

AL/OE-TR-1996-0036



**RADIOFREQUENCY RADIATION AND TERATOGENESIS:
A COMPREHENSIVE REVIEW OF THE LITERATURE PERTINENT
TO AIR FORCE OPERATIONS**

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June 1996

Final Technical Report for Period January 1994 to November 1995

Approved for public release; distribution is unlimited.

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE June 1996		3. REPORT TYPE AND DATES COVERED Interim, January 1994–November 1995
4. TITLE AND SUBTITLE Radiofrequency Radiation and Teratogenesis: A comprehensive Review of the Literature Pertinent to Air Force Operations			5. FUNDING NUMBERS PE - 62202F PR - 7757 TA - B3 WU - 09	
6. AUTHOR(S) Louis N. Heynick and Peter Polson				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) AUSA 18985 Tuggle Avenue Cupertino, CA 95014			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Armstrong Laboratory Occupational and Environmental Health Directorate Radiofrequency Radiation Division 8305 Hawks Road Brooks Air Force Base, TX 78235-5324			10. SPONSORING/MONITORING AGENCY REPORT NUMBER AL/OE-TR-1996-0036	
11. SUPPLEMENTARY NOTES Armstrong Laboratory Technical Monitor: James H. Merritt (210)536-4703				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) This report on analyses of various research investigations that sought teratogenetic effects of exposure to radiofrequency radiation (RFR) is one of a planned series of various topics dealing with actual or possible biological effects of RFR and their potential consequences regarding human health. In this report, critiques are presented of the research papers (in English) on the topic RFR-induced teratogenesis, selected predominantly from the peer-reviewed literature. With few exceptions, presentations at scientific symposia or abstracts thereof were excluded from consideration in expectation that more detailed, peer-reviewed accounts of such studies will appear subsequently. Endeavors were made to obtain and analyze virtually all of the peer-reviewed papers published to date, though some papers may have been missed. Most of the teratogenic studies with animals were done with RFR levels well in excess of current safety guidelines. Taken collectively, those studies indicate that teratogenic effects can occur in subjects from RFR exposure only at levels that produce significant bodily temperature increases. For mammals, increases in maternal body temperature that exceed specific thresholds (for each species) are necessary for inducing teratogenic effects. None of the epidemiologic studies of possible congenital anomalies provide credible evidence that chronic exposure of human mothers during pregnancy or of potential fathers to RFR at levels at or below the current maximum guidelines would cause any anomalies in their offspring.				
14. SUBJECT TERMS Radiofrequency radiation bioeffects Teratogenesis Birth defects			15. NUMBER OF PAGES 124	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT UL	

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[21 November 1994]

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RFR-TERATOGENESIS: A COMPREHENSIVE REVIEW OF THE LITERATURE PERTINENT TO AIR
FORCE OPERATIONS

[REVISION: 21 November 1994]

1 INTRODUCTION

1.1 GENERAL

This report on analyses of various research investigations that sought teratogenetic effects of exposure to radiofrequency radiation (RFR) is one of a planned series on various topics dealing with actual or possible biological effects of RFR and their potential consequences regarding human health. In this report, as is planned in the reports on other topics, critiques are presented of the research papers (in English) on the specific topic, selected predominantly from the peer-reviewed literature. This topical series is to include revisions of and additions to the critiques, in Heynick (1987), of the then representative RFR-bioeffects papers published through about 1986, as well as critiques of subsequently published papers. With few exceptions, presentations at scientific symposia or abstracts thereof were excluded from consideration in expectation that more detailed, peer-reviewed accounts of such studies will appear subsequently. Because of their pertinence to the present topic, the sections on RFR safety standards and on measurements of environmental levels of RFR in the first report of this series, entitled "Human Exposure to RFR," are included herein.

The acronym "RFR" used herein refers to the emission and propagation of electromagnetic waves in the frequency range nominally from 3 kHz to 300 GHz. Such waves are characterized as nonionizing radiation because the intrinsic (quantum) electromagnetic energy absorbed by a body at any frequency within this range is much too low to ionize (eject electrons) from molecules of the body. Equivalent terms found in the literature on RFR bioeffects include electromagnetic radiation (EMR), nonionizing radiation (NIR), nonionizing electromagnetic radiation (NIEMR), microwave radiation, microwave fields, radiofrequency electromagnetic (RFEM) fields, and electromagnetic fields (EMF). It should be noted, however, that the acronyms "EMF" or "EMFs" lately have become associated primarily with possible bioeffects of 50-Hz and 60-Hz electric and magnetic fields from powerlines.

Endeavors were made to obtain and analyze virtually all of the peer-reviewed papers published to date on each topic. It is likely, however, that some papers were missed. If so, the authors of this report would be most appreciative of any suggested additions. Such papers, together with those published after this report is issued, may serve as the basis of a later update on those topics.

1.2 RFR SAFETY STANDARDS

Terms such as "safety standards" and "exposure standards" generally refer to, and are frequently used interchangeably with, specifications or guidelines on maximum permissible exposure levels to electromagnetic fields for the general public or for those in occupations and/or in working areas where they may be periodically exposed to higher than background levels of such fields. In both situations, such levels are usually expressed as maximum permissible incident field intensities and/or power densities in specific frequency ranges for stated exposure durations.

In most guidelines for human exposure to RFR, the maximum permissible exposures (MPEs) are stated in terms of the maximum allowable incident power densities, expressed in milliwatts per square centimeter (mW/cm^2) or in watts per square meter (W/m^2 , with $1 \text{ W}/\text{m}^2 = 0.1 \text{ mW}/\text{cm}^2$). Such MPEs are selected on the basis of the highest values of "specific absorption rate" (SAR) that were found not to be harmful to animals in experimental studies. SAR is defined as the rate at which RFR energy is absorbed in any small volume of a body, and is usually expressed in watts per kilogram (W/kg) of the mass in that volume (or sometimes in milliwatts per gram, with $1 \text{ mW}/\text{g} = 1 \text{ W}/\text{kg}$). For any specific value of incident power density, the SAR thus defined varies with location within the body, so it is frequently called the "local SAR".

Internal variations of SAR are difficult to determine for most complex bodies, so the term "whole-body SAR" is often used to represent the spatially averaged value of SAR for the body, a quantity that can be measured (e.g., by calorimetry) without a need to know the spatial variations of local SAR. The term "partial-body" or "part-body" SAR is used in appropriate cases, such as when absorption of RFR occurs primarily in a specific region of the body due to exposure from a nearby emitter (a hand-held transmitter for example).

For certain specified exposure conditions, such as at frequencies below about 300 MHz and/or within the "near-field" distance of an antenna emitting electromagnetic energy, it is usually necessary to consider the electric and magnetic fields separately. For such conditions, exposure guidelines are expressed in terms of maximum allowable electric fields in volts per meter (V/m) and/or maximum allowable magnetic fields in amperes per meter (A/m). Again, such guidelines are based on whole-body or part-body SARs.

Voluntary occupational guidelines and/or guidelines for exposure of the general public to RFR have been developed by various organizations, and such guidelines are reexamined for possible revisions on a cyclic schedule usually encompassing several years.

In 1974, the American National Standards Institute (ANSI) had published a standard (ANSI, 1974) applicable to those occupationally exposed to RFR and to exposure of the general public to RFR. Such exposures were not to exceed $10 \text{ mW}/\text{cm}^2$ or the equivalent electric and magnetic field strengths ($200 \text{ V}/\text{m}$ and $0.5 \text{ A}/\text{m}$, respectively) independent of frequency over the entire range 10 MHz to 100 GHz. The Federal Occupational Safety and Health Administration (OSHA), which had promulgated the $10\text{-mW}/\text{cm}^2$ level as a voluntary occupational standard, subsequently found that the standard was legally unenforceable.

In 1982, ANSI had issued a revision (ANSI, 1982) of the 1974 guidelines, also applicable to both occupational and general-public exposure, based on critical analyses of the then current knowledge about the biological effects of RFR. The highest allowable incident field strengths or plane-wave equivalent power densities were based on a maximum whole-body SAR of $4 \text{ W}/\text{kg}$, which rendered those allowable levels frequency-dependent; the range covered by ANSI (1982) was 300 kHz to 100 GHz. The $4\text{-W}/\text{kg}$ SAR was the level at or above which significant detrimental effects were observed in experimental studies with laboratory animals. A safety factor of 10 was incorporated in the ANSI (1982) guidelines, reducing the maximum allowable SAR to $0.4 \text{ W}/\text{kg}$. As in ANSI (1974), the limits in ANSI (1982) were not to be exceeded for

exposures averaged over any six-minute period. At 0.4 W/kg, the smallest maximum allowable incident power density was 1 mW/cm² for the subrange 30-300 MHz, in which RFR absorption by the human body as a resonant entity (much like a dipole antenna) is highest.

In 1988, the functions of the various ANSI subcommittees on developing guidelines for RFR-exposure were transferred to Subcommittee IV of Standards Coordinating Committee (SCC) 28, a new body under the jurisdiction of the Institute of Electrical and Electronics Engineers (IEEE). SCC 28 produced a revision of the 1982 ANSI guidelines, based on the selection and analyses of the important research papers in an updated data base of the RFR-bioeffects literature. The revision, "IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz," was approved by the IEEE in 1991 and published in 1992. It was also approved by ANSI in 1992, and is referred to herein as the ANSI/IEEE (1992) guidelines.

As in ANSI (1982), the ANSI/IEEE (1992) guidelines, expressed in terms of MPEs, are largely based on 0.4 W/kg (4 W/kg reduced by a safety factor of 10). They cover the frequency range from 3 kHz to 300 GHz (instead of 300 kHz to 100 GHz), and separately specify MPEs in "uncontrolled environments" (in areas accessible by the general population) and in "controlled environments" (such as occupational exposure). The guidelines for controlled environments and uncontrolled environments are displayed in Tables 1 and 2, respectively. The averaging times are given in minutes.

**TABLE 1: ANSI/IEEE (1992) MAXIMUM PERMISSIBLE EXPOSURE LIMITS
FOR CONTROLLED ENVIRONMENTS***

<u>Frequency Range</u> (MHz)	<u>E</u> (V/m)	<u>H</u> (A/m)	<u>Power Density, S</u> (mW/cm ²)	<u>Averaging Time</u> E ² , H ² , or S
0.003 - 0.1	614	163	**	6
0.1 - 3.0	614	16.3/f	**	6
3 - 30	(1 842)/f	16.3/f	**	6
30 - 100	61.4	16.3/f	**	6
100 - 300	61.4	0.163	1.0	6
300 - 3 000			f/300	6
3 000 - 15 000			10	6
15 000 - 300 000			10	(616 000)/f ^{1.2}

The specified limits on incident fields were not to be exceeded for exposures averaged over any 6-minute period. For a fixed maximum SAR, the guidelines on maximum incident fields were frequency-dependent; the frequency range covered by ANSI (1982) was 300 kHz to 100 GHz. The smallest maximum limit on incident power density was 1 mW/cm² for the subrange 30-300 MHz in which RFR absorption by the human body as a resonant entity (much like a dipole antenna) is highest.

**TABLE 2: ANSI/IEEE (1992) MAXIMUM PERMISSIBLE EXPOSURE LIMITS
FOR UNCONTROLLED ENVIRONMENTS***

Frequency Range (MHz)	E (V/m)	H (A/m)	Power Density, S (mW/cm ²)	Averaging Time	
				E ² , S	H ²
0.003 - 0.1	614	163	**	6	6
0.1 - 1.34	614	16.3/f	**	6	6
1.34 - 3.0	823.8/f	16.3/f	**	f ² /0.3	6
3.0 - 30	823.8/f	16.3/f	**	30	6
30 - 100	27.5	158.3/f ^{1.668}	**	30	0.0636f ^{1.337}
100 - 300	27.5	0.0729	0.2	30	30
300 - 3 000			f/(1 500)	30	
3 000 - 15 000			f/(1 500)	(90 000)/f	
15 000 - 300 000			10	(616 000)/f ^{1.2}	

*In both tables above, the exposure values in terms of electric and magnetic field strengths are the values obtained by spatially averaging values over an area equivalent to the vertical cross section of the human body (the projected area).

**The equivalent plane-wave power densities for E (V/m) and H (A/m), expressed in W/m², can be calculated from the equations $S = E^2/377$ and $S = 377H^2$, where 377 (ohms) is the impedance of free space. To obtain the corresponding values of S in mW/cm² as shown in the tables, divide the values expressed in W/m² by 10. Note that even though such calculated equivalent power densities are not appropriate for near-field conditions, they are useful for comparing them with the power density limits for the higher frequency ranges.

For controlled environments, those guidelines also specify the following limits on pulsed RFR:

In the frequency range 0.1 to 300 000 MHz, the peak temporal MPE, expressed in terms of the electric field, is 100 kV/m. For single RFR pulses of duration less than 100 milliseconds in this frequency range, the peak MPE is given by the E-field equivalent power-density MPE of Table 1 in the formula:

$$\text{Peak MPE} = \text{MPE} \times \text{averaging time} / (5 \times \text{pulse duration}).$$

A maximum of five such pulses, with a pulse repetition period of at least 100 milliseconds, is permitted during any period equal to the averaging time.

For pulse trains of more than 5 pulses or for pulse durations that exceed 100 milliseconds, the following formula applies for averaging over any 100-millisecond period:

$$\Sigma \text{ Peak MPE} \times \text{pulse duration} = \text{MPE} \times \text{averaging time} / 5.$$

Also included in the ANSI/IEEE (1992) guidelines are maximum allowable values of radiofrequency current flow induced within the feet of a person immersed in an RFR field or by a person's contact with an inanimate object (such as a fence or vehicle) electrically charged by immersion in an RFR

field. The limits for controlled and uncontrolled environments, shown respectively in Tables 3 and 4, are applicable only within the frequency range from 3 kHz to 100 MHz (where such effects can occur).

**TABLE 3: ANSI/IEEE (1992) LIMITS ON INDUCED AND CONTACT CURRENTS
IN CONTROLLED ENVIRONMENTS**

<u>Frequency Range (MHz)</u>	<u>Maximum Current (mA)</u>		
	<u>Through both feet</u>	<u>Through each foot</u>	<u>Contact</u>
0.003 - 0.1	2000f	1000f	1000f
0.1 - 100	200	100	100

**TABLE 4: ANSI/IEEE (1992) LIMITS ON INDUCED AND CONTACT CURRENTS
IN UNCONTROLLED ENVIRONMENTS**

<u>Frequency Range (MHz)</u>	<u>Maximum Current (mA)</u>		
	<u>Through both feet</u>	<u>Through each foot</u>	<u>Contact</u>
0.003 - 0.1	900f	450f	450f
0.1 - 100	90	45	45

The ANSI/IEEE (1992) guidelines also specify exclusions for exposures, under controlled and uncontrolled environments, from devices that emit RFR of low power.

For several years, the Environmental Protection Agency (EPA) had been planning to issue RFR-exposure guidelines for the general population. The rationale for those guidelines was to be based on a literature review by Elder and Cahill (1984). On 30 July 1986, EPA had published a *Notice of Proposed Recommendations* (EPA, 1986) in which three options based on risk, benefit, and cost analyses were proposed: a tenfold, fivefold, or no reduction from 0.4 W/kg (i.e., to 0.04, 0.08, or 0.4 W/kg). However, EPA subsequently decided not to issue such exposure guidelines for the general population, and it has not done so to date.

In the absence of a governing Federal standard (but not necessarily for that reason), various state, county, and municipal bodies have promulgated ordinances on exposure of the general population to RFR that are usually more stringent than those of ANSI (1982) or ANSI/IEEE (1992). Most such standards refer to the 4-W/kg SAR used as the basis of the 1982 ANSI guidelines, but with a safety reduction factor of 50 [to 0.08 W/kg] instead of 10.

More recently (on 26-27 April 1993), the EPA conducted a workshop in Bethesda, MD, to review the current status of research on biological effects of RFR. Formal presentations were given by invited experts on various topics, including dosimetry, magnetic resonance imaging (MRI), thermal physiology, epidemiology, and a general review of the scientific literature. The formal presentations were followed by workshops on those and other topics, and then by summaries at a plenary session. Last, the Chair of the plenary session (a member of the EPA's Science Advisory Board) proposed the following two-part motion, which was overwhelmingly approved by those present:

- 1) That the EPA resume its activities on RFR-bioeffects research with the intent of establishing a national standard for RFR-exposure.

