ON THE ASSESSMENT OF RISK TO ULTRASOUND

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ABSTRACT. A reliable assessment of risks and benefits associated with exposure to ultrasound is essential because of the rapid development and increasing utilization of ultrasound in the healing arts and in industrial and consumer applications. Disproportionately low and insufficient attention has been directed to the development of information on the biological implications of exposure to ultrasound. Interactions between ultrasound and biological systems have been documented, and include degradation of biological molecules, destruction of cells and cell organelles, and formation of lesions in tissues. Much available information is based on inadequate dosimetry for purposes of realistic risk assessments. A unified concept is essential to relate exposure to energy distribution and deposition in tissues. To develop this concept, identification of biologically important physical parameters of exposure is necessary. Specific attention must be given to identify biologically significant and sensitive indicators of damage. Dose-effect relationships must be quantitated. Substantive studies are needed to answer questions about possible delayed, cumulative, and synergistic effects. Proper epidemiologic designs must be employed to evaluate the impact of ultrasound exposure on human development. Information from an effective national research effort will facilitate risk assessment as an integral part of the development of radiation safety performance standards for ultrasound generating electronic products, for which the Bureau has responsibility under Public Law 90-602.

Early predictions of expansion of use of ultrasonic energy have been realized. Further expansion is anticipated. The magnitude and diversity of use in the United States leads to considerations of the potential hazards of ultrasound and estimates of health risks to the population. This paper presents a summary of the known biological effects against a background of ultrasound usages, and points out current needs for adequate health risk assessments. It must be realized that the quality and quantity of the available bio-effects information establishes the reliability and adequacy of the risk assessment.

The use of ultrasound is increasing rapidly in the clinical practice of medicine and dentistry, as well as in industrial, scientific and consumer applications. A market analysis in 1969 predicted that the dollar value of the ultrasonics market would increase 300% during the period between 1968 and 1973 (Harris, 1970). According to Harris, Department of Commerce statistics showed a relatively steep increase in shipments of industrial ultrasonic equipment in the late 1960's.

Many of the uses and medical applications of ultrasonic energy are listed in Table 1. Ultrasound is used in the healing arts for therapeutic, diagnostic and monitoring procedures (Smith Kline, 1967). A usual therapeutic procedure is ultrasonic diathermy, used in physical therapy and post-operatively following oral surgery to increase the tissue temperature. Typically, the ultrasound at a radiation frequency of 1 to 10 MHz is applied to the surface of the affected area at intensity levels up to approximately 5 W/cm^2 (Lehman & Guy, 1972). Ultrasound at a radiant intensity level of 10 to 20 W/cm^2 is effective to destroy selectively the vestibular portion of the inner ear in treating Meniere's disease (Kossoff, 1972). In a restricted study conducted in 1971 on the use of diathermy therapy devices of all types, it was found that 13,000 patients out of a total county population of 500,000 were being treated per month. Of these 13,000, almost half were being treated with ultrasonic diathermy (Remark, 1971).

In dentistry, ultrasonic frequencies around the 25 kHz range at radiant intensities as high as 64 W/cm^2 are utilized by applying a shear force for the removal of tenacious calcific deposits from teeth (Lees, 1972).

By virtue of small acoustic impedance differences between various soft tissues, the ultrasonic pulse-echo technique is utilized to visualize soft tissue interfaces. The typical frequency range is 1 to 30 MHz depending upon the compromise between resolution and depth of penetration required. Peak ultrasonic intensities have been found to be as high as 100 W/cm^2 (Hill, 1969). Average intensities are much lower owing to duty cycles of approximately 0.1 percent.

Ultrasonic monitoring devices employing both continuous and pulsed regimes are used to detect movement of anatomical structures such as the heart or to measure the rate of blood flow. These instruments generally employ the Doppler principle at frequencies from 1 to 10 MHz and utilize average intensities less than 0.1 W/cm^2.

The extensive use of ultrasound in industry has been reviewed by Steinberg (1965). Frequencies from the upper limit of human hearing, 16 kHz, up to 10 MHz are utilized over the average radiant intensity range from 10^{-3} to 10^5 W/cm^2. Non-destructive testing and flow detection employ the lower intensities and higher frequencies whereas cleaning and welding employ the higher intensities and lower frequencies.

