/cm^2)
Cardiac	430	190	310
Peripheral Vessel	720	190	310
Ophthalmic	17	28	50
Fetal and Other*	94	190	310

* Abdominal, Intraoperative, Small Organ (breast, thyroid, testes), Neonatal Cephalic, Adult Cephalic

FDA (1987)

The original approval method included the application specific limits seen here. Systems can still be approved using this system such that controls or labeling are required to indicate the proper use of mode and transducers for specific types of examinations. Information about the output of ultrasound systems are provided in the manual and it is important to be familiar with this, particularly with regards to the use of appropriate probes for fetal examinations.

FDA's Track 3 510(k) Limits

$I_{SPTA.3}$: 720 mW/cm^2
$I_{SPPA.3}$: 190 W/cm^2 or MI: 1.9

For ophthalmic use
TI at surface: 1.0
$I_{SPTA.3}$: 50 mW/cm^2
MI: 0.23

FDA (1997)

In the more recent approval method, the application specific limits have been removed. In particular, note the increase in output allowed in the case of fetal ultrasound if the operator uses the highest possible settings. Although no specific evidence exists to indicate any impact from these changes, this does represent an increase in exposure and few epidemiological studies would include large numbers of these exposures.

Output Display Standard

- Voluntary standard for Track 3 applications
- Commonly referred to as the Output Display Standard (ODS)
- Published jointly by the AIUM and National Electrical Manufacturers Association (NEMA) to provide the display of system output to the operator in some form.

To obtain approval in Track 3, there are requirements for providing information to the operator as to the acoustic output from the system. Many manufacturers use the Output Display Standard (ODS). One component often overlooked is the need to educate the user on the ODS. It was intended that eventually the FDA limits would be relaxed in favor of an informed and responsible decision that limits be exceeded when necessary. This should increase diagnostic confidence but will likely not happen until the ODS is more widely understood.

Physical Effects of Ultrasound

1. **Thermal**
2. **Nonthermal**

Radiation Force - pressure, torque

Acoustic Streaming

Cavitation - heat and pressure (free radicals), microstreaming, radiation forces around bubbles, bubble collapse

The effects of ultrasound can be broadly divided into two areas. Thermal effects are those most commonly understood. Increases in local temperature result from the absorption of ultrasound by tissue. The remaining effects, generally classed as nonthermal, are largely mechanical in nature and include those listed here. As we will see later, this division has resulted in two specific bioeffects parameters being monitored in the ODS.

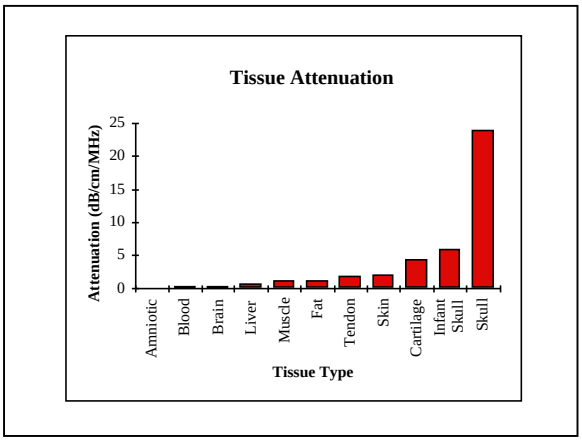
Thermal Effects

Two Particular Areas of Interest

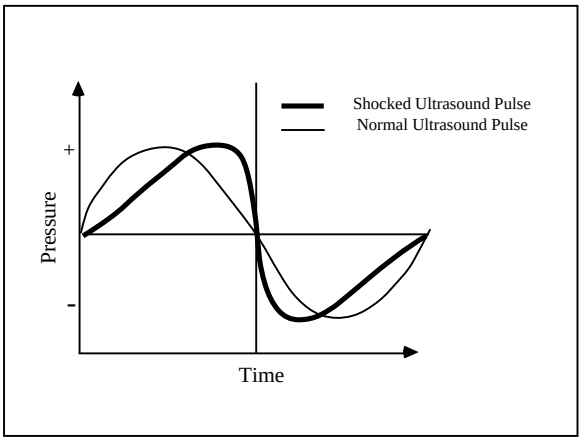
Bone

Soft Tissue

In terms of thermal effects there are two specific areas of interest. The propagation of ultrasound in soft tissue can result in temperature increases due to attenuation. And when ultrasound is incident on bone, the absorption is significantly higher.