2) That in the interim, the EPA adopt the ANSI/IEEE (1992) standard.

Other bodies in the USA and in other countries have issued exposure guidelines and/or are engaged in the cyclic process of revising previously published guidelines.

1.3 MEASUREMENTS OF ENVIRONMENTAL LEVELS OF RFR IN SELECTED U.S. CITIES AND AT SPECIAL LOCATIONS

More than a decade ago, the EPA had measured the environmental field intensities at selected locations in 15 U.S. cities. Even though a long time has elapsed since those measurements, the data remain valuable in the absence of comprehensive subsequent measurements.

The sites in each city were selected to permit analyses and estimations of cumulative fractions of the total population in each city exposed at or below various average power densities, based on the population figures derived from the 1970 census-enumeration districts. Tell and Mantiply (1980) and Janes et al. (1977) presented the results for those cities (a total of 486 sites). Those results were also summarized in Hankin (1985) and in EPA (1986).

Measurements of field intensity were made at 6.4 m (20 ft) above ground at each site in the following frequency ranges (Janes et al., 1977): 0.5-1.6 MHz (the standard AM-radio broadcast band), 54-88 MHz and 174-216 MHz (the VHF-TV bands), 88-108 MHz (the standard FM-radio broadcast band), about 150 and 450 MHz (land-mobile bands), and 470-890 MHz (the UHF-TV bands). The signals in each band were received with separate antennas specifically designed for each band. However, measurements in the standard AM-radio broadcast band were not included in the analyses because that band was below the then prevailing 10-MHz lower frequency limit of the 1974 ANSI standard.

The measured field strengths at each site were integrated over the frequency bands (54 to 890 MHz) included in the analyses and converted into equivalent average power densities. The site values in each city were then used, with the population figures for the census enumeration districts, in a statistical model designed to estimate the population-weighted median exposure value for that city, and for calculating other statistics of interest.

The population-weighted median value for each city was defined as the average power density at or below which half the population of the city was being exposed. The estimates were based on the assumption that the people were under continuous exposure at their place of residence; the estimates did not try to account for population changes since the 1970 census, population mobility, exposure at heights greater than 6.4 m (20 ft), attenuation of signals by buildings, or periods of time when any of the contributing RFR sources were not transmitting. The fifteen cities and their median values are shown in Table 5:

TABLE 5: ESTIMATED POPULATION EXPOSURES FOR 15 U.S. CITIES
[Tell and Mantiply (1980)]

<u>City</u>	<u>Median Exposure</u> <u>($\mu\text{W}/\text{cm}^2$)</u>	<u>Percent Exposed to Less Than</u> <u>1 $\mu\text{W}/\text{cm}^2$</u>
Boston	0.015	98.50
Atlanta	0.016	99.20
Miami	0.0070	98.20
Philadelphia	0.0070	99.87
New York	0.0022	99.60
Chicago	0.0020	99.60
Washington	0.009	97.20
Las Vegas	0.012	99.10
San Diego	0.010	99.85
Portland (Oregon)	0.020	99.70
Houston	0.011	99.99
Los Angeles	0.0048	99.90
Denver	0.0074	99.85
Seattle	0.0071	99.81
San Francisco	0.002	97.66
All cities	0.0048	99.44

The median exposures ranged from 0.002 $\mu\text{W}/\text{cm}^2$ (for San Francisco and Chicago) to 0.020 $\mu\text{W}/\text{cm}^2$ (for Portland) and the population-weighted median for all 15 cities was 0.0048 $\mu\text{W}/\text{cm}^2$. Also, the percentages of the population exposed to less than 1 $\mu\text{W}/\text{cm}^2$ in each city ranged from 97.2% (for Washington, D.C.) to 99.99% (for Houston), with a mean for all cities of 99.44%. The major contributions to those exposure values were from FM-radio and TV broadcast stations.

In the context of human exposure to environmental levels of RFR, many people are unaware that at normal body temperature, all of us are emitters of electromagnetic energy. Based on the well established physics principle of "black-body" radiation and assuming an emissivity of 1, Osepchuk (1990) [page 543] has calculated that at 98.6 °F (37 °C or 310 °K), a body emits continuous radiation that peaks in the infrared region (at a wavelength of approximately 12 micrometers), and that in the RFR part of the emission curve (continuous frequency range up to about 300 GHz), the emission level of the body is about 0.3 $\mu\text{W}/\text{cm}^2$. Osepchuk (1990) also cites several calculations by others, based on the same principle, that are erroneous.

The EPA also measured RFR levels at sites close to single or multiple RFR emitters, for example, at the bases of transmitter towers and at the upper stories (including the roof) of tall buildings or hospital complexes in the vicinity of transmitter towers. At the base of an FM tower on Mount Wilson, CA, the fields were found to range from the equivalent of about 1 to 7 mW/cm^2 (Tell and O'Brien, 1977). Most measurements in tall buildings near FM and TV transmitters yielded values well below 0.01 mW/cm^2 (10 $\mu\text{W}/\text{cm}^2$), but a few values were close to or slightly exceeded 0.2 mW/cm^2 (e.g., 0.23 mW/cm^2 on the roof of the Sears Building, Chicago).

In Hawaii, however, considerably higher levels were found subsequently by EPA and Federal Communications Commission (FCC) personnel in a few sites very close to AM (550 kHz to 1.5 MHz) broadcast towers and FM (88-108 MHz)

broadcast towers (MICROWAVE NEWS, January/February 1985). The highest levels were in the vicinity of several AM-broadcast stations. For example, next to a tower in Kaimuki having one FM station and three AM stations, the maximum AM magnetic field was 9 A/m, the square of which is about 32 times higher than the 1982 ANSI standard for the frequency range 0.3-3 MHz. Whether transient or intermittent exposure to such AM-RFR levels would be harmful is subject to debate. In most areas accessible by the general public, the RFR levels were within the 1982 ANSI standard. Since then, however, the use of wireless communications in a growing variety of applications has continued to explode, a trend likely to be maintained during the 1990s. At present, there appears to be little information on current levels of exposure of the general public to RFR.

2 RFR-TERATOGENESIS IN NONMAMMALIAN SPECIES

2.1 INSECTS

Teratogenesis refers to the causation of anatomical aberrations (terata) in a developing fetus, but more generally also includes fetal death and/or resorption, and postnatal abnormalities in the offspring. Such effects occur naturally at low rates in most mammals, and relatively little is known about their causes. In some cases, however, specific physical or chemical agents have been shown to cause significant effects, and hence the possibility that such effects could occur from exposure to RFR is an appropriate matter for public concern. The term usually is applied to mammalian fetuses and infants, but effects of RFR on nonmammalian subjects have been sought also.

Various studies were performed on pupae of the darkling beetle (*Tenebrio molitor*). In an early study, Carpenter and Livstone (1971) exposed single pupae to 10-GHz RFR for 2 hours at 17 mW/cm² (40 W/kg estimated dose rate per unit body mass, hereinafter termed "SAR") or at 68 mW/cm² (160 W/kg) for 20 or 30 minutes. As representative results, only about 20% of pupae exposed at the lower RFR level developed into normal beetles; about 4% died and 76% had gross abnormalities. Exposure for 20 minutes at the higher RFR level yielded about 24% normal beetles, 25% dead ones, and 51% with gross abnormalities. By contrast, 90% of the sham-exposed pupae developed normally. About 75% of the pupae heated conventionally to the temperature obtained with 17 mW/cm² emerged as normal beetles, leading the authors to conclude that abnormal development of RFR-exposed pupae could not be explained as a thermal effect.

Lindauer et al. (1974), in an effort to verify the findings of Carpenter and Livstone (1971), exposed groups of 4 *Tenebrio molitor* pupae in Styrofoam blocks for 2 hours along the center line of a waveguide to 9-GHz CW RFR at an input power of 20 mW, which was equivalent to a free-space power density of 17.1 mW/cm². The authors noted that, in contrast with Carpenter and Livstone (1971), they made no attempt to match pupa impedance with the holder.

A plot of temperature rise within a pupa exposed at 20 mW, with its posterior toward the source, versus exposure duration (Figure 3 of the paper) shows a rise of 1.38 °C. It is noteworthy that most of the rise, to a near plateau, occurs within about 5 minutes after exposure start, and then rises more slowly, with equilibrium attained in about 8 minutes. The temperature increase within a pupa with its anterior toward the source was 1.76 °C. In both of those orientations, the long axis of the pupa was perpendicular to the

electric component of the transverse-electric [TE₁₀] mode for an empty waveguide. Other pupae were similarly sham-exposed, and still others were used as temperature controls; the latter were held for 2 hours in an oven at 29 °C, which was 8 °C higher than ambient and larger than the <2-°C rises in RFR-exposed pupae.

To ascertain whether teratogenic effects were ascribable to average RFR power level or to peak fields, other pupae were exposed to 9-GHz, 0.25-μs pulses of 50-W peak power at 1600 pps or to pulses of 5-kW peak power at 16 pps, both corresponding to an average power of 20 mW. Still other pupae were exposed to the CW RFR with axes parallel to the electric field (transverse to the waveguide), and others were exposed at only 10 W (8.6 mW/cm² equivalent power density) respectively for 4 hours or 2 hours, to seek a threshold and possible dependence of effect on total energy.

The results were tabulated in terms of the numbers and percentages of emergent dead beetles, 3 categories of damaged beetles (later combined), and normal beetles. The chi-squared test was applied to determine statistically significant differences among the treatments. Although some RFR-related differences were significant (p<0.05), no clear dependence of effect on dose rate or total dose was found. Also, there were no significant differences in results between exposure of pupae perpendicular and parallel to the electric field or between pulsed and CW RFR at the same average power density. RFR-absorption measurements in pupae yielded an SAR of 41 W/kg for 20 W (17.1 mW/cm²).

Liu et al. (1975) extended this work at 9 GHz and found significant teratogenesis for 2-hour exposures at power densities as low as about 0.17 mW/cm² (0.41 W/kg). In addition, exposures at various levels and durations corresponding to a constant incident energy dosage of 4 mW-hour (of which about a third was absorbed by each pupa) yielded evidence of an inverse (reciprocal) relationship between power and duration.

Green et al. (1979) found that *Tenebrio* pupae cultured and exposed to 9-GHz RFR in ambient relative humidities of less than 35% were more susceptible to RFR teratogenesis than pupae similarly treated at higher humidities. At the lower humidities, they observed a slight rise in the incidence of terata with increasing applied RFR power (2-hour constant exposure) up to 34 mW/cm² (80 W/kg). At 272 mW/cm² (640 W/kg), they observed a further increase in teratogenic incidence, with an increase in pupa death before completion of development. The authors attributed the apparent "power window" at 34 mW/cm² (80 W/kg) to antagonism between nonthermal teratogenic effects and protective effects ascribable to the rise in temperature.

Olsen (1977a) exposed *Tenebrio* pupae to 4.0-GHz or 5.95-GHz CW RFR. For each exposure, groups of 12 pupae each were mounted in 3x4 rectangular arrays within thin Styrofoam sheets, which were irradiated in the far field of a standard gain horn within an anechoic chamber. Three sheets, spaced at a distance equivalent to a quarter wavelength, were placed at right angles to the horizontal propagation direction of the horn. At a quarter-wavelength distance beyond the sheets was a large (61x61-cm) metal reflecting plate, which produced standing waves: a maximum standing-wave magnetic field (H-field) in the plane of the center sheet and a maximum standing-wave electric field (E-field) in the planes of the two outer sheets. The pupae within each

sheet were spaced about 2/3 of a wavelength, and the arrays were offset to prevent mutual shadowing of pupa arrays from the RFR. Separate exposures were done in each plane with the long axes of the pupae oriented vertically (parallel to the E-field) and horizontally (parallel to the H-field).

With the reflecting sheet removed, the incident power densities in the region of the three sheets were measured with a Narda 8306B isotropic probe. The input levels used were 24 mW/cm² at 4.0 GHz and 21 mW/cm² at 5.95 GHz. With the reflecting sheet in place, the squares of the E-fields were measured with a National Bureau of Standards EDM-1B probe. At 4.0 GHz, reliable results were obtained in the plane of the second E-field maximum; those results showed that the levels over the area to be occupied by the pupae were essentially uniform. In that plane, the E-field strength at 4.0 GHz was 602 V/m, and at 5.95 GHz was 562 V/m.

The cooling-curve method of Johnson and Guy (1972) was used to estimate the corresponding SARs in the plane of the second E-field maximum. At 4.0 GHz and 5.95 GHz, the respective results were 29.1 ± 2.6 (SD) W/kg and 806 ± 78 W/kg. The SARs were also measured for dead pupae oriented perpendicular to the E-field and in both orientations in the plane of maximum H-field, and all were found to be much smaller than those for the parallel orientation in the plane of the second E-field maximum.

The pupae studied were derived from larvae cultured in unlighted boxes and fed Purina dairy meal. In control experiments, only two morphological defects were observed in adult beetles from nearly 200 sham-exposed pupae. Exposure of pupae to 5.95-GHz RFR for 30 minutes at 806 W/kg in the E-plane killed most of them, but exposure at 126 W/kg in the H-plane killed only one pupa. However, exposure to 5.95-GHz RFR at lower dose rates (ranging from 212 W/kg for 1 hour in the E-plane to 51 W/kg for 4 hours in the H-plane) caused no deaths, but did produce morphological defects in some of the adult beetles. Specifically, exposure of groups of 12 pupae each for 4 hours at 106 W/kg in the E-plane or at 102 W/kg in the H-plane respectively yielded morphological defects in half and about two-thirds of the insects. These levels and durations corresponded to total doses of 1526 and 1468 J/g. On the other hand, exposures at about 50 W/kg in either plane for up to 4 hours yielded no morphological defects. In exposures to 4.0-GHz RFR for 6 hours, a dose rate of 29.1 W/kg in the E-plane (total dose 629 J/g) yielded 1 defect in 23 insects, and a dose rate of 5.9 W/kg in the H-plane (total dose 127 J/g) yielded 2 defects in 24 insects. No defects were seen for exposures at those dose rates for 2 or 4 hours.

In a subsequent study, Pickard and Olsen (1979) used *Tenebrio* pupae from two sources. "Colony-pupae" were those derived initially as larvae from one supplier and raised on Purina dairy meal; "K-pupae" were purchased as larvae in three batches from another supplier and raised on Kellogg's Special K. Groups of K-pupae from the first batch and colony-pupae were sham-exposed or exposed at 6 GHz to: a standing-wave electric field (E-field) of 91 V/m (equivalent free-space power density of 2.2 mW/cm²) for 2 hours, with their long axes parallel to the E vector; a standing-wave magnetic field (H-field) of 1.53 A/m (88.3 mW/cm²) for 2 hours, with their long axes parallel to the H vector; or a traveling-wave electromagnetic (far) field of 11 mW/cm² for 13 hours, with the long axes parallel to either the E vector or the propagation direction. As in the earlier study, the standing-wave fields were produced by

use of a reflecting plane in the far field of a horn, and the pupae were placed in the planes of maximum E and H; removal of the reflecting plane yielded the traveling-wave field. The corresponding SARs were 130, 54, and 130 W/kg. Pupae were also exposed for 4 hours to traveling-wave 10-GHz RFR at 5 mW/cm² (45 W/kg).

The differences in the incidences of abnormalities between the groups exposed to the E-field and the corresponding control colony-pupae and K-pupae were not significant. However, the proportion of nonnormal beetles from the control K-pupae was significantly larger than from the control colony-pupae. Also, H-field exposure produced significant effects on K-pupae from the first batch but not on colony-pupae, but repetition of the H-field experiment with K-pupae from the other two batches yielded ambiguous results, ranging from "doubtfully deleterious" to "significantly beneficial" effects. Ambiguous results were also obtained from exposures for 13 hours to the 6-GHz traveling-wave RFR (130 W/kg) and for 4 hours to the 10-GHz RFR at 5 mW/cm² (45 W/kg). The authors suggested that these variations may have been due to uncontrolled differences in such non-RFR factors as the source of the larvae, pupae-maintenance regimes and handling protocols, the pupae containers used for pupation, and ambient temperature, an explanation that could account for the variabilities among the results of the other investigators cited.