In research and testing laboratories, ultrasound is used at a range of radiant intensities. High intensity uses include disruption of cellular and macromolecular structures and cleaning. Lower intensity uses include determinations of elastic properties of fluid and solid materials, such as geological specimens (Simmons, 1965), the kinetic and relaxational behavior of fluids (Piercy, 1965; Atkinson, et al., 1965) and the thermodynamic properties of solids (Thurston, 1965) are examined by ultrasonic energy.

Based upon an analysis of project summary obtained from the Smithsonian Institute's Science Information Exchange, development of the medical, industrial, consumer and scientific applications of ultrasound is being actively encouraged without a corresponding effort to evaluate the potential risks to man associated with its use. The summary in Table 2 indicates that out of 160 federally funded ultrasonic research studies, 141 were for development of applications while only 19 were for investigating biological effects of ultrasound. In terms of financial support (normalized), $4,757,816 was directed for applications and $628,917 for bioeffects research, or a ratio in favor of applications development of 7.5 to 1.

TABLE 1: USES AND PROPOSED USES OF ULTRASOUND

HEALING ARTS

THERAPY

- Diathermy to promote wound healing in dentistry
- Diathermy for physical therapy
- Tissue modification in ophthalmology and other specialties
- Scaling of calcified deposits from teeth

DIAGNOSIS

- Soft Tissue Visualization
  - Neurology and Neurosurgery
    - Determination of position of diencephalic midline
    - Determination of ventricular size
    - Transdural ranging for intracerebral tumor
  - Cardiology
    - Diagnosis of mitral valvular disease
    - Detection of tricuspid valvular disease
    - Detection of pericardial effusion
    - Detection of pleural effusion
    - Diagnosis of pulmonary embolism
    - Determination of cardiac output
    - Determination of heart wall thickness
  - Obstetrics
    - Fetal cephalometry
    - Placental localization
    - Detection of intrauterine life
    - Diagnosis of multiple pregnancy

DIAGNOSIS (Continued)

- Gynecology
  - Differentiation of pelvic masses (solid vs. cystic)
  - Diagnosis of hydatidiform mole
  - Diagnosis of missed abortion
- Ophthalmology
  - Diagnosis of retinal detachments
  - Diagnosis of intra- and extra-ocular tumor
  - Localization of intraocular foreign body
  - Extraction of non-magnetic intraocular foreign bodies
- General Surgery
  - Localization of biliary tract calculi
  - Diagnosis of metastatic carcinoma in liver
  - Localization of foreign bodies
- Vascular Surgery
  - Detection of arterial occulusion or stenosis
  - Detection of venous thrombosis or incompetence
  - Diagnosis and assessment of abdominal aortic aneurysm
  - Determination of aorta wall thickness
  - Measurement of blood flow rate
- Urology
  - Localization of renal calculi
  - Diagnosis of prostatic hypertrophy
  - Measurement of urinary bladder residue

INDUSTRY

LOW POWER APPLICATIONS

- Non-destructive testing
- Control applications
- Delay lines
- Viscosity measurements
- Light modulation

HIGH POWER APPLICATIONS

- Cleaning
- Welding
- Soldering and tinning
- Impact Grinding

HIGH POWER APPLICATIONS (Continued)

- Defoaming and Deaerating
- Homogenizing
- Atomization
- Metallurgical processing
- Drilling
- Chemical processing
- Nebulizers and emulsifiers
- Sewing machine
- Sonar

CONSUMER PRODUCTS

- Sewing machines
- Clothes and dish washers
- Pest controls
- Burglar alarms
- Remote control devices
- Cleaning

SCIENTIFIC INVESTIGATION

- Degradation of polymers
- Degradation of cellular and microbial structures
- Studying kinetic phenomena
- Determination of elastic properties of geological specimens
- Cleaning

TABLE 2: SUMMARIZED RESEARCH ACTIVITY IN ULTRASOUND *

	Medical & Other Applications R & D			Biological Effects Research		
Agency	No. Projects	No. Projects, Funds Known	Known Funding	No. Projects	No. Projects, Funds Known	Known Funding
DEPARTMENT OF HEW	42	37	2,110,633	9	8	290,730
ATOMIC ENERGY COMMISSION	4	0	-	0	0	
VETERANS ADMINISTRATION	16	0	-	2	0	-
DEPARTMENT OF AGRICULTURE	16	0	-	3	0	-
AMERICAN AND LOCAL HEART ASSOCIATIONS	36	31	162,035	0	0	
OTHER: NATIONAL SCIENCE FOUNDATION DEPARTMENT OF DEFENSE ENVIRONMENTAL PROTECTION AGENCY DEPARTMENT OF INTERIOR DEPARTMENT OF STATE	27	12	426,802	5	3	73,375
TOTAL	141	80	2,699,470	19	11	364,110
NORMALIZED TOTALS		(141)	4,757,816		(19)	628,917