Here is a summary of the ultrasound attenuation for various tissues. As you can see the attenuation in bone is considerably higher and this is particularly important when considering the later term fetus where the calcification of bone is significant. However, the first trimester fetus is also more vulnerable to insult from a variety of sources due to the large scale organogenesis occurring at that time.



The effect of nonlinear propagation is one area of particular interest for further developing the models used to predict thermal effects in tissue. As the ultrasound travels it can develop into a shock wave due to "finite amplitude distortion". The result is more high frequency ultrasound being produced locally which in turn is absorbed more rapidly due to the frequency dependence of attenuation. The more likely location for this to occur is in long fluid paths such as through amniotic fluid or the urinary bladder.

Factors Contributing to Thermal Effects

1. Ultrasound Frequency - Higher frequencies are attenuated faster.

2. Spatial Focusing - How is the transducer focused ? This may be important both at the focus and at the transducer face.

3. Tissue Type - What tissues are being exposed, how absorptive are they? Can the exposed tissue get rid of the heat efficiently? Are the tissues particularly susceptible?

4. Time of exposure - or dwell time.

There are a number of factors that have to be considered in estimating the potential for temperature increases due to ultrasound. Some of these are listed here. Of these, it is important to realize that dwell time is not considered in the ODS commonly used for operator feedback. The operator must understand that to minimize exposure, examinations at a specific site should be as short as possible while still obtaining the diagnostic information needed. This means that the well-trained operator is the safer operator since the necessary information is documented most efficiently.

The Thermal Index

To more easily inform the physician of the operating conditions which could, in some cases, lead to a temperature elevation of 1˚C, a thermal index is defined as

$$TI = W_0 / W_{deg}$$

where W_{deg} is the ultrasonic source power (in watts) calculated as capable of producing a 1˚C temperature elevation under specific conditions. W_0 is the ultrasonic source power (in watts) being used during the current exam.

In order to make the problem of tracking the potential for bioeffects simpler for the operator the ODS models the potential for temperature increases, taking into account many factors such as frequency, focusing, tissue perfusion, etc. The potential for temperature rise is then displayed in the form of the Thermal Index (TI) as defined here. Understand that this is only an indication of the potential for a temperature increase. There are a number of assumptions that must be made in the calculation of the TI but the benefit lies in the TI being updated as the system parameters are changed by the operator.

Thermal Indices

- **TIS - Thermal index for soft tissue**
- **TIB - Thermal index for bone distal to transducer**
- **TIC - Thermal index for transcranial applications (bone proximal to transducer)**

Because of the increased attentuation in bone described earlier, the TI is actually calculated for three situations. The TIS is the general result for all soft tissue in the absence of bone. For bone not near the scanhead, the TIB is the appropriate value to monitor. The TIC is the value for the potential heating of tissues when the bone is near the surface as in the case of transcranial Doppler. Each of these is calculated in the ODS but it is up to the operator to realize which is appropriate for the current imaging circumstance.

Summary on Thermal Effects

- **Exams resulting in a 2˚C temperature rise or less are not expected to cause bioeffects. (Many ultrasound examinations fall within these parameters)**
- **Ossified bone is a particularly important concern for ultrasound exposure.**
- **Even though an FDA limit exists for fetal exposures, temperature rises can exceed 2˚C.**
- **Thermal indices are expected to track temperature increases better than any single ultrasonic field parameter.**

So in summary, here is a list of some important facts about the thermal effects of ultrasound. Perhaps the most important is the realization that the operator has a responsibility to recognize and minimize the displayed TI value while maintaining the diagnostic quality in the image. One should not be concerned about routine examinations of short duration where the TI values are low. It is important to recognize what is being exposed in the tissue, i.e. bone, fetal tissue, etc.