The authors nevertheless concluded that their results indicated that RFR can be teratogenic in *Tenebrio* but left unproved the nonthermal hypothesis of Carpenter and Livstone (1971). Moreover, Olsen and Hammer (1982) measured spatial distributions of SAR thermographically within pupae during exposure to 1.3-GHz, 6-GHz, or 10-GHz RFR. They found large variations of local SAR that would not occur from the radiant heating used by Carpenter and Livstone (1971).

In yet another study, Olsen (1982a) exposed groups of *Tenebrio* pupae to a standing-wave, 6-GHz field in an anechoic chamber for 1.5, 3.0, 6.0, 12, or 24 hours at intensities inversely proportional to duration, to yield a constant total dosage of 1123 J/g in each pupa. Half of the insects were exposed in the maximum-E-field plane with their long axes perpendicular to the E vector and the other half in the maximum-H-field plane with their long axes parallel to the H vector. With these orientations, the SARs were both 208 W/kg at the highest intensity used, i.e., for the 1.5-hour exposures. The exposures were done without or with the use of a ventilating fan. With the fan operating, the temperature rise in the chamber was less than 4.5 °C, as contrasted with about 11 °C with the fan off. The control experiments consisted of sham-exposures for 6, 12, and 24 hours.

The results of the control experiments showed no morphological defects, in sharp contrast to the relatively large incidence of anomalies observed in control pupae by Liu et al. (1975). For the 1.5-hour exposures at 208 W/kg in the absence of chamber ventilation, Olsen (1982a) reported that 11 of 12 pupae exposed in each plane had died during pupation and that the twelfth pupa was abnormal; however, there were no deaths in the groups exposed for 3, 6, 12, or 24 hours at successively halved SARs and there were only 2 abnormal pupae in total. Moreover, in the 120 pupae comprising the 10 groups exposed with the fan operating, there were no deaths and only 1 anomaly. The author remarked the absence of reciprocity or a graded response in his results, and suggested the existence of a hyperthermia threshold of approximately 40 °C for deleterious effects on *Tenebrio molitor* pupae.

Thus, in contrast with the findings of Carpenter and Livstone (1971), Lindauer et al. (1974), and Liu et al. (1975), the results of the various studies by Olsen and coworkers indicated that the deleterious effects of RFR on the darkling beetle were thermally based, and that non-RFR factors could have influenced the differences in findings in the prior studies.

2.2 BIRDS

McRee and coworkers did a variety of studies on Japanese quail (*Coturnix coturnix japonica*). In an early investigation, McRee et al. (1975) exposed 4x5 arrays of Japanese-quail eggs to far-field 2.45-GHz CW RFR, with the long axes of the eggs parallel to the E vector (vertical). Five arrays were exposed for 4 hours, one each at the end of the first five successive days of incubation. A sixth array was exposed for 4 hours at the end of all five incubation days. The ambient temperature and relative humidity were 24 °C and 40%. The power density was 30 mW/cm², selected to yield egg temperatures (at this ambient temperature) of about 37 °C, the incubator temperature.

Egg temperatures at the surfaces facing the RFR source, determined by infrared microscopy during exposure of a test array, ranged over the array from 30.6 to 34.7 °C. Measurements of internal temperature with a thermistor yielded values about 2 °C higher at the centers of the eggs than the surfaces. The center temperatures ranged from about 33 to 37 °C, with a spatial average of about 35 °C. From cooling curves taken on exposure cessation, the whole-egg SAR corresponding to 35 °C was found to be 14 W/kg. Control arrays were sham-exposed at 35 °C ambient temperature and 40% relative humidity. Before treatment and afterward for the remainder of the incubation period (16 to 17 days), the eggs were incubated at 37 °C and 60% relative humidity. Two days after the onset of hatching, the quail were weighed, euthanized, and examined for gross deformities. Blood samples were taken and assayed for hematocrit, hemoglobin level, red-blood-cell (RBC) count, white-blood-cell (WBC) count, and differential WBC percentages, and the mean of each endpoint was plotted (with error bars) versus day of treatment.

By paired t-test, the differences between RFR-exposed arrays and their corresponding sham-exposed arrays were nonsignificant ($p > 0.05$) in hatching results, which included average body weights, numbers and percentages of eggs hatched, and numbers and percentages of hatched and unhatched live and dead birds. Also, no deformities were found in the hatched quail. By paired t-test of all arrays, there were also no significant differences in any of the blood parameters assayed. By Mann-Whitney U-test, however, some differences in blood parameters were significant ($p < 0.05$), notably an 11% decrease in hemoglobin for RFR-exposure on day 2, but there was no consistent pattern to the differences. The authors ascribed such differences partly to blood values that change more rapidly during day 1 after hatching than subsequently.

In a subsequent study, Hamrick and McRee (1975) similarly exposed eight 4x5 arrays of quail eggs to 2.45-GHz RFR (30 mW/cm², 14 W/kg) and sham-exposed eight arrays, but for 24 instead of 4 hours, at the start of day 2 of incubation. RFR-exposed and sham-exposed eggs were not turned during the 24-hour treatment. The quail were kept for 24 to 36 hours after hatching, after which the birds were weighed, examined for gross deformities, euthanized, and examined externally and internally for abnormalities. Blood assays were

performed, and the heart, liver, gizzard, adrenals, and pancreas of each bird were weighed. The results for the RFR-exposed arrays were pooled, as were those for the sham arrays, and the differences were analyzed with the two-sided Mann-Whitney U-test. The differences between the RFR and sham groups were all nonsignificant ($p > 0.1$) except for hemoglobin, which was about 4% lower for the RFR group than the sham group at the $p = 0.06$ level.

In another similar study, McRee and Hamrick (1977) exposed three 6x5 arrays of Japanese-quail eggs to 2.45-GHz CW RFR at 5 mW/cm² (4 W/kg) daily for 24 hours/day during the first 12 days of development. In this study, the eggs were turned 90° automatically every 2 hours during exposure to avoid the sticking of embryos to their shells. On exposure completion, the eggs were incubated normally for the remaining 5 days.

One of the arrays was exposed to the RFR with the chamber at 37 °C (the optimum incubation temperature). Egg temperatures stabilized at between 39.5 and 40 °C, so the corresponding control array was sham-exposed in a chamber at 40 °C, the highest egg temperature attained during RFR-exposure. At the end of the incubation period, only two of the RFR-exposed eggs and none of the control eggs had hatched, and 22 of the RFR-exposed and only one of the control embryos had developed past the eleventh day, results that were clearly ascribable to hyperthermia.

The other two 6x5 arrays were exposed to RFR at ambient temperature 35.5 °C, which yielded egg temperatures ranging from 37.5 to 38.0 °C. Therefore, the sham-exposures were done at 38.0 °C. Fifty-two of the RFR-exposed eggs hatched versus 35 of the control eggs, a result ascribed by the authors to the lower temperatures (< 38.0 °C) attained by some of the RFR-exposed eggs. No gross deformities were found in the quail when they were euthanized and examined 24 to 36 hours after hatching. By Mann-Whitney U-test, there were no significant differences in total body weight or the weights of the heart, liver, gizzard, adrenals, and pancreas between the RFR-exposed and sham-exposed groups. The hematological assays indicated 4% higher hemoglobin ($p < 0.034$) and 31% lower monocyte counts ($p < 0.004$) in the RFR-exposed birds, but the differences in the other blood parameters were not significant. The egg-to-egg variations in temperature in the RFR-exposed arrays were as much as 0.5 °C, rendering it difficult to associate these positive findings with the RFR per se.

In yet another study, Hamrick et al. (1977) similarly exposed groups of eggs and reared the birds for five weeks after hatching. No significant differences in mortality or mean body weights at 4 and 5 weeks were found between RFR and sham groups. (For a discussion of the immunological findings of this study, see the report on "Immunology and Hematology" when available).

Two subsequent studies (Galvin et al., 1980a; Hamrick and McRee, 1980) were directed toward ascertaining whether exposure of Japanese-quail eggs to 2.45-GHz pulsed or CW RFR would affect the development or beat rate of the embryonic heart. (For a discussion of those cardiovascular findings, see the report on "Physiology and Biochemistry", subtopic "Cardiovascular Effects" when available.)

Inouye et al. (1982a) exposed an array of 80 fertilized Japanese quail eggs to 2.45-GHz RFR continuously during incubation days 1-12 at a spatial mean power density of 5 ± 0.52 mW/cm² (mean SAR 4.03 W/kg; range 4.08-5.82

W/kg) in an anechoic chamber that held egg temperature at 37.5 ± 0.25 °C (the usual incubation temperature). Another array was similarly sham-exposed. On incubation days 12, 13, and 14, groups of 9 to 11 embryos each from exposed and control eggs were removed and weighed, and the cerebella were weighed and examined histologically. The mean weights (and SDs) are shown in Table 6 (adapted from Table 1 of the paper).

TABLE 6: BODY AND BRAIN WEIGHTS OF QUAIL EMBRYOS

[Inouye et al. (1982a)]

<u>Incubation</u> <u>Day</u>	<u>Exposure</u>	<u>No. of</u> <u>Embryos</u>	<u>Mean Body</u> <u>Weight (g)</u>	<u>Mean Brain</u> <u>Weight (mg)</u>	<u>Brain/Body</u> <u>Weight (10^{-3})</u>
12	Sham	11	2.36 ± 0.18	189 ± 12	80 ± 5.8
	5 mW/cm ²	11	$2.02 \pm 0.22^{**}$	$168 \pm 10^{**}$	83 ± 7.0
13	Sham	11	2.97 ± 0.33	222 ± 18	75 ± 3.5
	5 mW/cm ²	9	2.91 ± 0.28	211 ± 23	73 ± 8.1
14	Sham	11	3.86 ± 0.33	273 ± 19	71 ± 3.6
	5 mW/cm ²	10	3.64 ± 0.45	$253 \pm 17^{*}$	70 ± 6.1

* $p < 0.025$; ** $p < 0.001$

By t-test, both the mean body weight and the mean brain weight of the RFR-exposed embryos examined on incubation day 12 were significantly smaller ($p < 0.001$) than their sham-exposed controls. The mean brain weight of the RFR-exposed embryos examined on incubation day 14 was also significantly smaller ($p < 0.025$) than for their sham-exposed controls, but the difference in their mean body weights was not significant. In either case, however, there was no significant difference in the mean brain-to-body weight ratios. The embryos examined on incubation day 13 showed no significant differences in mean body weight or brain weight.

For histologic examination of each embryo group, 5 brains were selected that had weights similar to the mean weight of the group, and 6- μ m sagittal sections were prepared and stained with hematoxylin and eosin. The results indicated that the cerebella of the day-12 RFR-exposed embryos were slightly retarded in development, but that the development of the RFR-exposed embryos examined on day 13 was comparable to that of the controls. Minor differences in development were found between the RFR and sham groups examined on day 14, but the authors remarked that no gross malformations were seen in any of the embryos.

Other arrays of exposed and control eggs were allowed to hatch, and the quail were reared until 8 weeks of age. At that age, the quail were weighed, euthanized, and their brains were removed and weighed. The cerebella of 22 RFR-exposed birds were dissected, and 6- μ m and 8- μ m sagittal sections were prepared and stained with hematoxylin and eosin or thionin. Sham-exposed quail were similarly treated. Five randomly selected cerebella from each group were processed for 30 days with a Golgi-Cox solution, and 150- μ m sagittal sections were prepared.

There were no significant differences in mean body weight, mean brain weight, or mean weight ratio between the RFR-exposed and sham-exposed groups of quail of either sex. Also, no pathologic changes were found in cerebellum

morphology of RFR-exposed quail, and there were no significant differences between the groups in any of the specific morphologic endpoints measured. The authors concluded that the RFR-induced slight retardation in development of the cerebellum seen in this study did not have any effect on the later development of the cerebellum in hatched quail.

McRee et al. (1983), in three experiments, exposed one group each of 30 fertilized Japanese quail eggs to 2.45-GHz CW RFR continuously at 5 mW/cm² (mean SAR 4 W/kg) during the first 12 days of incubation, with the incubator held at 35.5 °C to achieve egg temperatures of 37.5 °C (optimum incubation temperature). As controls, one group each of 30 eggs was sham-exposed at the latter temperature. Hatched quail of both treatment groups were reared for four weeks, after which the males and females were maintained separately in mating cages at room temperatures in the range 20-30 °C. RFR-exposed males were then mated with sham-exposed females, and sham-exposed males were mated with sham-exposed females. The paired matings were started at age 7 weeks and maintained for 15 days, after which the former group of sham-exposed females was exchanged with the latter group of sham-exposed females and the mating was continued for another 15 days. This sequence was continued until age 22 weeks. At age 23 weeks, the females were removed from the mating cages, and semen was collected from some of the males (totals of 17 RFR-exposed and 22 sham-exposed males) on alternate days, and was assessed for sperm motility, numbers, viability, and gross morphology by an investigator who did not know which treatment the birds had undergone. Motility was scored on a scale from 1 (poor) to 5 (excellent). The testes of each bird were then weighed.

In the fertility assessment, the results from the three experiments did not differ significantly from one another, so the data were pooled. The data showed that 645 of 803 eggs (80.4%) from the females mated with sham-exposed males were found to be fertile, but 396 of 550 eggs (72.5%) from the females mated with RFR-exposed males were fertile; the latter percentage was said to be significantly lower ($p < 0.05$) than the former, but no statistical treatment of those data was given.

The sperm-motility results for each of the three experiments, in which at least three semen samples were assessed from each bird, were tabulated. The table displayed the means and SEs for the RFR-exposed and control birds in each experiment. There were 4 exposed and 4 control birds in experiment 1, 5 exposed and 10 control birds in experiment 2, and 8 exposed and 8 control birds in experiment 3. Noted in the table was that sperm motility was significantly lower at the $p < 0.01$ level for the RFR-exposed birds than for their corresponding controls. (Although the numbers of birds were noted, not clear is whether the tabulated means and SEs refer to the numbers of birds or the numbers of semen samples in each experiment.)

Findings similar to those for sperm motility were reported for sperm counts. However, the percentages of live sperm from the RFR-exposed birds did not differ significantly ($p > 0.05$) from the corresponding percentages for the control birds.

The results for sperm morphology varied from experiment to experiment. In experiment 1, for example, occurrences of sperm with coiled tails, bent heads, broken tails, balloon heads, or swollen acrosomes were mostly higher for the control birds than for those exposed to the RFR *in ovo*, but the

converse was true in experiment 3, and the results for experiment 2 were mixed. Also, in most of the specific morphologic categories, the percentages for the three control groups differed among themselves, e.g., 2.7%, 4.3%, 7.6% for the coiled-tail category. Last, no significant differences were found between exposed and control groups in weights of left or right testes.

The authors concluded that the results of this study indicate adverse effects of exposure of fertile quail eggs to 2.45-GHz RFR "in the absence of a discernible rise in temperature during exposure". However, as shown by Clarke and Justesen (1983) and others, the spatial variation of temperature within eggs exposed at relatively high SARs, e.g. 4 W/kg, can be large, thereby yielding spatial-maximum temperatures higher than the basically uniform temperatures within conventionally incubated eggs.

Byman et al. (1985) did a study related to the Glaser (1968) concept of the satellite power system (SPS): a satellite in a geostationary orbit for converting solar power into microwaves (2.45 GHz) and beaming that power to a suitable site on the earth's surface, where the power would be received and rectified by an array of antennas ("rectenna") about 10 km in diameter and transmitted to population centers via conventional high-power lines. The power density at the rectenna would vary from about 1 mW/cm² at the edge of the rectenna to about 223 mW/cm² at its center. The SPS concept is no longer being considered, but the results of the Byman et al. (1985) study remain of some interest.