*Based on analysis of data supplied by the Science Information Exchange, Smithsonian Institution

In view of the magnitude of ultrasound and the increasing trends of use, efforts must be directed to the evaluation of the health risks that may be associated with exposure to ultrasound. The assessment of risks is essential to provide a rational basis for benefit-risk judgments associated with diagnostic and therapeutic uses of ultrasound, and to provide for safety in industrial, consumer and scientific applications of ultrasound technology. An extensive literature documents actions of ultrasonic energy and biological materials. Grabar (1953) presented one of the earliest reviews of the biological actions of ultrasound on macromolecules, microorganisms, cells, organs and tissues along with a discussion of interaction mechanisms. El'piner (1964) has reviewed the literature on the physical, chemical and biological actions of ultrasound. He summarized the effects on macromolecules including polymerization, depolymerization and macroradical formation; effects on biomacromolecules including nucleic acids, globular and fibrous proteins, polysaccharides, mucopolysaccharides and enzymes; effects on viruses, bacteriophages, and other microorganisms; effects on cellular organisms including both unicellular and multicellular and, briefly, animal organisms; and briefly effects on organs and tissues.

A recent comprehensive review of ultrasonic bioeffect research was conducted during the Workshop on the Interaction of Ultrasound and Biological Tissues, held in Seattle, Washington, November, 1971 (Reid and Sikov, 1972). Review-type position papers summarize the effects on macromolecules including DNA, hemoglobin, serum albumen, ovalbumen, synthetic polyamino acids, amino acids, enzymes, and polyelectrolytes. At the cellular level, reviews described effects on chromosomal damage and elevated frequency of mutations, microstreaming, death and mitosis. Heat and cavitation mechanisms were discussed in relation to cellular effects. These effects were described on plant root tips, leukocytes, carcinoma cells, ova, <u>Escherichia coli</u>, bone marrow cells, erythrocytes, amoebae, microbes, protozoa, and cell membranes. Effects on tissues and organs were also described and included muscle fat, nerves, liver, skin, testes, kidney and teeth.

A research area which was not reviewed in the Workshop was human epidemiology of ultrasound effects. Studies of exposed human fetuses and adults have been performed with negative results (Donald and Abdulla, 1967; Bernstine, 1969; Hellman et al., 1970). The lack of follow up and other parameters of good epidemiological design are serious deficiencies in these studies. This is illustrated by the human x-ray experience. Diagnostic x irradiation of fetuses results in no demonstrable effects at birth. However, a follow-up period of ten years established a relationship between the diagnostic exposure and increased risk of leukemia and other cancers (Stewart, 1971). Furthermore, possible effects on chromosomes were published in original research papers in the May, 1972 British Journal of Radiology, along with experimental findings from studies of possible effects on chromosomes.

The difficulty with much of this literature is that its emphasis has been qualitative on the basic interaction mechanisms between ultrasound and biological materials, not quantitative on the relationship between the amount of stress applied and the biological effect produced, i.e., dose-effect study.

Research has been reported with the relationship between the amount of stress and the biological effect (Fry et al., 1970; Dunn and Fry, 1971). These studies show a linear relationship between the log of exposure duration for single exposures from 20,000 W/cm^2 at 200μsec. to 100 W/cm^2 at 10 sec. over the frequency range of 1-6 MHz, and the development of biological lesions in the mammalian brain.

An additional difficulty which impedes risk assessment and which is reflected in much of the ultrasound literature is the characterization of the radiant field in biological materials. In order to say that a specific radiant energy level is required to produce a particular effect, it is necessary to have the techniques to measure that level at the site at which the effect occurs. Techniques are available to measure many of the field parameters of ultrasound in a macroscopic homogeneous, isotropic low-loss medium such as water. But when the medium is inhomogeneous, anisotropic, lossy and dynamic, such as living materials, knowledge of the magnitude of ultrasonic field parameters is extremely difficult to obtain. Techniques to characterize the ultrasonic field in dynamic biological tissues are far more difficult to develop than techniques for inanimate materials. Thus far, satisfactory methods have not been developed.