Potential Cavitation Sites

- **Air-filled lung tissue**
- **Intestine containing gas**
- **Contrast agents containing gas**
- **Any other sites where gas bodies are likely to exist**
- **See the February 2000 issue of JUM**

There are a number of possible nonthermal effects from ultrasound but the effect that has received the most attention has been cavitation. In the context of diagnostic ultrasound, cavitation is the response of gas bubbles to the pressure changes of the acoustic field. A bubble will oscillate and can grow and collapse causing a variety of mechanical, thermal and chemical effects. Therefore, the presence of some form of gas is the most likely location for such effects. A summary of these effects is available (JUM 2000).

Mechanical Index

The index is designed to indicate acoustic outputs which have the potential for producing cavitation based on the existence of free bubbles with a broad size distribution. It is defined as

$$MI = P^*/f^{*a}$$

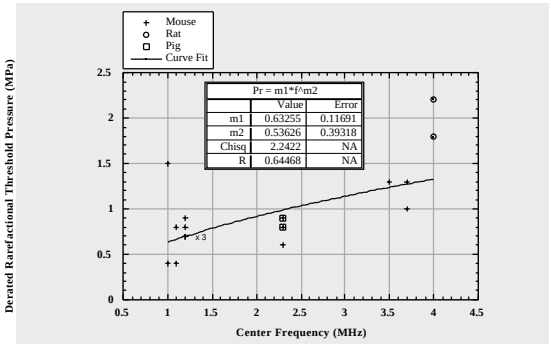
where the normalized pressure is P*=P/(1 MPa), P is the peak negative pressure in the acoustic field which is derated according to 0.3 dB/cm-MHz to allow for in vivo attenuation, f*=f/(1MHz), f is the center frequency of the transducer, and a ~ 0.5 for physiologically relevant fluids.

In similar fashion to the TI described above, a Mechanical Index (MI) was defined to predict the potential for effects due to cavitation. The MI predicts the conditions for rapid growth and collapse of microbubbles assumed to be present in the field. The MI reflects the fact that it is more difficult to the cause cavitation at higher ultrasound frequencies as indicated by its inverse relationship. The MI is displayed as a part of the ODS also and limited to a value of 1.9 under FDA Track 3.

Ultrasound Induced Hematoma in Rat Lung

1.5 min exposure to 4 MHz pulsed Doppler at MI = 1.6 (Holland *et al.*, 1996)

One of the areas receiving particular attention is the potential of ultrasound to produce petechial hemorrhage in gas-filled lungs. This has been demonstrated in a variety of animal models as represented here by the work from Holland et al. It is important to remember that the hemorrhage produced by ultrasound may not be significant, in that such events occur for many different reasons and are resolved naturally. In addition, there are indications that species differences in structure may make human lung less susceptible to this type of damage.



Adapted from Mechanical Bioeffects from Diagnostic Ultrasound: AIUM Consensus Statements, *J. Ultrasound Med*. 2000; 19(2):68-168.

This figure shows the frequency dependence of the threshold for lung hemorrhage for a variety of animal models with the experiments conducted in different laboratories. Note that the fitted curve of the data results in an approximately $f^{1/2}$ dependence which is the same as used in computing the MI used in the ODS. In addition to the lung, gas pockets are found naturally in the intestine and ultrasonically-induced hemorrhage has also been observed in animals models. There continues to be debate as to the appropriate frequency dependence for these effects.