The primary objective of that study was to determine whether bird eggs in nests on a rectenna would be adversely affected by exposure to the RFR from an SPS, specifically regarding egg hatchability and embryo development. The species selected was the Japanese quail. Three series of experiments were done: in series 1 and 2, eggs were exposed to 2.45-GHz CW RFR for 30 minutes per day during the 17-day incubation period at 25 mW/cm² with a standard gain horn within an anechoic chamber; in series 3, the power density was 50 mW/cm². For each series, 120 eggs were divided into Groups I-IV of 30 eggs each, with each group placed 0.5 cm apart in egg cartons and incubated at 37.5 °C until hatched or for 19 days if unhatched. Groups I-III were removed from the incubator twice a day for 30-minute treatments as follows: Group I was exposed to the RFR, Group II was held at about 24 °C in a second incubator, Group III was kept at laboratory ambient temperature (19-20 °C), and Group IV was maintained within the incubator for the entire experiment except when all four groups were weighed every 4 days. The normalized mean SAR for the eggs exposed to the RFR, determined by the cooling-curve method, was 0.5 W/kg per mW/cm², yielding 12.5 W/kg at 25 mW/cm² and 25 W/kg at 50 mW/cm².

Egg weight losses due to water evaporation through the eggshells were calculated for the various ambient temperatures. At incubation end, the differences in mean weight loss among the four groups in each series were nonsignificant ($p > 0.05$). The mean loss for Group I in the third series (50 mW/cm²) was 1.31 ± 0.39 (SD), which was significantly lower than 1.55 ± 0.37 for Group I in the first series (25 mW/cm²), but the control values for the corresponding Groups IV (held at 37.5 °C) were 1.67 ± 0.74 and 1.45 ± 0.62 , respectively.

Regarding hatchability, Groups I-III in the first and second series had comparable numbers of hatchlings (ranges of 17-19 and 20-23 hatchlings, respectively). However, only 6 eggs in Group I of the third series hatched

versus 17 in Group IV of that series, a difference ascribed by the authors to the higher temperatures in the eggs exposed at 50 mW/cm².

All chicks that hatched from the eggs in the second series were removed from the incubator within 12 hours, placed within a commercial brooder, and visually examined for gross physical abnormalities and weighed every 2-3 days for 26 to 28 days; those from the third series were similarly examined and weighed but only for 15 days. No abnormalities were seen and no significant differences in weights were obtained.

Gildersleeve et al. (1987a), in an extension of the study by McRee et al. (1983), sham-exposed and exposed groups of quail eggs to 2.45-GHz CW RFR at 5 mW/sq cm (4 W/kg) during the first 12 days of embryogenesis at 37.5 °C, the optimum incubation temperature. Incubation was completed on 6 groups of 78 RFR-exposed and 78 sham-exposed eggs each for a total of 468 hatchlings for each treatment. Thirty-five days after hatching, males and females were paired in the four treatment combinations, and their reproductive performance was determined daily until 224 days of age. In addition, the reproductive performance of non-sibling pairs of progeny from each initial pair of birds was assessed during ages 35 to 180 days.

The results indicated that exposure to the RFR during embryogenesis did not affect any of the endpoints studied, including: hatchability, mortality after hatching, egg production, egg weight, and fertility of the initial groups, and the reproductive performance of the progeny, thus not confirming the findings of McRee et al. (1983) for the corresponding endpoints.

Spiers and Baummer (1991) investigated whether repeated exposures of Japanese quail eggs to 2.45-GHz CW RFR can alter embryonic metabolism, temperature, and growth rate, and whether such RFR can be used to supplement conventional heating to provide an optimal temperature for growth. During incubation between treatments, eggs were held at ambient temperature (T_a) of 37.5 ± 0.1 (SE) °C and relative humidity 60%, and were automatically rotated 45° every 2 hours. Two Styrofoam chambers temperature-controlled by a common forced-air-flow supply were used for RFR- and sham-exposure. For both treatments, groups of 9 eggs each were inserted in a vertical Styrofoam block 1 cm thick as 3x3 arrays on 12-cm centers, and one such block at a time was mounted within each chamber. One of the two chambers was then placed within an anechoic chamber for RFR-exposure and the other chamber was placed outside the anechoic chamber for sham-exposure. A nonperturbing probe was inserted through the rear of the central egg of the array to measure its internal temperature during exposure. Previous measurements of the temperatures of the eggs in the center and the four corners of an array indicated little spatial variation.

Groups I-IV of eggs were exposed to the RFR 8 hours a day for 1 to 15 days of incubation: Groups I-III at 5 mW/cm² and Group IV at 20 mW/cm². By calorimetry on 15-day-old euthanized embryos (of mean mass about 9 g), the normalized SAR was found to be 0.66 W/kg per mW/cm², yielding SARs of 3.3 and 13.2 W/kg for the two power densities. The ambient temperatures of the four groups were held respectively at 30.9, 33.1, 35.4, and 30.0 °C; and the corresponding mean internal egg temperatures were 31.9, 34.8, 37.4, and 37.3 °C, with an average SE of ±0.1 °C. Five groups were sham-exposed at T_as of 27.9, 29.6, 32.5, 35.0, and 37.5 °C, respectively. The average internal temperature of each group was within 0.2 °C of its T_a.

The endpoints of interest were determined on incubation day 16. All eggs were opened at that time and the contents were examined for embryo viability. The percentage of fertile eggs in all treatment groups ranged from 67% to 87%, with no significant difference in percentage of developed eggs between RFR-exposed and sham-exposed groups. Also, the fertility percentage for those exposed at 5 and 20 mW/cm² (69% and 75% respectively for Groups I and IV) did not differ significantly, indicating no reduction in viability. Thus, the authors concluded that they had found no evidence of abnormal physiological embryo development from the RFR-exposure regimens used. They also presented results indicating that RFR-irradiation of eggs can be used to increase egg temperature and growth rate at T_s below those normally used for incubation without altering the basic metabolic and thermal characteristics of the developing birds.

Fisher et al. (1979) studied the development of chicken embryos in eggs exposed to 2.45-GHz CW RFR 24 hours/day for either 4 or 5 days. The eggs were exposed within an incubator in 6x6 arrays at power densities that ranged over the array from 1.4 to 6.2 mW/cm², with a spatial mean of 3.46 mW/cm² (SARs not determined). The long axes of the eggs were placed in a plane parallel to the propagation and electric vectors and were tilted 30° relative to the electric vector. All of the axes were shifted to the symmetric 30° orientation every 24 hours. The optimal incubation temperature for chicken embryos is about 38 °C, so lower incubator temperatures, ranging from 32 °C to 36 °C over the egg sites, were used to compensate for the additional heat absorbed from the RFR. However, incubator temperature at each site was constant. Embryo temperatures were measured for 6 sample eggs of a 6x6 array with a thermocouple inserted through an opening in each shell. The results, together with the spatial temperature variations among the 36 egg sites within the incubator, were used to estimate the temperatures of the other 30 embryos. Sham-exposed arrays served as controls. After treatment completion, the embryos were excised, the extraembryonic membranes were removed, the wet masses were measured, and each embryo was photographed.

The development stage of the eggs RFR-exposed for 4 days at 32 °C embryo temperature was found to be significantly later (smaller cranial lengths and wet masses) than for the sham-exposed controls. The converse was true at 36 °C, with the crossover (no difference) at embryo temperatures of about 34 °C. Similar results, but with larger differences, were obtained for the eggs RFR-exposed for 5 days. The authors also stated that the frequency of premature deaths and of sterility did not differ significantly among groups.

Those results are difficult to analyze because the paper did not include the temperature measurements of the 6 sample embryos, the locations of those eggs in the array, and the calculated temperatures of the other embryos. For the aforementioned range of power densities in the array, it seems likely that the distribution of embryo temperatures over an RFR-exposed array would have been significantly different from the distribution for a sham-exposed array. Also, the findings of this study are open to question because the nonuniform SAR distributions within the RFR-exposed eggs undoubtedly yielded internal temperature gradients that were much larger (Clarke and Justesen, 1983) than those within the sham-exposed eggs.

Saito et al. (1991) continuously sham-exposed or exposed groups of 10 fertilized chicken eggs, laid within 24 hours, to 428-MHz RFR during the

entire incubation period. Each group of 10 eggs was arranged on a wooden rack in a square array, as displayed in Figure 1. For treatment, the rack was placed between two horizontal 34x36-cm aluminum electrodes spaced 14 cm apart within an incubator, which was held at 37 ± 0.5 °C and 80% relative humidity. The RF from the source was fed at the center of one edge of each electrode as shown in Figure 1. Thus, egg site 2 was closest to those two edge locations, with egg sites 1 and 3 next closest, a point of possible importance discussed later. The long axes of all eggs were parallel to the electric field, and were automatically turned once each hour.

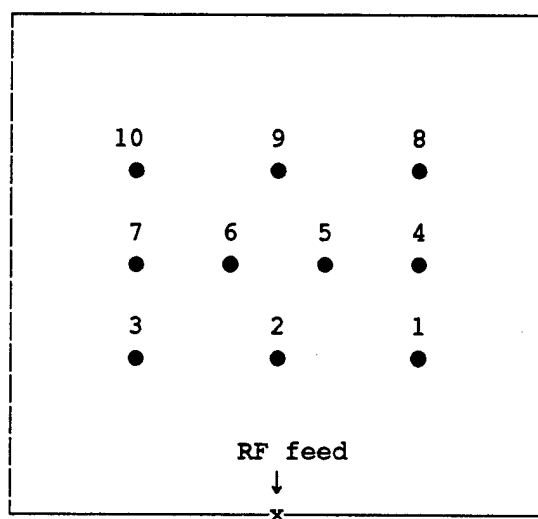


FIGURE 1: EGG ARRAY

Seven experiments were done, of which the first and fourth experiments were sham-exposures. The viability of the eggs was checked conventionally once a day during the incubation period. More detailed inspections were done on days 10, 20, 21, and 22 of incubation, to determine whether embryo death occurred before or after day 10. Within 6 hours of hatching, the chick body weights were measured. They were then euthanized and necropsied, and various organs were weighed. The organs were fixed, embedded in paraffin, sliced, stained, and examined by light microscopy.

As indicated in a block diagram (Figure 2 of the paper), the RF was fed to the electrodes through an in-line power meter; the power was set at 6.8 W. The authors divided this value by the electrode area (1,224 cm²) to obtain a "theoretical" power density of 5.5 mW/cm². They also measured the electric and magnetic fields at each egg position with a Holaday Model HI3002 survey meter, noting however, that the magnetic field measurements may be inaccurate because the survey meter was designed for measuring magnetic fields within the frequency range 5-300 MHz only. They then calculated the SAR by the method of Fujiwara and Amemiya (1982) under the assumption that the egg is ellipsoidal, with major and minor axes 6 cm and 4.5 cm. The results are displayed in Table 7 (adapted from Table 1 of the paper) in terms of the square of the electric field (E^2), the square of the magnetic field (H^2), and the SAR at each of the 10 numbered egg sites.

TABLE 7: SPATIAL VALUES OF FIELDS AND SARs IN AN EGG ARRAY
[Saito et al. (1991)]

<u>Egg Site</u>	<u>E²</u> (V/m) ² x10 ³	<u>H²</u> (A/m) ² x10 ⁻²	<u>SAR</u> mW/kg
1	1.1	1.4	11.0
2	1.2	4.2	33.0
3	1.6	6.6	47.1
4	0.2	0.7	5.5
5	0.2	0.4	3.1
6	0.2	0.5	3.9
7	0.2	0.6	4.7
8	0.2	0.6	4.7
9	0.2	0.7	5.5
10	0.2	1.1	8.6

The highest values of E², H², and SAR were at site 3, with the next two lower values at sites 2 and 1. Those results may be a consequence of the nearness of those sites to RF feed locations discussed above. Remarkably, the values of E² were all 0.2 at sites 4 through 10, but those of H² varied over the range from 0.4 at site 5 to 1.1 at site 10.

The authors also measured the RFR-induced temperature rises in 4 eggs in which their contents were replaced with 25% gelatin. They inserted a Luxtron fluoroptic thermometer into each altered egg, kept the egg for 1 hour at 37 °C in the incubator, and then exposed it for 20 minutes to the RFR at site 3. Those measurements showed a constant temperature of about 37.7 °C at 0, 10, and 20 minutes, with no perceptible rise during exposure. Not explained was the 0.7 °C rise above the incubator temperature.

The mean hatchability for the RF-exposed eggs was 38.0%, with about 25% of the deaths within 10 days of incubation. By contrast, mean hatchability for the sham-exposed eggs was 84.2%. However, hatchability varied with egg site, and the authors noted that the severest effect was at sites 8-10, where the SARs were relatively low [4.7-8.6 mW/kg], and that all of the eggs exposed at site 1, where the SAR was relatively high [11.0 mW/kg], had hatched. The body and organ weights of the chicks varied widely and were not included in the paper. The examinations of the tissue slices by light microscopy showed no abnormalities.

A number of problems are evident regarding the exposure arrangement and the dosimetry. First, the RF feed probably was mismatched to the electrode pair, causing a significant fraction of the RF power to be reflected toward the source, but no provision was shown in the aforementioned block diagram for measuring reflected power. Thus, the "theoretical" power density (5.5 mW/cm²) was likely erroneous. However, the authors did note that the power density calculated solely from the electric-field measurements ranged from 0.05 to 0.42 mW/cm². Second, feeding the RF at an edge of the electrodes probably rendered the fringe fields very nonuniform, presumably affecting egg sites 1-3 most. Third, the 14-cm spacing between the electrodes was about a fifth of a wavelength at 428 MHz, so use of the Holaday meter for measuring the fields between them is questionable. Fourth, any differences in the RFR-absorption properties of gelatin and real egg contents apparently was not considered by

the authors, rendering the temperature measurements meaningless. Moreover, to characterize the RF-exposures as nonthermal is questionable, in view of the unexplained 0.7 °C rise mentioned above.

In summary of this study, little if any credibility can be given to any findings in this study of RF-induced nonthermal embryoletality or the other reported teratogenic effects.

Braithwaite et al. (1991) noted the proposal by Pound (1980) to use RFR as a more efficient heating source than infrared radiation or warm air for providing thermal comfort to humans (an idea now in limbo), and a more recent suggestion by Morrison et al. (1986) to use RFR for supplemental heating of poultry. Regarding the latter idea, Braithwaite et al. (1991) suggested that such heating could be most economically provided within a multimode microwave cavity, but they also recognized the need to determine whether such usage of RFR would adversely affect embryonic development. Toward that end, they sought possible effects on the fertility and hatchability of chicken eggs from exposure to 2.45-GHz CW RFR in a specially designed multimode, mode-stirred microwave cavity.

The cavity was a 65-cm-wide metal cube with an applicator horn mounted in its roof and fed by a 2.45-GHz magnetron. (The use of a magnetron as the source renders questionable that the RFR was CW.) An RF attenuator and a bidirectional coupler were inserted between the magnetron and the horn, the former for varying the input power to the cavity and the latter (equipped with power meters) for measuring forward and reflected powers. For exposure, 8x6 arrays of chicken eggs held in a plastic tray 48 cm x 58.5 cm were placed horizontally 20 cm above the cavity floor. The power densities within the cavity were calculated by subtracting the reflected power from the forward power and dividing the result by the area of the cavity floor.

A fiberoptic thermometer was used to measure the internal temperatures at three depths within eggs placed at two diagonally opposite corners and near the center of an array right after exposure at 5 mW/cm² for 120 minutes, with the remainder of the sites occupied by eggs. The results showed that at each of the sites, the mean temperature at a depth of 2.5 cm from the blunt end of the egg was significantly higher than at depths of 1.0 and 5.3 cm, and that there was a significant gradient of mean temperature from the center to the periphery of the array, with the outer eggs about 0.6 °C cooler than the inner eggs. From the specific heat capacity and temperature-versus-time data for a "monitor" egg immediately after each exposure, the normalized SAR was calculated to be 0.80 W/kg per mW/cm².

In two replicates, three treatment groups of 15 eggs each were placed at randomized sites within 45-egg arrays (along with three eggs for monitoring temperature) and each array was exposed to a spatial mean power density of 3.6 ± 0.02 mW/cm² (SE). Treatment groups 1, 2, and 3 were RFR-exposed from incubation day 0 to: day 7, 14, and 19, respectively. The corresponding mean SAR was 2.9 W/kg. For each replicate, treatment groups 4, 5, and 6 were placed horizontally in the center of a conventional incubator as controls. The eggs in all groups were turned 90° once each hour and were candled on days 7 and 19 of incubation. After treatment, the eggs in each group were transferred to a hatcher. Percent hatchability was calculated as the number of chicks hatched divided by the number of fertile eggs. On day 21, hatched chicks were sexed, weighed, and wing-banded, and the contents of unhatched eggs were examined.