Another difficulty which impedes risk assessment is the characterization of the perturbed biological system. Normal biological systems are extremely complex, very possibly among the most complex to study. While a number of features have been characterized, the systems remain poorly understood and unexplained in physical and chemical terms. When the systems are perturbed, the level of complexity is increased and the characterizations of the systems become even more uncertain. Thus, it is not entirely surprising that even the studies of interaction mechanisms between ultrasound and biological material remain poorly understood.

The intent of this discussion is not to paint a bleak picture, but rather to point out, realistically, the extremely complex problems confronting a research program which aims to assess the biological consequences of ultrasound exposure.

In order to surmount these, hopefully not impossible, obstacles, a "team effort" is essential. Such a team should include individuals who have insight into the physical phenomena of acoustic wave propagation and intimate knowledge of the biological system under investigation. These individuals must have enough understanding of the other's field so as to permit effective scientific communication. Such a "team effort" facilitates the achievement of realistic research goals.

Realistic research goals include the dose-effect studies which are essential to the assessment of health risks of ultrasound exposure -- a matter of significant public health concern. The current ultrasonic bioeffect literature may provide a basis for the selection of endpoints for dose-effect studies. However, the current status of dosimetry does not permit measurement of the pertinent ultrasonic field parameters in biological material.

It is appropriate to review briefly the three mechanisms by which effects are induced in biological material. The mechanisms are termed thermal, mechanical and cavitation. Operating definitions of the mechanisms, as used in ultrasound bioeffects research, are developed in the discussions below.

Whenever ultrasonic energy is absorbed by any biological material, heat results. Biological tissues absorb ultrasound at a relatively high rate. For example, at 1 MHz and 37°C, the absorption in liver tissue is approximately 600 times greater than that in water. Absorption is approximately two times greater in muscle tissue than in liver tissue while fat tissue than in liver tissue while fat tissue absorbs ultrasonic energy at about half the rate (Goldman & Hueter, 1956).

The heat distribution within tissue depends on the beam geometry as well as on the absorption coefficient and intensity. The initial rate of rise of temperature is the same for both plane waves and focused beams. However, the heat diffusing effects make the temporal development of temperature markedly different. The time dependence of temperature in focused and plane wave beams at 1 MHz is such that the time constant for a focal beam is of the order of 0.1 sec. For plane waves, the time constant can be up to a minute (Pond, 1968). For the therapeutic use of ultrasound around 1 MHz, plane, continuous wave techniques are typically utilized. However, reflections and scattering could cause focusing.

The selective heating at tissue interfaces can be ascribed to a thermal mechanism. The propagating longitudinal ultrasonic wave comes in contact with an interface and mode conversion results. This means that part of the longitudinal wave is converted to a shear wave. Shear waves have absorption coefficients orders of magnitude greater than longitudinal waves in tissues and, consequently, the wave energy quickly dissipates as heat within the immediate neighborhood of the interface. However, the shear absorption coefficient in bones is unknown (Lehman & Guy, 1972). The effect of mode conversion is much more pronounced at interfaces between bone and soft tissue than at interfaces between soft tissues. The extent to which selective heating occurs during the applications of ultrasound is unknown, along with the role of reflections and scattering of the energy. As a result, during the application of ultrasound, temporal and spatial distribution of temperature in tissue is unknown.

Since ultrasound is the propagation of mechanical energy, mechanical properties such as displacement, velocity, acceleration, and peak acoustic pressure must be associated with the biological effects of ultrasonic energy. Consider the numerical values of these parameters in Table 3, as calculated from idealized plane wave equations, at an ultrasonic frequency of 1 MHz over the indicated intensity range. Within this range of intensities, which represents approximately the range employed in the healing arts, the displacement in the tissue ranges from 18 to 1800Å, the velocity ranges from 12 to 120 cm/sec. and the acceleration ranges from 7,400 to 740,000 g's. That such extremely high acceleration forces could possibly shake something loose would not be at all surprising. An example of such a disruption is the dislodgement of ribosomes within a cell (Selman & Jurand, 1964). At the higher intensity levels, finite amplitude effects occur causing distortion of the wave shape and acoustic streaming results. Ultrasonically induced shearing stresses associated with acoustic streaming have been implicated as a mechanism inducing biological damage (Rooney, 1972a, 1972b). These stresses cause stretching, twisting and, finally, rupture of membraneous structures. It has been reported that a steady shear stress in the range of 3000 to 4500 $dynes/cm^2$ is sufficient to hemolyze the erythrocyte (Rooney, 1970). Other consequences of these stresses have been eddying motions, rotations and other movements of intracellular bodies within the cell (Nyborg, 1972). It is, however, difficult to determine the extent of these steady shearing stresses on dynamic biological processes <u>in vivo</u> since much of this experimental work has been performed in the low kilohertz frequency range.