Contrast destruction in the presence of imaging ultrasound

- Acoustic pressures of 0.5 to 3 MPa at diagnostic frequencies.
  - Known at least as early as 1991.
  - Rate of destruction increases with increasing negative pressure.
  - Reduction in frequency of exposure reduces rate of destruction. (Porter et al., 1997) Referred to as TRI and also developed as Flash-Echo.

Ultrasound contrast agents are another source of gas bubbles. Most of the contrast agents, in development or available commercially, are based on stabilized gas bubbles. It has been known for some time that ultrasound can actually disrupt the contrast agent, causing a signal loss. The exact mechanism is not understood nor is it understood whether significant cavitational activity results but several observations do indicate that contrast agents can serve as sites for cavitation activity.

***In Vivo* Experiments - Pulsed US**

- Dalecki et al. (1997) - Murine heart
  - Albunex ® injected 4 times for total 0.1 ml.
  - Correcting for chest wall, the threshold at the surface of the heart at 1.2 MHz is an MI of 1.8.
  - Hemolysis at 2.4 MHz and 10 MPa was only 0.46 %. (Near values for shams and controls.)
  - Similar high frequency dependence.
- Raeman et al. (1997) - Murine lung
  - Albunex® did not increase the risk of US-induced lung hemorrhage.(1.2 MHz, with 2 MPa)

Hemolysis has been observed following ultrasound exposure in the murine heart when contrast agent was administered. At higher frequencies, the effect was diminished to sham levels. The presence of Albunex did not increase the incidence of lung hemorrhage in the same model.

***In Vivo* Experiments - Pulsed US**

- Dittrich et al. (1998) - Hemolysis Measures
  - Rabbit model scanned with a commercial US system and infused with FS069 (Optison).
  - Blood samples drawn from femoral and carotid arteries and analyzed for blood count, serum free hemoglobin, and serum LDH.
  - No significant changes observed that were attributed to the ultrasound and agent.

Other studies have indicated the absence of hemolysis based on a number of assays. There remain questions as to the sensitivity of some experiments to the presence of such biological effects. In addition, it is important to note the relative significance of some bioeffects such as hemolysis. Additionally, studies have indicated production of petechial hemorrhage in muscle and other tissues in the presence of microbubble contrast. The significance of these effect to contrast studies in humans is not yet known.

Summary on Cavitational Effects

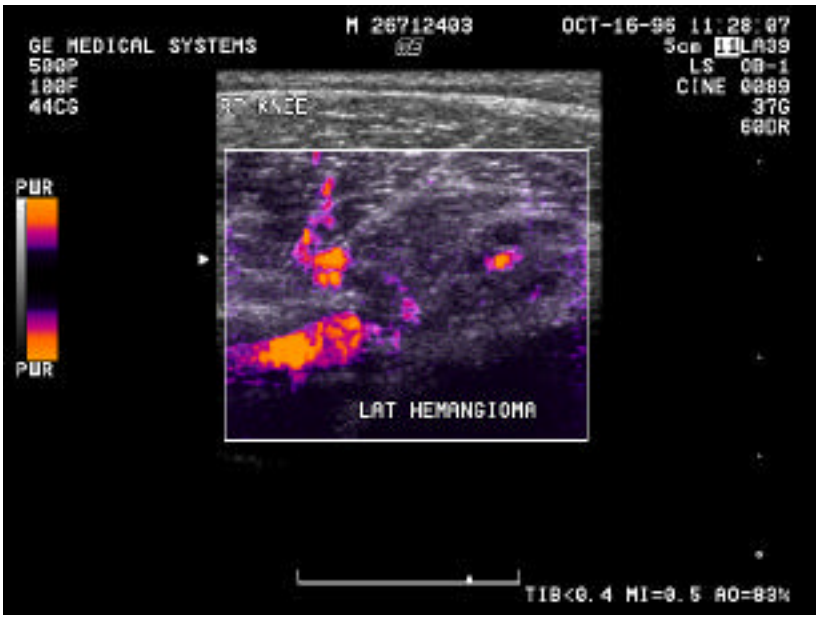
- **Current ultrasound systems can produce cavitation in vitro and in vivo and can cause blood extravasation in animal tissues.**
- **A Mechanical Index can gauge the likelihood for cavitation and apparently works better than other field parameters in predicting cavitation.**
- **Several interesting results have been observed concerning animal models for lung damage which indicate a very low threshold for damage, but the implications for human exposure are not yet determined.**
- **In the absence of gas bodies, the threshold for damage is much higher.**