The tabulated hatchability results showed no statistically significant differences between each RFR group and its control group. The authors noted that hatchability appeared to be nonsignificantly lower in the eggs exposed through day 19 in replicate 1 but not in replicate 2, so they suggested that the finding was not likely to be RFR-related. Regarding the unhatched eggs, three eggs of treatment group 3 contained chicks that were alive, but whose development was delayed by about 24 hours. The authors suggested that the delay may have been due to lower internal egg temperature during days 12 and 13 of exposure. Plots of the ambient temperature, power density, and egg temperature versus treatment day all showed large but correlated variations, with deep dips on those days, the latter problem ascribed by the authors to an interruption of the water supply used to maintain the ambient temperature within the exposure chamber. However, this point does not account for the other temperature variations seen in the plots. Indeed, inadequate measures to control the temperatures during RFR-exposure and the presence of a spatial gradient within the exposure chamber are major flaws in an otherwise well designed study.

In four experiments, Hills et al. (1974) exposed groups of 30 fertile chicken eggs at various stages of development and durations to 6.0-GHz CW RFR at a spatial mean power density of 0.2 mW/cm² (range 0.1 to 0.4 mW/cm²) within one chamber of a special two-compartment incubator. Each chamber was 60 cm wide, 81 cm long, and 72 cm high. The exposure chamber was lined with copper screen "to confine the microwaves to this unit". It had an egg-turning device of wood and the eggs were held in plastic trays "to minimize reflection of microwaves". The authors denoted such exposure levels as "low" but gave no description of the RFR source or exposure arrangement, or of how the power densities within the chamber were measured. The other chamber was unlined and had a metal turning device. The authors indicated that there was a "trace field density below 0.005 mW/cm²" in the latter chamber. In a fifth experiment, there were 25 turkey eggs per treatment group. The results of those five experiments showed no significant effect on the hatchability or growth of chickens or turkeys up to two weeks of age.

In "high-density" experiments involving treatment groups of 30 each, chicken eggs were exposed singly after 0, 1, or 2 days of incubation to 2.45-GHz RFR (stated to be CW) from a Phillips D 260 1.2 kW magnetron as indicated below. Again, no description was given of the exposure arrangement or of the how the RFR levels were measured.

- a) 1020 mW/cm² for 20, 30, or 45 seconds
- b) 246 mW/cm² for 90, 120, or 150 seconds
- c) 123 mW/cm² for 150, 180, or 210 seconds
- c) 51 mW/cm² for 210, 240, or 300 seconds.

The exposures to the high RFR levels indicated the following results:

No significant differences were seen in chick body weights or mortality up to age 2 weeks for exposure at 51, 246, or 1020 mW/cm² with 0 (no prior) incubation time before treatment. By contrast, exposure at 246 or 1020 mW/cm²

after 2 days of incubation resulted in complete failure to hatch, and exposure at 246 mW/cm² for 90 or 150 seconds or at 1020 mW/cm² for 45 seconds after 1 day of incubation yielded greatly reduced hatchability. The authors suggested the possibility that these results were due to coagulation of protein in the eggs or in the embryos themselves, but also speculated about possible nonthermal mechanisms.

In the absence of information on exposure methodology or dosimetry, as well as other details about spatial ambient-temperature uniformity within the exposure chamber, egg-turning arrangement and scheduling, and the like, little credence can be given to either the negative or positive findings of this study.

Hall et al. (1982) diluted and centrifuged semen from 10-month-old turkeys to remove the seminal plasma, and prepared sperm suspensions to a concentration of 500 million sperm/ml. Specimens thereof were exposed to 2.45-GHz CW RFR in a special waveguide system filled with distilled water (Galvin et al., 1981b). The waveguide impedance was matched to that of free space by a water-tight quarterwave dielectric plate. Each specimen to be exposed was enclosed within a tube, and the tube was placed against the surface of the plate immersed in the water. For each such tube, a control tube was mounted at a distance of 9.5 cm from that plate surface, thereby receiving essentially no RFR because of attenuation by the intervening water. The distilled water within the waveguide was circulated continuously through a constant-temperature water bath, which maintained both the exposed and control tubes at 40.0 ± 10.5 °C. SARs were determined from initial heating and time-temperature profiles of specimens without water circulation.

Sperm specimens were exposed to the RFR for 30 minutes at a mean SAR of 1, 10, or 50 W/kg. Aliquots of exposed and control specimens were treated with live-dead stain for poultry semen, slides were prepared with 200 sperm per slide, and the sperm were classified as normal, abnormal, or dead; viable sperm with balloon heads or with broken, bent, or twisted tails were regarded abnormal. The resulting data were expressed as percentages of viable and abnormal sperm. Other aliquots were assayed for enzymatic activity [lactate dehydrogenase (LDH) and glutamine-oxaloacetic transaminase (GOT)].

Removal of the seminal plasma had no effect on spermatocyte viability either before or after exposure; about 90% of the control and exposed sperm were viable, with no significant differences related to SAR. The percentages of abnormal sperm also did not differ significantly with SAR, nor did the percentage release of LDH. The percentage release of GOT at 1 W/kg was lower than for the control specimens and those exposed at 10 and 50 W/kg, but again the differences were not significant ($p > 0.05$). Thus, the authors concluded that the RFR-exposures had no adverse effects on turkey sperm.

Hall et al. (1983) subsequently exposed suspensions of turkey sperm held at either 25 or 40.5 °C to 2.45-GHz CW RFR for 30 minutes at 10 or 50 W/kg in the water-filled waveguide system. The pH of each suspension (an indicator of metabolic activity of the suspended cells) was measured just before and after treatment. Within 2 hours after treatment, suspensions each containing about 200 million sperm were used to perform single artificial inseminations of 6 groups of 16 virgin turkey hens in the following 2x3 design: 25 °C and 40.5 °C by sham-, 10-W/kg, and 50-W/kg exposure. Starting on the day after the

inseminations, the eggs were collected daily and incubated. On days 28 and 29 of incubation, the numbers and weights of the hatched birds were recorded; the remaining eggs were broken open and classified as fertile or infertile; and dead embryos were classified as early (days 1-5), middle (days 6-23), or late (days 24-28).

Mean pH values after treatment were significantly lower ($p=0.015$) than pretreatment values for all 6 treatments, but the RFR-related differences among the treatments were nonsignificant ($p>0.05$). The differences among the groups in mean total number of eggs laid by each hen and mean number of eggs laid per week were nonsignificant (analysis of variance with week as the repeat measure). The percentage of fertile eggs, in terms of a moving 7-day time average, diminished with time for all groups, but the differences among groups in mean number of fertile eggs per group, total and per week, were also nonsignificant, as were the differences in percentage hatchability.

The authors, indicating that there were few middle deaths, presented data on the early and late deaths only, with each class tabulated in terms of numbers and percentages of deaths by week and treatment. They stated: "There were approximately 15% early and late deaths over the 10-week experimental period, and there was no difference among the groups for any treatment or temperature." However, they provided no statistical analyses of those data. A cursory examination of the data showed no consistent RFR-related pattern.

2.3 SUMMARY

The findings of the various studies on RFR-teratogenesis in nonmammalian species are summarized in Tables 8A-8E. Studies in which pupae of *Tenebrio molitor* (darkling beetle) were exposed to RFR were done by Carpenter and Livstone (1971), Lindauer et al. (1974), Liu et al. (1974), Green et al. (1979), Olsen (1977a), Pickard and Olsen (1979), Olsen and Hammer (1982), and Olsen (1982a), with SARs up to 806 W/kg. All found significant numbers of dead or deformed beetles.

Carpenter and Livstone (1971) reported that 90% of pupae conventionally heated to the same temperature as with RFR at 40 W/kg yielded normal beetles, and they therefore hypothesized that the effect with the RFR was nonthermal. However, Pickard and Olsen (1979) were not able to confirm the nonthermal hypothesis of Carpenter and Livstone (1971). They noted that the differences in findings among the studies were due to non-RFR factors. Specifically, Pickard and Olsen (1979) obtained pupae from two different sources and fed them differently ("K-pupae" and "colony-pupae"). The authors found no significant differences in incidences of gross abnormalities between pupae exposed to an E-field at 91 V/m (130 W/kg) and controls from either source; however, the proportion of nonnormal beetles from the K-pupae controls was significantly larger than from the colony-pupae controls. Olsen (1982a) found the incidence of anomalies to be temperature-dependent, with a 40 °C hyperthermia threshold.

Various studies with Japanese quail eggs were carried out by McRee et al. (1975), Hamrick and McRee (1975), McRee and Hamrick (1977), Hamrick et al. (1977), Inouye et al. (1982a), McRee et al. (1983), Byman et al. (1985), Gildersleeve et al. (1987a), and Spiers and Baummer (1991). All of those

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Carpenter and Livstone (1971)	Tenebrio molitor	10 GHz	17 mW/cm ² 68 mW/cm ²	40 W/kg 160 W/kg	2 hours 20-30 min	20% of beetles normal 24% of beetles normal	90% of beetles were normal with conventional heating; nonthermal effect hypothesized
Lindauer et al. (1974)	Tenebrio molitor	CW or pulsed 9 GHz	17.1 or 8.6 mW/cm ²	41 or 21 W/kg	2 hours	Significant incidences of terata	Some RFR-related differences significant, but with no clear dependence of effect on dose rate or total dose. No significant differences in results between pulsed and CW RFR at the same average level
Liu et al. (1975)	Tenebrio molitor	9 GHz	0.17 mW/cm ²	0.41 W/kg	2 hours	Significant incidences of terata	Level x duration=4 mW-hr; an inverse relation
Green et al. (1979)	Tenebrio molitor	9 GHz	0-34 mW/cm ² 272 mW/cm ²	0-80 W/kg 640 W/kg	2 hours	A slight increase in terata with RFR level Further terata increase	Susceptibility to damage higher at <35% relative humidity
Olsen (1977a)	Tenebrio molitor	6 GHz 4 GHz	Up to 562 V/m Up to 602 V/m	806 W/kg at 562 V/m; 29.1 W/kg at 602 V/m	0.5, 2, 4, or 6 hours	6 GHz at 806 W/kg for 30 minutes killed most of the pupae; 51 W/kg for 4 hours caused no deaths or defects, but 106 W/kg yielded defects in half the insects. 4 GHz at 29.1 W/kg for 2 or 4 hours caused no defects.	Total dose was 1526 J/g at 106 W/kg (6 GHz) for 4 hours, and 127 J/g at 29.1 W/kg (4 GHz) for 6 hours.
Pickard and Olsen (1979)	Tenebrio molitor	6 GHz 10 GHz	91 V/m (*3.4 mW/cm ²) 1.53 A/m (*88.3 mW/cm ²) 11 mW/cm ² 5 mW/cm ²	130 W/kg 34 W/kg 130 W/kg 45 W/kg	2 hours 13 hours 4 hours	The differences in anomaly incidences from E-field exposure were not significant, but gross abnormalities were much higher in control "K-pupae" than in control "colony-pupae". Other results were ambiguous.	Nonthermal hypothesis of Carpenter & Livstone (1971) unproved; differences in findings among studies due to non-RFR factors *Free-space equivalent power density
Olsen and Hammer (1982)	Tenebrio molitor	1.3, 6, 10 GHz	High	High	Short	Distributions of SAR in pupae by thermography	Local SAR variations different than for conventional heating
Olsen (1982a)	Tenebrio molitor	6 GHz	Fixed dose: 1123 J/g	208 W/kg	SAR for 1.5 hours at the highest RFR level	Temperature dependence of anomaly incidences; 40 °C hyperthermia threshold for effects	Exposures done with and without cooling

TABLE 8A: TERATOGENESIS IN NONMAMMALIAN SPECIES

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
McRee et al. (1975)	Japanese quail-egg arrays	2.45 GHz	30 mW/cm ² at 24 °C ambient*	14 W/kg	4 hr on one day or 4 hr per day on 5 days	Sought in hatchlings were lower weights, gross abnormalities, and effects on various blood parameters. Differences between RFR and sham groups not significant.	RFR level was chosen to yield egg temperatures of about 37 °C (the usual incubator temperature); the temperatures at egg centers were about 2 °C higher than at their surfaces.
Hamrick and McRee (1975)	Japanese quail-egg arrays	2.45 GHz	30 mW/cm ²	14 W/kg	24 hr	No significant endpoint differences between RFR- and sham-exposed hatched quail	Post-hatching endpoints included weight and occurrence of deformities
McRee and Hamrick (1977)	Japanese quail-egg arrays	2.45 GHz	5 at 37 °C ambient 5 at 35.5 °C ambient	4 W/kg	24 hr for 12 days	Egg temperatures ~40 °C; few eggs hatched Egg temperatures 37.5-38.0 °C; most eggs hatched; no gross deformities	Few control eggs heated at 40 °C ambient hatched Most control eggs heated at 38 °C ambient hatched; no gross deformities
Hamrick et al. (1977)	Japanese quail-egg arrays	2.45 GHz	5 at 35.5 °C ambient	4 W/kg	24 hr for 12 days	No significant differences in mortality or body weights between RFR and sham groups at ages 4 and 5 weeks	No significant differences in immunologic endpoints
Inouye et al. (1982a)	Japanese quail-egg arrays	2.45 GHz	5 mW/cm ²	4 W/kg	24 hr for 12 days	Body and brain weights of RFR-exposed embryos on incubation day 12 significantly smaller than controls; brain but not body weights smaller on incubation day 14; no significant differences on incubation day 13; no malformations seen on any day At age 5 weeks, no significant morphologic or weight differences between RFR- and sham-exposed quail	No significant differences between RFR and sham groups in brain-to-body weight ratios Slight cerebellum retardation in embryos had no effect on later quail development

TABLE 8B: TERATOGENESIS IN NONMAMMALIAN SPECIES (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
McRee et al. (1983)	Japanese quail-egg arrays	2.45 GHz	5 mW/cm ²	4 W/kg	24 hr for 12 days	Hatched female quail from eggs sham-exposed at 37.5 °C were mated with hatched male quail from eggs RFR-exposed at 35.5 °C. Fewer fertile eggs than from matings with sham-exposed males were noted. RFR-exposed quail had no significant differences in sperm counts or morphology, but lower motility than sham-exposed quail. No differences in testes weights were evident.	Although the authors concluded that the RFR-exposure had adverse effects "in the absence of a discernible rise in temperature during exposure," they apparently disregarded the spatial variation of temperature within eggs exposed at relatively high SARs, e.g. 4 W/kg [Clarke and Justesen (1983) and others].
Byman et al. (1985)	Japanese quail-egg arrays	2.45 GHz	25 or 50 mW/cm ² versus incubation at 37.5 °C	12.5 or 25 W/kg	30 min a day for 17 days	Differences in egg-mass loss, hatchability, or chick weights were not significant at 12.5 W/kg; no abnormalities seen. Hatchability was much lower at 50 W/kg.	This study was related to the Glaser (1968) concept of the satellite power system (SPS). The reduced hatchability at 50 W/kg was ascribed to the higher egg temperatures.
Gildersleeve et al. (1987a)	Japanese quail-egg arrays	2.45 GHz	5 mW/cm ²	4 W/kg	24 hr a day for 12 days	Differences between RFR- and sham-exposed quail in reproduction were not significant.	Endpoints were: hatchability, mortality after hatching, egg production, egg weight, fertility of the initial groups, and reproductive performance of the progeny.
Spiers and Baummer (1991)	Japanese quail-egg arrays	2.45 GHz	5 or 20 mW/cm ² at a T _a of 30.9, 33.1, 35.4, or 30.0 °C	3.3 or 13.2 W/kg	8 hr a day for 1-15 days	Differences in fertility or viability between groups at the two RFR levels and between RFR and sham groups held at T _a s of 27.9, 29.6, 32.5, 35.0, and 37.5 °C were not significant.	The authors concluded that they had found no evidence of abnormal physiological embryo development from the RFR-exposure regimens used.
Fisher et al. (1979)	Arrays of chicken eggs (6x6)	2.45 GHz	Array mean: 3.46 mW/cm ² ; range: 1.4-6.2 mW/cm ² ; exposures at below 38 °C (normal incubation)	Not determined	24 hours a day for 4-5 days	Exposure for 4 days at 32 °C embryo temperature yielded significantly later embryo development than for sham-exposed controls; converse results were seen at 36 °C, and no difference (crossover) at 34 °C.	The results are difficult to analyze because of the large spatial range of RFR levels and the likelihood of larger internal temperature gradients than within sham-exposed eggs (Clarke and Justesen, 1983).