TABLE 3: MECHANICAL PROPERTIES OF A PROPAGATED ULTRASONIC WAVE (ρ = 1gm/cc c =1500m/s f = 1MHz)

I (W/cm^2)	(Å)	U (cm/sec.)	Acc.(g's)	P (atm)
0.01	18	1.2	7400	0.17
0.1	58	3.7	23,000	0.55
1	180	12	74,000	1.7
10	580	37	230,000	5.5
100	1800	120	740,000	17

Cavitation is the general term used to describe the growth and subsequent dynamic behavior of gas bubbles in an ultrasonically irradiated medium. The bubble, once formed, can either remain stable and radially oscillate or continue to grow, become unstable and collapse. The latter, known as transient cavitation, produces intense hydrodynamic shearing forces within the vicinity of the collapsing bubble which can disrupt the surrounding material. Transient cavitation has been reported to occur in central nervous system tissue at very high intensity levels of 1500 W/cm^2 or greater (Dunn & Fry, 1971).

Stable cavitation has been investigated in biological materials (Rooney, 1970) at lower frequencies than those utilized in the healing arts. In the event that such oscillating bubbles occur adjacent to a cell, both rotational and irrotational forces could be induced with consequent, localized vibration of the cell surface resulting in steady stress field toward the oscillating bubble and particles within the cell would tend to accumulate near the vibrating area. Additionally, the particles would be set into steady rotation and move in circular paths. Motion pictures have demonstrated the existence of these phenomena in isolated cells at frequencies well below those utilized in diagnosis and therapy. An acoustic streaming boundary layer is formed.

Because transient cavitation has been reported at much higher ultrasonic intensities and stable cavitation has been studied at ultrasonic frequencies much lower than those used in the healing arts, the question of whether or not cavitation occurs in biological tissue of diagnostic and therapeutic ultrasound is not yet resolved.

Even though three mechanisms of ultrasonic action with biological material can be described, the current status of dosimetry does not permit adequate assessment of the <u>dose-related</u> biological consequences of these mechanisms. Ideally, the spatial distribution of the instantaneous values of particle velocity and particle pressure, along with their relative phase, is required to completely characterize the ultrasonic field. The lack of adequate ultrasonic dosimetry is a most serious obstacle to the assessment of risk associated with the exposure of ultrasound. It is, however, important to recognize that the lack of standardization and of dosimetry are common problems in all radiation bioeffect research. Theoretical and experimental techniques must be developed which will adequately quantify the spatial and temporal ultrasonic field parameters within the exposed biological system.

One possible area of investigation is phantom dosimetry. A model can be fabricated, say a sphere or cylinder, which would possess acoustical properties similar to that of the tissue being simulated. Ultrasonic energy at the appropriate frequency can be made incident upon the model. The distribution of the ultrasonic field parameters within the model would be analyzed experimentally and theoretically. The contributions of scattering, reflections, refractions, and mode conversions, all leading to the eventual *in vivo* assessment of the ultrasonic field parameters must be considered in developing body-equivalent or man-equivalent models.

Summary

The uses of ultrasonic energy are rapidly increasing in the healing arts, as well as in scientific, industrial and consumer applications. This increasing use will require an assessment of risks, which will be based on available bio-effect knowledge. The available literature documents a large number of effects which occur as a result of exposure to ultrasound. However, meager information is available on dose quantification for any given biological effect. The knowledge of interactions between ultrasound and biological systems, as well as dosimetry in complex biological materials, requires further improvement and expansion. The quality and quantity of biological effect information which serves as the basis for risk assessment will establish the reliability and adequacy of the risk assessment.

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