In summary, some bioeffects have been observed in animal models and particularly in those locations where gas naturally occurs or as a result of the introduction of gas bubbles such as in the case of contrast agents. The MI is designed to provide some guidance as to the likelihood of such events but is only a guide and the conditions being imaged, i.e. gas content, need to be noted. In all cases the MI should be minimized, while providing the necessary diagnostic information.

Output Display/On-screen Labeling

- **Begins to appear when the instrument exceeds an index value of 0.4. Display not required if indices are all < 1.0.**
- **Often only one index will be displayed at a time.**
- **Requires default output settings be in effect at power-up, new patient entry, or when changing to a fetal examination.**
- **No factors associated with the time taken to perform the scan. Efficient scanning is still an important component in limiting potential bioeffects.**

The TI and MI are major components of the Output Display Standard that provides the operator feedback as to the output conditions for the ultrasound image and how that relates to possible biological effects. A system is not required to display anything if the indices never exceed 1.0. If a system can exceed an index of 1.0 then display must begin at 0.4. (See example below). There are default conditions that provide for lower output at the start of exams but remember that there is nothing in the ODS regarding the time of the scan and this should be minimized.



Typical Display of ODS Indices

ALARA

"AS LOW AS REASONABLY ACHIEVABLE"

1. Expose tissue for as short a period of time as necessary.
- **How long does it take to get a useful image?**
- **What scanning techniques can you use to limit exposure?**

2. Know how the system is setup and how it is controlled.
- **What kind of mode is it?**
- **What is the startup condition and can you do better?**

The key to all of this is the use of the ALARA principle. In everything, the ultrasound used should be As Low As Reasonably Achievable. Get the useful information and complete the exam as quickly as possible. The system can be optimized and some controls have less impact on the potential for bioeffects. Though systems will come up in a specific configuration, some modification is to be expected to optimize the image.

How do you control the system?

Direct Controls

1. Application Types
- **Let the machine do some of the work**
- **If these are not avaliable then manual adjustment is required.**
- **"Don't use the cardiac settings for a fetal exam."**

2. Output Intensity
- **May be called "power", "output", "transmit", etc.**
- **Use as little output intensity as consistent with good image quality.**

The operator now has the information related to the output but of all the possible controls that can be adjusted, there are some that are most effective in limiting the potential for bioeffects. First of all, the manufacturers have an interest in making the best image possible and using their settings, such as the anatomic presets, will likely optimize the image for the given situation. The most important adjustment is the acoustic power. It should be as low as possible for good image quality. There are several other adjustments that can be effective without raising the acoustic output as will be seen later.

Indirect Controls

1. System Mode
- **Whether the beam is moving or stationary will affect the energy absorbed.**

2. Pulse Repetition Frequency
- **Increasing the number of ultrasound pulses per second will increase the time average intensity.**

3. Focusing Depth
- **Focusing at the correct depth can improve the image without requiring an increased intensity.**

Other controls are considered in the calculation of the ODS, such as whether the beam is being scanned for imaging. Selecting the correct PRF and the appropriate imaging depth will also limit the rate at which pulses are being transmitted. The image quality is substantially improved with focusing and this will reduce the acoustic output required.

Indirect Controls

4. **Pulse Length or "burst length" or "pulse duration"**
   For example in pulsed Doppler, increasing the Doppler sample volume length will increase the burst length.
5. **Transducer Selection**
   If you are maximizing the output and gain and still have a poor image maybe a lower frequency will work better.