TABLE 8C: TERATOGENESIS IN NONMAMMALIAN SPECIES (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Saito et al. (1991)	Chicken eggs in rows of 3x4x3	428 MHz fed to edges of two parallel plates	Egg arrays exposed between the plates; mean intensity: 5.5 mW/cm ² ; range: 0.05-0.42 mW/cm ²	Spatial SAR ranged from 3.1 to 33.0 W/kg; highest value was at egg nearest the RF feed.	Exposures for 24 hr a day in at 37 °C in an incubator	Mean hatchabilities were 38.0% and 84.2% for RFR-exposed and sham-exposed eggs, respectively, but with large spatial differences and severest effects at egg sites of relatively low SARs. The chick body and organ weights varied widely; data were not given. No abnormalities were seen in tissue examination by light microscopy.	This study suffers from faulty experimental-design and methodology; little if any credence can be given to its positive or negative findings.
Braithwaite et al. (1991)	Chicken eggs	2.45 GHz	8x6 arrays of eggs exposed in a multimode microwave cavity at 3.6 mW/cm ² (spatial mean).	2.9 W/kg (spatial mean)	24 hours a day from day 0 to: day 7, 14, 19 (groups 1, 2, 3).	For each of the three treatment groups, there were no significant hatchability differences relative to their control groups. Three unhatched eggs in treatment group 3 had live chicks of delayed development, ascribed to lower egg temperature during days 12 and 13 of exposure.	Measurements of internal egg temperatures during exposure revealed a spatial temperature gradient of about 0.6 °C from center to periphery. Plots of ambient temperature, power density, and egg temperature versus day of treatment all showed large but correlated variations. Inadequate control of the temperatures during RFR-exposure and the spatial gradient within the exposure chamber are major flaws in an otherwise well designed study.
Hills et al. (1974)	Groups of chicken or turkey eggs in plastic trays	"Low" level: 6-GHz "High" level: 2.45-GHz	Range 0.1 to 0.4 mW/cm ² ; spatial mean 0.2 mW/cm ² 51, 123, 246, or 1020 mW/cm ²	SARs were not determined.	The 6-GHz exposures were at various stages of development for various periods. At 2.45-GHz, the durations ranged from 300 to 20 seconds.	At 6 GHz, no significant effects were seen on the hatchability or growth of either fowl species up to two weeks of age. For 2.45 GHz, exposure at any level with no incubation prior to treatment yielded no significant effects on chick body weights or mortality. However, exposures after 1 or 2 days of incubation caused reduced hatching or failure to hatch.	The 6-GHz exposures were done in a metal-lined chamber of a two-chamber incubator. A description of the RFR source or the RFR-level measurement method was not given. The 2.45-GHz source was a magnetron. In the absence of information on exposure methodology or dosimetry, as well as other details about spatial ambient-temperature uniformity within the exposure chamber, egg-turning arrangement and scheduling, and the like, little credence can be given to any findings of this study.

TABLE 8D: TERATOGENESIS IN NONMAMMALIAN SPECIES (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Hall et al. (1982)	Turkey semen	2.45 GHz	Incident power density not stated	1, 10, or 50 W/kg in a water-cooled waveguide (Galvin et al., 1981b)	30 min. at 40.0 ± 10.5 °C	About 90% of the control and exposed sperm were viable, with no SAR-related significant differences. Abnormal sperm percentages from exposed and control specimens also did not differ significantly with SAR, nor did assays of lactate-dehydrogenase (LDH) release. Lower but nonsignificant release of glutamine-oxaloacetic transaminase (GOT) was seen at 1 W/kg than at 0, 10, or 50 W/kg.	Semen collected from 10-month-old turkeys were treated to remove the seminal plasma, and sperm suspensions (500 million sperm/ml) were prepared. Viable sperm with balloon heads or with broken, bent, or twisted tails were classified as abnormal. Removal of the seminal plasma had no effect on spermatoocyte viability either before or after RFR-exposure. The authors concluded that the RFR-exposures had no adverse effects on turkey sperm.
Hall et al. (1983)	turkey sperm	2.45 GHz	Incident power density not stated	10 or 50 W/kg in the Galvin et al. (1981b) water-cooled waveguide	30 min. at 25 or 40.5 °C	Semen suspensions before and after treatment were assayed for pH, and were used after treatment for artificial inseminations of 6 groups of 16 turkey hens in a 2x3 design: 25 °C, 40.5 °C times 0, 10, 50 W/kg. No significant RFR-related differences in mean pH, or in egg laying, fertility, or hatchability were seen among the 6 treatment groups.	The authors presented data on early and late deaths, with each class tabulated in terms of numbers and percentages of deaths by week and treatment. They stated: "There were approximately 15% early and late deaths over the 10-week experimental period, and there was no difference among the groups for any treatment or temperature." However, they provided no statistical analyses of the data. A cursory examination of those data showed no consistent RFR-related pattern.

TABLE 8E: TERATOGENESIS IN NONMAMMALIAN SPECIES (CONCLUDED)

studies were done with 2.45-GHz RFR, and the SARs ranged from 3.2 to 25 W/kg. The endpoints included hatchability, hatchling weights, viability, and the incidences of abnormalities. The findings showed no significant differences between RFR-exposed and sham-exposed eggs in any endpoints except when RFR-exposure raised internal egg temperatures by a few degrees above normal incubation temperatures. An important difference between RFR-exposure and maintenance of eggs at the same surface temperature by conventional means is the non-uniform spatial internal-temperature distribution in RFR-exposed eggs, with consequent higher local temperatures within them.

Chicken and turkey eggs were also studied. Fisher et al. (1979) exposed arrays of chicken eggs to 2.45-GHz RFR at an array mean of 3.46 mW/cm² (SAR not determined), the only positive finding was a delay in embryo development. The results were difficult to analyze or accept because of the large spatial range of RFR levels (1.4-6.2 mW/cm²) over each egg array and the likelihood of larger internal temperature gradients than with sham-exposed eggs (as observed by Clarke and Justesen, 1983). Saito et al. (1991) did a study with arrays of chicken eggs exposed at 428 MHz, in which mean percentage hatchabilities were much lower for RFR-exposed than sham-exposed eggs. That study suffered from faulty experimental design and methodology, e.g. a spatial SAR range of 3.1-33.0 W/kg, so little if any credence can be given to any of its positive or negative findings.

Braithwaite et al. (1991) exposed arrays of chicken eggs to 2.45-GHz RFR at a spatial mean SAR of 2.9 W/kg in a multimode microwave cavity. They found no significant differences between exposed and controls in hatchability, but a few chicks from a group of eggs exposed through day 19 of incubation exhibited delayed development, a finding ascribed to lower egg temperatures during days 12 and 13 of incubation. The study was well designed, but inadequate control over the ambient temperature and its spatial variations within the microwave cavity rendered the findings questionable.

Hills et al. (1974) exposed arrays of chicken and turkey eggs in various stages of development to 6-GHz RFR at "low" level (spatial range 0.1-0.4 mW/cm²) and 2.45-GHz RFR at "high" level (51, 123, 246, or 1020 mW/cm²). No effects were seen at 6 GHz but reduced hatchability or failure to hatch was reported with 2.45 GHz. Little credence can be given to either the negative or positive findings in the absence of information on the exposure methodology or dosimetry, spatial temperature uniformity within the exposure chamber, and egg treatment during exposure.

Hall et al. (1982), in one of two studies, exposed turkey semen to 2.45-GHz RFR at 1, 10, or 50 W/kg in a special water-cooled waveguide (Galvin et al., 1981b) and assessed sperm samples for viability and abnormalities. No significant SAR-related differences between exposed and control samples were found in either endpoint. In the other study, Hall et al. (1983) assayed RFR-exposed semen suspensions for pH, and used such samples to inseminate turkey hens. The authors found no significant RFR-related differences in mean pH or in egg laying, fertility, or hatchability, but their findings are open to question because they provided no statistical treatment of their data.

2.4 CONCLUSIONS ON NONMAMMALIAN SPECIES

Based on the foregoing, the observed incidences of RFR-teratogenesis in *Tenebrio molitor* were thermally induced, with no scientifically valid evidence

for any nonthermal RFR effects. However, the relationship of those findings to possible RFR-teratogenic effects in humans is unclear at best. Collectively, the various studies on Japanese quail, chickens, and turkeys also yielded RFR-related effects ascribable to significant temperature increases in the exposed specimens. No credence can be given to the results of a few of the studies because of inadequate methodology and/or dosimetry.

3 RFR-TERATOGENESIS IN NONHUMAN MAMMALS

3.1 MICE AND HAMSTERS

Among the early RFR-teratogenesis studies in mice was that of Bollinger et al. (1974), who investigated the effects of exposure to RFR on growth and reproduction, in an experimental design involving C3H/He dams and successive generations thereof. The exposures were to 25-kHz synchronous, orthogonal electric and magnetic fields (the equivalent of plane-wave CW RFR) in a combined capacitor and Helmholtz-coil system. Some groups were exposed at 15 kV/m and 7.5 A/m, equivalent respectively to 59.5 and 2.12 W/cm² ("full-power"). This level was selected to yield a 3-°C rectal-temperature rise in mouse carcasses in 1 hour. Other groups were exposed at 10.6 kV/m and 5.3 A/m, equivalent respectively to 29.8 and 1.06 W/cm² ("half-power"). Durations of exposure at either level were 1 hour/day, 5 days/week, for a total of 50 hours. Control mice were sham-exposed. The results showed no statistically detectable effects of the RFR at either level on the growth, reproductive ability, and metabolism of neonates or on the growth of their subsequent offspring.

Bollinger et al. (1974) also sham-exposed and exposed groups of 4-day-old mice for 10, 20, 40, 70, or 100 hours at half-power or full-power. The mice were sacrificed postexposure, and no significant differences were found between RFR and sham groups in hematologic assays or major-organ weights, and no pathological changes were seen in the organs. Also, cytological analysis revealed no obvious effects of the RFR on the number or the architecture of bone-marrow chromosomes. However, the authors reported that exposure to RFR stimulated the uptake of tritiated thymidine in lymphocyte cultures and that the presence of common mouse parasites in RFR-exposed and control groups could not account for this effect. One other finding noted by the authors was no incidence of C3H/He-mouse mammary-tumor development up to 98 days of age.

Stavinoha et al. (1975), in one of two experiments, exposed groups of 4-day-old mice in plastic containers for 20 minutes to 10.5-, 19.27-, or 26.6-MHz RFR pulses (pulse duration and duty cycle not stated) in a rectangular-coaxial transmission-line (TEM) system (Mitchell, 1970) at an electric field strength of 5.8 kV/m. Control groups were kept in similar containers outside the exposure chamber. The mice were weighed daily for the next 21 days. Graphs of weight versus age at each frequency showed virtually no differences between exposed and control mice at corresponding ages.

In the second experiment, litters of 4-day-old pups from 20 mice were divided into three groups:

(1) Control pups, kept in individual cages.

(2) Thermal-control pups, held at 37 °C for 40 minutes/day on five consecutive days.

(3) Irradiated pups, exposed to 19-MHz CW RFR for 40 minutes/day on five consecutive days in a near-field synthesizer (Greene, 1974), in which the electric field was 8 kV/m, the magnetic field was 55 A/m, and the two fields were parallel (vertical) in coincident planes.

After thermal or RFR treatment, the mean increase in rectal temperature was 1.5 °C. The pups were weighed before each daily treatment and until they were 21 days old, at which time the males and females were separated. The mice were then weighed weekly for 13 additional weeks.

Statistical analyses of growth curves showed no significant differences among the three groups of either sex. (The final weights of the males were somewhat higher than those of the females.) As the authors noted, although the fields used were very intense, relatively little RFR energy was absorbed by the mice because their sizes were much smaller than the wavelengths used. Thus, it would be inappropriate to apply these negative findings to humans exposed to RFR at frequencies in the same range.

The results of the second experiment above with mouse pups were also presented in Stavinocha et al. (1976), which included data on mortality after the 5-day treatment as well. Of 30-female and 30-male control mice, 1 female died; of 30 females and 29 males in the thermal-control group, there were 1 female and 6 male deaths; and of 40 females and 40 males in the RFR group, 2 females and 11 males died, i.e., relatively high death rates for males.

In addition, Stavinocha et al. (1976) had similarly treated adult mice in control, thermal-control, and irradiated groups; the latter two treatments yielded a mean rectal-temperature increase of 1.6 °C. Within 45 minutes after treatment, the mice were exposed to very intense 2.45-GHz RFR for brain enzyme inactivation, which required 300 milliseconds, following which various brain regions were assayed for adenosine 3':5'-cyclic phosphate (cyclic AMP). No significant differences among the three groups were reported.

Rugh et al. (1974, 1975) exposed groups of CF-1 female mice to 2.45-GHz RFR at 138 mW/cm² (SAR about 123 W/kg) for various durations in a waveguide system under controlled conditions of temperature, relative-humidity, and air-flow to determine "D/M", the mean dose (power density x duration) per unit body mass, for lethality. The D/M for lethality was about 11 cal/g (10.65 cal/g for mice in estrus and 11.50 cal/g for mice in diestrus) or 46.1 J/g. They then exposed unrestrained timed-mated pregnant mice on gestation day 8.5 (previously found to be the time of highest sensitivity to ionizing radiation) to the RFR at 123 mW/cm² for 2 to 5 minutes, corresponding to sublethal values of D/M ranging from about 3 to 8 cal/g (12.6 to 33.5 J/g), at 25.0 °C and 50% relative humidity. From the dose-rate data, the SAR was about 110 W/kg. Most pregnancies were terminated on gestation day 18 and the mice were examined for resorptions and for dead, stunted, and malformed fetuses, all classified as anomalies, and for apparently normal fetuses.

In a plot of percentage of total anomalies per litter versus D/M, at least 40 litters (points too dense to count exactly) had 0% (all normal fetuses), spanning the exposure range from 3.4 to 7.8 cal/g; 5 litters had 100% (no normal fetuses), within the range from 5.8 to 7.7 cal/g; and the remaining litters (at least 140) had various intermediate percentages of

anomalies, spread over the entire dose range. A plot of only the resorption percentages versus D/M showed at least 40 litters with 0%, from 3.3 to 7.7 cal/g; 3 with 100% resorptions, all above 5.9 cal/g; and the remaining litters (about 130) with intermediate percentages, spread over the entire dose range.

The percentages per litter of fetuses with exencephaly (brain hernia, produced consistently in CF-1 mice by ionizing radiation) versus D/M were plotted also. Exencephaly was absent in at least 45 litters, spanning the total dose range; 2 litters had 60%, the highest incidence, at about 7 cal/g; and the remainder (about 50 litters) had intermediate percentages, in the range 4.3-7.8 cal/g.

Apparently no control mice were studied, presumably under the assumption that the natural incidence of exencephaly is relatively rare. However, Chernovetz et al. (1975), in a similar study (discussed below) with C3H/HeJ rather than CF-1 mice, reported that about 20% of the fetuses from their control dams were abnormal.

The authors stated that they could not find any teratogenesis threshold. However, a reanalysis of their data on the percentages of resorptions and of dead, stunted, and malformed fetuses versus D/M indicated that at doses less than about 3 cal/g or power densities less than about 1 mW/cm², 100% of the fetuses examined were normal and that there were thresholds of about 3.6 cal/g for the occurrence of exencephaly and about 3.5 cal/g for resorptions.

Chernovetz et al. (1975), in the first of two regimens, exposed 4 groups of 5 pregnant C3H/HeJ mice to 2.45-GHz RFR for 10 minutes, 1 group each on gestation days 11, 12, 13, and 14 (totaling 20 dams). The mice in each group were concurrently exposed in a multimode, mode-stirred microwave cavity (at 22 °C and 50% relative humidity) with the mice free to move about. At a mean SAR of 38 W/kg (estimated), the energy absorbed was 22.8 J/g or 5.44 cal/g. The authors noted that in a pilot study, 10-minute exposures at 40 W/kg (24 J/g or 5.7 cal/g) were fatal to about 10% of a large number of pregnant mice, so 38 W/kg was just sublethal. Four other groups were similarly sham-exposed. In addition, eight other groups were injected with cortisone (a teratogen), and four of them were exposed to the RFR and the other four were sham-exposed.

Colonic temperatures were measured before and after RFR exposure for 10 cortisone-injected and 9 noninjected dams. The mean pre-exposure and post-exposure temperatures of the cortisone-injected dams were 34.59 and 39.93 °C, respectively; those for the noninjected dams were 38.58 and 40.60 °C.

All mice were euthanized on gestation day 19, at which time the numbers of implantations and resorptions were counted and the fetuses were examined for structural abnormalities. For the noncortisone RFR and sham-exposed groups, there were no statistically significant differences in percentages of normal fetuses and structural abnormalities and no dependence on gestation day of treatment. However, the percentage of normal fetuses was 61% for the cortisone-with-sham-exposure and 50% for the cortisone-with-RFR groups. The difference in the percentages was nonsignificant ($p > 0.1$), but both percentages were significantly lower ($p < 0.1$, the authors' significance criterion) than for the noncortisone RFR-exposed and sham-exposed groups (both 81%).

In the second regimen by Chernovetz et al. (1975), the treatments were similar, but the exposures were done only on gestation day 14 and with a total

of 60 dams, 15 in each of the four treatment groups (RFR, sham-RFR, cortisone-with-RFR, cortisone-with-sham-RFR). All dams were allowed to carry to term, and the numbers of pups that survived to weaning at postpartum age 21 days were noted. (The behavior of the surviving pups was studied; for the findings thereof, see the planned report on "Behavior," when available.)

For the noncortisone groups, 93 pups from RFR-exposed dams and 81 pups from sham-exposed dams survived to weaning, a nonsignificant difference. For the cortisone groups, however, 25 pups from RFR-exposed dams but only 2 pups from those sham-exposed survived to weaning, values that were significantly lower than for the noncortisone RFR and sham groups, and the differences between groups were also significant.

These results of Chernovetz et al. (1975) indicated that absorption of 5 cal/g of 2.45-GHz RFR is not teratogenic to mice, a finding at variance with those of Rugh et al. (1974, 1975). It is also noteworthy that the mean dosage for lethality found by Chernovetz et al. (1975) was about 5.7 cal/g or about half the mean value found by Rugh et al. (1974, 1975), hence their conflicting characterizations of doses with respect to lethality. Possible reasons for these contradictory findings include their respective differences in exposure systems (cavity versus waveguide), use of multiple-animal versus individual-animal exposures, gross uncertainties in the actual doses, the mouse-strain difference (C3H/HeJ versus CF-1), the variations in dam handling, and the differences in gestation day of treatment (day 11 through 14 versus day 8). As noted previously, Chernovetz et al. (1975) found fetal anomalies in about 20% of their control mice, whereas Rugh et al. (1974, 1975) apparently used no controls. Both groups of investigators indicated that extrapolation of their findings to higher mammalian species is a question subject to experimental validation. Chernovetz et al. (1975) also noted that in view of their D/M value for lethality (5.7-cal/g), their results indicate that RFR teratogenesis would occur in pregnant mice only at levels close to lethality for the dams.

Berman et al. (1978) exposed pregnant CD-1 mice in 5x5-, 7x4-, or 3x5 arrays to far-field 2.45-GHz CW RFR for 100 minutes daily on gestation days 1 through 17 at 3.4, 13.6, or 14.0 mW/cm², or on gestation days 6 through 15 at 28 mW/cm². The exposures were done at 20.2 °C ambient temperature and 50% relative humidity. The SARs were determined by twin-well calorimetry. For 5x5 arrays exposed at 10 mW/cm², the SAR varied with location in the array from 4.05 to 7.37 W/kg, with an array mean of about 5.9 W/kg, yielding 2.0, 8.1, and 8.3 W/kg for 3.4, 13.6, and 14.0 mW/cm², respectively. No data were given on spatial variations of SAR for the 7x4 or 3x5 arrays, but the mean SAR at 28 mW/cm² was 22.2 W/kg (a value not twice the spatial mean for 14 mW/cm²). Control mice were sham-exposed similarly. All mice were euthanized on day 18 and their uteri were examined for the number of resorbed and dead conceptuses and live fetuses, and the live fetuses were examined for gross morphological alterations and weighed.

The numbers of litters with one or more anomalous fetuses were tabulated in terms of 10 types of anomalies in increasing order of severity; litters with more than one anomaly were counted only once for the most severe anomaly. (The numbers of fetuses affected in each litter were not presented.) Those results are displayed in Table 9 (adapted from Table 5 of the paper).

TABLE 9: LITTER OCCURRENCE OF EXTERNAL MORPHOLOGIC DEFECTS IN MICE
[Berman et al. (1978)]

	POWER DENSITY (mW/cm ²)									
	Sham	3.4	Sham	13.6	Sham	14	Sham	28	Sham	RFR
Total litters	117	103	106	109	73	62	40	44	336	318
<u>Anomaly</u>									<u>Total Litters</u>	
Hematoma	0	4	3	2	1	0	1	0	5	6
Omphalocele	0	0	0	1	0	0	0	0	0	1
Kinked tail	1	0	0	1	0	1	0	0	1	2
Small jaw	0	0	0	0	0	1	0	0	0	1
Club-foot	1	3	1	0	0	0	0	2	2	5
Open eye(s)	0	1	2	1	0	0	0	0	2	2
Syndactyly	0	0	1	0	0	0	0	0	1	0
Palatoschisis	0	0	0	0	0	0	1	1	1	1
Schistocele	0	1	0	1	0	0	0	0	0	2
Cranioschisis	0	1	0	1	0	3	0	2	0	7
Totals affected	2	10	7	7	1	5	2	5	12	27

As seen above, 27 of the 318 RFR-exposed litters (irrespective of power density) had 1 or more live abnormal fetuses, versus 12 of the 336 sham-exposed litters. Regarding the numbers of litters affected at each RFR level, the authors indicated that the difference between exposure at 3.4 mW/cm² (10 litters) and sham-exposure (2 litters) was significant ($p=0.009$), but that the corresponding differences at the higher RFR levels were not significant.

For most of the individual anomalies, either the numbers of litters affected were too small for statistical treatment or no RFR-related pattern was apparent. To exemplify the latter, 4 of the litters exposed at 3.4 mW/cm² (2.0 W/kg) exhibited hematoma, with none in the corresponding sham-exposed group; however, 2 of the litters exposed at 13.6 mW/cm² (8.1 W/kg) and 3 of the sham-exposed litters were affected, and no litters were affected at 14.0 (8.3 W/kg) or 28.0 mW/cm² (22.2 W/kg), compared with 1 litter in each of their corresponding controls. However, particularly noted by the authors was the incidence of cranioschisis (akin to exencephaly or brain hernia) in 7 RFR-exposed litters (irrespective of RFR level) and none in the sham-exposed litters, a significant difference ($p=0.007$).

Regarding the abnormal fetuses, the validity of statistically analyzing the numbers of litters rather than the numbers of fetuses affected is open to question. Also questionable was the summing of all RFR litters that exhibited cranioschisis (irrespective of power density) and ascribing such significance to RFR-exposure. Thus, ascribing the findings to RFR-exposure is dubious in view of the relatively large spatial ranges of power densities over the mouse arrays and the absence of a clear dose response relationship.

The mean live fetal weights of the litters exposed at 3.4, 13.6, or 14.0 mW/cm² (2.0, 8.1, or 8.3 W/kg) were not significantly different from those of the corresponding sham-exposed litters; however, the mean weight of those treated at 28.0 mW/cm² (22.2 W/kg) was significantly lower than for the sham-exposed litters, indicating the possible existence of a threshold between 14 and 28 mW/cm² for such weight deficits.

In a subsequent similar study, Berman et al. (1982a) sham-exposed or exposed time-bred CD-1 mice within individual vented plastic cages to 2.45-GHz CW RFR at 28 mW/cm² (array mean 16.5 W/kg $\pm$ 4.5 W/kg SD) at 20.2 °C ambient temperature and 50% relative humidity for 100 minutes daily on gestation days 6 through 17. On arrival, the mice were caged in pairs and each pair was assigned to one of two groups and positions in a 5x5 array. Specifically, a pair assigned to Position 1 was either RFR- or sham-exposed, and their fetuses were examined on gestation day 18; a pair assigned to Position 2 was similarly treated, but allowed to come to term; and the pairs in successive positions in the array were similarly alternated. Two replicates were done, for totals of 50 RFR-exposed and 50 sham-exposed mice.

In the mice examined on day 18, the incidence of pregnancy; the number of live, dead, and resorbed fetuses; and total number of fetuses were found to be comparable for the RFR-exposed and sham-exposed mice, findings at variance with those of their previous study (Berman et al., 1978). However, as seen in Table 10 (adapted from Table 3 of the paper), the mean body weight of the live fetuses in the RFR group was significantly smaller (by 10%) than of the live fetuses in the sham group, a finding consonant with their previous results (Berman et al., 1978). In addition, ossification of sternal centers was significantly delayed in the RFR-exposed fetuses.

TABLE 10: LITTER MEAN WEIGHT $\pm$ SD (g) PER MOUSE FETUS OR 7-DAY NEONATE
[Berman et al. (1982a)]

<u>Age Group</u>	<u>Sham-Exposure</u>	<u>28 mW/cm²</u>
18-Day Fetuses	1.10 $\pm$ 0.11	0.99 $\pm$ 0.11
No. of Litters	14	17
7-Day Neonates	4.32 $\pm$ 0.48	3.89 $\pm$ 0.38
No. of Litters	12	10

For the mice permitted to come to term, the live and dead neonates were counted on the morning after birth. At 7 days of age, the live pups in each litter were counted again and the pups were weighed as a litter. There were no significant differences between RFR and sham pups in the counts. However, as seen in Table 10, the mean body weight of the 7-day RFR-exposed pups was significantly smaller (by 10%) than for the sham-exposed pups. The survival rates of the RFR and sham groups were comparable, but the growth retardation was permanent.

In a followup study, Berman et al. (1984) exposed a group of 25 bred female CD-1 mice in a 5x5 array to 2.45-GHz CW RFR at 28 mW/cm² (16.5 $\pm$ 4.5 W/kg) for 100 minutes daily on gestation days 6 through 17, with another 5x5 array sham-exposed, and the mice were allowed give birth naturally. Three replications were done, totaling 75 RFR-exposed and 75 sham-exposed mice. Of those, 37 mice were not pregnant and the remaining 113 mice delivered litters. Twenty-four of those mice were deleted for various experimental reasons or for the presence of one or more dead pups. Of the remaining 89 mice, 40 had been sham-exposed and 49 had been RFR-exposed, and all had similar litter sizes and ranges of gestation period.

At birth, however, the mean litter weights and SEs of the neonates were 1.74 $\pm$ 0.47 g and 1.57 $\pm$ 0.57 g, respectively. By F-test, the difference was

significant [$F(1,88)=6.48$, $p=0.0127$], indicating a lower mean litter weight for the RFR-exposed neonates.

To minimize weight differences due to variations in gestation duration, only litters born on gestation day 20 (when 78% of the dams gave birth) were selected. Of those, only litters with more than 7 live pups were studied, and litters with more than 8 were randomly normalized to 8 pups. This selection yielded only 15 sham-exposed and 26 RFR-exposed litters.

The litters were tested for body weight, brain weight, bone lengths, the ability to concentrate urine, and tolerance to ouabain (a medication used in humans to treat congestive heart failure and related disorders). The authors remarked that no single statistical method could be used for the variety of endpoints involved, and they therefore first analyzed the data on the body weights, urine concentrations, and bone lengths separately for each day by t-test, and where appropriate, used the Bonferroni method to set the level of significance. For example, the significance level they took for body weight measured on 6 days was $p = 0.05/6 = 0.008$ instead of the more conventional $p = 0.05$. Linear regression was used for each endpoint that was measured at several ages. The hypotheses tested were whether the regression lines for the RFR-exposed and sham-exposed pups were parallel (H1) and whether the means of the lines were similar (H2). They used probit analysis on the ouabain-tolerance data.

Body weights were measured at ages 1, 5, 10, 12, 15, and 17. Although the mean weights of the RFR-exposed mice were all lower than those of the sham-exposed mice at corresponding ages, by t-test only the difference at age 1 day was significant ($p=0.003$). An analysis of variance over the age span yielded no significant differences in the growth curves (H1) or the weight means (H2).

The lengths of the tibia and radius, and the diameter of the scapula blades were measured in 2 pups per litter euthanized at age 5 days and in 1 pup per litter euthanized at ages 10, 12, and 17 days. By either t-test of the data for each age or the H1 and H2 tests, there were no significant differences in any of those endpoints. The brain of each pup euthanized at ages 10, 12, and 17 days was weighed, and the data were adjusted for body weight by analysis of covariance. The results indicated consistently lower brain weights for the RFR-exposed pups.

The ability of untreated CD-1 mice to concentrate urine at ages 1 to 10 days was determined by removing 3-14 pups each day from their dams, forcing them to empty their bladders by perineal stimulation, depriving them of fluids for 5 hours, and then stimulating them to urinate into plain microhematocrit capillary tubes. After appropriate preparation of the samples, aliquots were measured for osmotic pressure and the results were plotted versus age, along with a curve for mice not fluid-deprived. Both curves were S-shaped. Through age 3 days, the urine concentration of the fluid-deprived mice was about 40% higher than for the mice not fluid-deprived and increased gradually with age, while the curve for the mice not fluid-deprived did not rise. At about age 4 days, the curve for the fluid-deprived mice rose more rapidly than previously, and exhibited near saturation at about age 6 days, but the curve for the mice not fluid-deprived rose at a much slower rate.

The method above was then used on 12 sham-exposed and 23 RFR-exposed mice fluid-deprived at age 5 days. Those results showed no significant differences in urine osmolarity between the two groups.

As a test for ouabain tolerance, sham-exposed and RFR-exposed pups (1 pup per litter) at age 15 days were injected intraperitoneally with ouabain (in physiologic saline) at 4, 6, or 8 mg of ouabain per kg of body weight. They were then returned to their dams and were examined 24 hours later for survivors. The authors noted that failures in the injection technique reduced the number of litters that could be included in the probit analysis from 41 to 31 for each of the three ouabain levels. Multivariate analysis of variance did not show any significant differences in pup-death incidences for the RFR-exposed pups. The survival rates for the three ouabain doses 24 hours after injection yielded calculated mean LD₅₀ values of 4.83 and 5.60 mg/kg for the sham-exposed and RFR-exposed pups, respectively, a difference indicated by the authors to be nonsignificant.

In their discussion, the authors noted that except on day 1, the mean body weights of the RFR-exposed pups did not differ significantly from those of the sham-exposed pups, indicating that the RFR-exposed pups were able to overcome their initial weight deficit, a result at variance with the continued weight deficits seen by Berman et al. (1982a). They ascribed the outcome of the present study to the normalization of litter size, thereby removing the influence of that variable on nutrition and growth during the suckling period. Regarding the significantly lower mean brain weight of the RFR-exposed pups at each age, they noted that the pattern of brain growth in the mouse is directly related to the growth of the body until 14-15 days of age, after which brain growth and development is almost nil, citing Kobayashi (1963) and Kobayashi et al. (1963), a pattern observed in the present study. Thus, unlike mean body weight, the initial brain-weight deficit persisted. The authors remarked that the whole-body SAR in this study, 16.5 W/kg, may have heat-stressed the mice, thereby causing the brain-weight deficit, citing the study of Purkinje-cell migration in rats by Albert et al. (1981a).