The burst length or sample volume size for Doppler will affect the acoustic output as well. One of the more important decisions is the appropriate frequency. Since the MI and TI are frequency dependent, the acoustic output may be more restricted at higher frequencies. The penetration at higher frequencies is also less, so that operators looking for the higher spatial resolutions may have a tendency to turn up the acoustic output in an attempt to get a better picture. A lower frequency may actually work better.

"FREEBIE" Controls

1. **Receiver Gain - IT IS FREE!!!**
   Always increase this first when available (some systems have overall gain tied to output and/or TGC). Use as much (receiver) gain as possible.

2. **Other controls affecting image quality**
   Time Gain Compensation (TGC) - NO COST!!
   Dynamic Range - NO COST!!
   Post Processing - NO COST!!

There are some controls that do not affect the acoustic output. The receiver should be adjusted to optimize the image with the minimum of acoustic output. (Reach for GAIN first then OUTPUT if needed it.) In some cases, the gain is tied to the output to compensate for changes. Just make sure you understand your system. Other "FREE" controls for improving the image are TGC, Dynamic Range, and any post processing controls. These should not affect acoustic output.

Remember

- Ultrasound is a safe and effective diagnostic tool when used properly.
- There are no confirmed studies that establish a causal relationship between diagnostic ultrasound as regulated by the FDA and any bioeffect.
- Use ultrasound when medically indicated.
- USE THE TI AND MI to limit your exposure.
- Perform your scanning efficiently.

Ultrasound is an important diagnostic tool and presently we have no indication that a diagnostic procedure should not be performed when indicated. We are still learning about some important new developments such as contrast agents and the impact of recent changes in FDA regulations. The operator now has output information to exercise the ALARA principle and as the awareness of the TI and MI increases the possibility exists to further expand the capabilities of diagnostic ultrasound. This will likely only happen if the operators understand how to limit the potential risks.

Below are some references that are available on the subject. A handy and practical summary of the ODS is provided in the booklet *Medical Ultrasound Safety.* Some form of this information (very often this same publication) is provided with each ultrasound scanner. This is part of the educational requirements associated with Track 3 approval.

REFERENCES

AlUM/NEMA (1998) *Standard for Real-Time Display of Thermal and Mechanical Acoustical Output Indices on Diagnostic Ultrasound Equipment (REV 1)*, American Institute of Ultrasound in Medicine and National Electrical Manufacturers Association, published by the AIUM, Laurel MD.

AIUM (1994) *Medical Ultrasound Safety*, American Institute of Ultrasound in Medicine, published by the AIUM, Laurel MD.

JUM (2000) Mechanical Bioeffects from Diagnostic Ultrasound: AIUM Consensus Statements, *J. Ultrasound Med*. 2000; 19(2):68-168.

OTHER REFERENCES

Apfel RE, and Holland,CK. Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound. *Ultrasound Med. Biol.* 1991; 17: 179-185.

Dalecki D, Raeman CH, Child SZ, et al: Hemolysis *in vivo* from exposure to pulsed ultrasound. Ultrasound Med Biol 23:301, 1997

Dittrich HC, Bales GL, Kuvelas T, et al: Myocardial contrast echocardiography in experimental coronary artery occlusion with a new intravenously administered contrast agent. J Am Soc Echocardiogr 8:465, 1995

Holland CK, Deng CX, Apfel RE, et al: Direct evidence of cavitation *in vivo* from diagnostic ultrasound. Ultrasound Med Biol 22:917, 1996

Lee W. How to Interpret the Ultrasound Output Display Standard for Higher Acoustic Output Diagnostic Ultrasound Devices, *J. Ultrasound Med*. 1998; 17:535-538.

Raeman CH, Dalecki D, Child SZ, Meltzer RS, et al: Albunex® does not increase the sensitivity of the lung to pulsed ultrasound. Echocardiography 14:553, 1997.