Berman et al. (1982b) exposed 8 Syrian hamsters dorsally in individual acrylic containers in a 3x3 array (with center position not used) to 2.45-GHz CW RFR at 20 mW/cm² (6 W/kg) at 22.2 °C and 50% relative humidity for 100 minutes daily on gestation days 6-14. An array of 8 hamsters was similarly sham-exposed. RFR-exposure at this level, for which rectal temperatures were about 0.4 °C higher than for sham-exposed hamsters, caused no significant change in fetal survival, body weight, skeletal maturity, or incidence of terata. By contrast, exposure at 30 mW/cm² (9 W/kg), which raised rectal temperatures by about 1.6 °C, caused significantly higher fetal resorptions, lower fetal body weights, and delayed skeletal maturity. The authors, citing Berman et al. (1978, 1982a), stated: "It appears that the hamster fetus may be more susceptible to microwave radiation than the mouse."

Nawrot et al. (1981) exposed circular arrays of 12 pregnant CD-1 mice to far-field 2.45-GHz CW RFR from above daily for 8 hours at one of three power densities in an anechoic chamber on gestation days 1-15, 1-6, or 6-15, all at 22 °C ambient temperature and 55% relative humidity. Spatial variations of power density over the circular array were about 10%. Other groups were sham-exposed under the same conditions. Still other groups were sham-exposed at 30 or 31 °C to obtain the same rises in colonic temperature as those for the two higher RFR levels.

Two groups were used for each treatment, one characterized as "handled" and the other as "nonhandled". Handled mice were transferred to Styrofoam cages (one per cage) for RFR-, sham-, or heat-exposure with no food or water available for the 4-hour periods 0800-1200 and 1300-1700, and were housed in polycarbonate shoe-box-type cages with food and water available during 1200-1300 and during 1700-0800. Non-handled groups were housed in shoe-box-type cages with food and water available for the entire 24-hour period and were sham-exposed or heated concurrently with the handled groups. Body weights of dams were recorded on gestation days 1, 6, 15, and 18. On day 18, the dams were killed, and the implantation sites, resorptions, dead fetuses, and live fetuses were counted. The fetuses were sexed, weighed, and examined for malformations.

In the first of three experiments, one handled group was exposed for 8 hours daily on gestation days 1-15 at 5 mW/cm² (6.7 W/kg), and one handled and one nonhandled group were sham-exposed. The pregnancy rates, maternal weight gains, and average fetal weights for both handled groups (RFR- and sham-exposed) were significantly lower than for the nonhandled-sham-exposed group, indicating that handling was the primary factor in the differences. The results for the other endpoints did not differ significantly among the three groups.

In the second experiment, one handled group was exposed at 21 mW/cm² (28.1 W/kg) and 22 °C ambient temperature, which caused a rectal-temperature rise of about 1 °C; one handled group was heated in ambient temperature 30 °C to obtain the same rectal-temperature rise; and one handled group was sham-exposed at 22 °C. Also, one nonhandled group was sham-exposed at 22 °C and another was heated at 30 °C ambient temperature. All groups were treated daily on gestation days 1-6. The same procedure was used for other handled and nonhandled groups, but on gestation days 6-15. For those treated on days 1-6, significantly smaller maternal weight gains were observed in the handled-RFR-exposed, handled-sham-exposed, and handled-heated groups than in the nonhandled-heated and sham-exposed groups. For the groups treated on days 6-15, the maternal weight gain was smaller for the nonhandled-heated group as well, and the largest decrease was for the handled-heated group. Thus, handling was again an important factor, but heating was as well. The other endpoints were not affected significantly.

The third experiment was similar to the second, but with treatment at 30 mW/cm² (40.2 W/kg) or at 31 °C, the latter to obtain a mean rise in rectal temperature of 2.3 °C, the same as for the former. Treatment on days 1-6 yielded a significant decrease in pregnancy rate for the handled RFR-exposed and sham-exposed groups relative to the nonhandled-sham and nonhandled-heated groups. The dams in all three handled groups gained significantly less weight than those in the nonhandled groups. The handled-RFR group had fewer implantation sites per litter than the other groups, but only the difference relative to the nonhandled-sham-exposed group was significant. Fetal weight was smaller in the handled-RFR group than in the handled- and nonhandled-sham-exposed groups, but was comparable to that of the handled-heated group. No increases in external, visceral, or skeletal malformations were seen in any of the groups.

For treatment on days 6-15, the dams of all handled groups gained significantly less weight than those in the nonhandled groups, and the mean

percentage of malformed fetuses per litter was larger for the handled-RFR group than any other group, with cleft palate the predominant malformation.

Based on the foregoing results, the authors concluded that the threshold for teratogenic effects in CD-1 mice is about 30 mW/cm² (whole-body SAR of 40.2 W/kg).

Nawrot et al. (1985) did experiments similar to the last one of Nawrot et al. (1981), i.e., exposures of groups of handled CD-1 mice to 2.45-GHz CW RFR at 30 mW/cm² (40.2 W/kg) or to an ambient temperature of 31 °C for 8 hours daily on gestation days 1-6 or 6-15. Comparisons were made with groups of handled and nonhandled sham-exposed mice, a nonhandled heated group, and a cage-control group (maintained in animal quarters during pregnancy). As before, all dams were euthanized on day 18; the implantation sites were counted; the conceptus at each site was classed as resorbed, dead, or alive; and the live and dead fetuses were sexed, weighed, and examined for external anomalies. All live and dead fetuses were examined for skeletal alterations. The fetuses with external anomalies and stunted fetuses (weighing less than 0.5 g or less than two-thirds of their mean litter weight) were examined for visceral abnormalities. For the handled dams treated during gestation days 6-15, during which most prenatal brain development occurs, fetal brains were examined for histopathology and assayed for cholinesterase activity.

Mean pregnancy rate (determined on day 18) of the dams exposed to the RFR on days 1-6 was significantly lower than for the other groups treated on days 1-6. Mean maternal weight gains for the handled groups treated during this period (RFR-exposed, sham-exposed, heated) were significantly lower than for the corresponding nonhandled groups (sham-exposed, heated, cage-control). Mean fetal weights were lower for all three handled groups than the nonhandled groups, but the differences were significant only for the sham-exposed and heated groups. The highest incidence of external malformations (cleft palate, open eyes) occurred for the handled sham-exposed group, but none of the differences among the groups was significant.

For the groups treated on days 6-15, mean maternal weight gains were also smaller in the handled than the nonhandled groups. Mean fetal weights were smaller for the handled-RFR-exposed and handled-heated groups than for the other groups, but the difference was larger for the handled-heated group. There were no significant differences in the other teratologic endpoints among the groups treated on days 6-15. Mean cholinesterase activities assayed in the fetuses from the three handled groups (RFR-exposed, heated, sham-exposed) did not differ significantly from one another. A few fetal abnormalities were found, but none was related to differences in treatment.

The authors suggested that the lower mean pregnancy rate in the group exposed to RFR on days 1-6 may have been due to preimplantation death and/or early postimplantation litter resorption, and that the absence of this effect in those exposed on days 6-15 may indicate that embryos in the earlier stage of gestation are more susceptible to the RFR. On the other hand, the authors noted that the decrease in mean pregnancy rate observed for mice exposed at 30 mW/cm² on days 1-6 in the previous study (Nawrot et al., 1981) resulted from handling, but that combining the data from both studies indicates that the effect was not due to handling alone. They ascribed the contribution of the RFR to this effect to higher local temperatures in the uterine region because

they had found that colonic temperature during exposure to the RFR rose about twice as fast than during treatment at the elevated ambient temperature used to attain the same final colonic temperature.

Inouye et al. (1982b) induced female CD-1 mice to superovulate and mated them. Groups of mice were then sham-exposed or exposed for 3 hours on either gestation day 2 (during the 2-cell stage) or day 3 (during the 4- to 8-cell stages) to far-field 2.45-GHz CW RFR at 9 or 19 mW/cm² (11.7 or 24.7 W/kg). The exposures were done in circular arrays in an anechoic chamber at 22 °C ambient temperature and 60% relative humidity. Also, one group was exposed at 38 °C ambient temperature and 60% relative humidity without RFR. No increase in colonic temperature was obtained at 9 mW/cm², 1 °C increase occurred at 19 mW/cm², and at least 2.2 °C occurred for the 38-°C heat treatment. All mice were euthanized on gestation day 4. The embryos were counted, examined for abnormalities, and classified by developmental stage as: morula (9 or more blastomeres but no blastocoelic cavity), early blastocyst (small blastocoelic cavity), or blastocyst (large blastocoelic cavity). Abnormal embryos were defined as underdeveloped (less than 9 blastomeres) and as fragmented and/or collapsed embryos.

There were no statistically significant differences in the number of fertilized mice, the number of embryos per mouse, or the percentage of abnormal embryos (total and per dam) among all of the groups. In addition, there were no significant differences in embryonic development or in abnormal embryos between RFR-exposed groups (at either power density) and sham-exposed groups for either treatment day. However, the heat treatment at 38 °C caused stunted embryonic development, i.e., significant increases in the number of morulae and decreases in the numbers of blastocysts compared with the numbers for sham-exposed mice on corresponding treatment days.

Direct comparisons of the results of this study with those of Nawrot et al. (1981), performed in the same laboratory with the same mouse strain (CD-1), are difficult because in the latter investigation, the dams were exposed for 8 hours/day over gestation days 1-6 or 6-15 (in contrast with a single 3-hour exposure on day 2 or 3), and the fetuses were examined at a much later stage of gestation (day 18 versus day 4). Moreover, the frequent handling of the dams was a significant factor in the earlier study. Nevertheless, the negative results by Inouye et al. (1982b) for exposure at 9 and 19 mW/cm² (11.7 or 24.7 W/kg) are consonant with the approximately 30 mW/cm² threshold found by Nawrot et al. (1981). Also, fetal stunting occurred in both studies from exposure of the dams to elevated ambient temperatures without RFR.

Chiang and Yao (1987) exposed pregnant mice in Plexiglas cages to pulsed 3-GHz RFR (1.2-μs pulses at 937 pps) at 8 mW/cm² for 5 hours daily throughout gestation, with their long axes parallel to the H-field (SARs in the range 3.0-3.5 W/kg). The exposures were done in an anechoic chamber at 21 °C (room temperature). The authors noted that no core-temperature rises had occurred after exposure. The exposures were continued for half the pups (RR group) from day 3 to day 20 after birth (SARs not estimated). The pups in the other half were sham-exposed (RC group). Other pregnant mice were similarly sham-exposed, and half those pups were exposed to the RFR (CR group) and the other half were sham-exposed (CC group).

On day 2 after treatment termination (age 22 days), 10 pups in each group were decapitated, and 10-micrometer-thick medial-sagittal sections of

brain were prepared for histochemical analyses. Such sections were assayed for succinate dehydrogenase (SDH), monoamine oxidase (MAO), and catecholamines (CA) by fluorescence spectrophotometry. Also assayed was SDH in the liver. The results were presented as bar graphs of relative fluorescence (with error bars) for the four groups.

For hypothalamic SDH, the mean relative fluorescence was highest in the CC group and successively lower for the RC, CR, and RR groups. The SDH levels in the liver were about twice those in the hypothalamus, but showed a similar succession of decreases. The succession of patterns for the constituents CA and MAO (in the hypothalamus) were also similar. The differences in results between each pair of groups for each constituent were compared by the authors for significance by analysis of variance. Most of the differences were stated to be significant at less than the 1% level.

The authors ascribed the decreases of SDH in the hypothalamus to either prenatal or postnatal exposure to the RFR, and the decreases of SDH in the liver and of CA and MAO in the hypothalamus primarily to postnatal exposure. They also remarked that such histochemical tests may be more sensitive and reliable indexes for determining the effects of RFR on development than those usually used.

Presumably because this paper was a "short communication," the authors did not present any data on, or discuss the incidences of terata in any of the groups, or the importance of their positive histochemical findings with regard to RFR-induced teratogenesis. Also, the results that were presented (mean relative fluorescence) were not in sufficient detail to do an independent statistical analysis of the findings.

3.2 RATS

Dietzel (1975) exposed 749 pregnant rats abdominally to 27.12-MHz RFR with a diathermy machine and applicator in three experimental groups at 55, 70, or 100 W once for up to 10 minutes between gestation days 1 and 16. The rectal temperature of each rat was monitored during exposure, and the rat was removed from the field when its temperature reached 39, 40.5, or 42 °C (in lieu of any other dosimetry). On day 20, the fetuses were removed, counted, weighed, and examined for external malformations. Also, embryos in resorption and corpora lutea were counted, and the preimplantation losses were calculated by subtracting the numbers of mature and resorbed fetuses from the number of corpora lutea.

Typical predominant abnormalities were neurocranial malformations from exposure on days 9 and 10, kinked or short tails and "hand" defects for days 13 and 14, and cleft palate for day 15. The maximum numbers of abnormalities occurred for exposure on days 13 and 14 and they correlated well with rectal temperature, showing that the abnormalities resulted from heating by the RFR.

The calculated preimplantation loss was about 55% for days 1 and 2, it diminished rapidly to less than 20% for days 7 and 8, and it was close to the control value of about 14% for most of the other gestation days of exposure. Postimplantation loss (after organogenesis) increased slowly from the 10% control value for exposure during days 1 through 6, and it rose rapidly to about 22% for exposure during days 15 and 16. The higher values were ascribed

to RFR-generated-heat accumulation in the amniotic sac. The lack of adequate dosimetry rendered it difficult to compare these results with those of other investigators.

Dietzel (1975) also compared the effect of tumor treatment with 461-MHz RFR on DNA synthesis with treatment with X-rays. Tumor heating to 42 °C with the RFR decreased the DNA-synthesis rate by 13% at 2 hours after treatment and by about 27% at 12 hours post-treatment. The decrease from X-ray treatment was negligible at 2 hours and only about 7% at 12 hours post-treatment.

Chernovetz et al. (1977) exposed 26 pregnant rats for 20 minutes on only one day during gestation days 10 through 17 to 2.45-GHz RFR. Exposures were done in a multimode, mode-stirred microwave cavity at a mean SAR of 31 W/kg at 22 °C ambient temperature and 50% relative humidity. They also exposed 26 pregnant rats to infrared radiation (IR) in an incubator at 47 ($\pm$ 7) °C and 10-15% relative humidity, conditions selected to produce the same colonic temperature rise of 3.5 °C as the RFR-exposure. For controls, 12 rats were sham-exposed in the microwave cavity, for a total of 64 rats. Three dams died after exposure to the IR, 7 died after exposure to the RFR, and none died in the control group.

On day 19 of gestation, the 54 surviving dams were euthanized and the numbers of implantations and resorptions were counted. In addition, each fetus was examined for morphological abnormalities and its mass and viability were determined. The percentages of living fetuses per dam were about 98% each for the control and IR groups and 87% for the RFR group, a statistically significant decrease. The mean fetal mass for the control groups was 1.63 g, and the values for the IR and RFR groups were 1.53 and 1.54 g, respectively, both significantly lower than the mean for the control groups. No structural abnormalities were evident in any of the 468 formed fetuses, all of which were alive when taken, but severe edema and hemorrhagic signs were endemic in the IR and RFR groups.

The brains of 60 fetuses (20 each from control, IR, and RFR groups) were assayed for norepinephrine (NE) and dopamine (DA) in four groups of five pooled brains for each treatment. The mean NE level for the RFR group was significantly lower than for the controls, but only marginally lower than for the IR group. The averaged levels of DA ranked similarly, but the differences were not statistically significant.

The authors concluded: "Considered in sum, our findings could be taken as evidence that a brief but highly thermalizing application of 2,450-MHz microwaves or of infrared energy have biological effects both comparable and different when averaged colonic temperature changes are equal."

One problem with this investigation was the small number of rats studied (a point recognized by the authors), which necessitated averaging the data in each group over the 10-day to 17-day gestation period, a procedure open to question both biologically and statistically. Perhaps a minor point was the use of the sham-RFR rats as controls for the IR group instead of a separate set of sham-IR controls, in view of the relative-humidity, ambient-temperature differences. Because of such problems, the validity of either the positive or negative results of this investigation is difficult to assess.

Shore et al. (1977) exposed 24 time-mated female Sprague-Dawley rats to 2.45-GHz RFR at 10 mW/cm² for 5 hours daily from gestation days 3 through 19. For exposure, each rat was housed in a rectangular Lucite box having internal dimensions 19 cm long, 11.4 cm wide, and 7.6 cm high, and an open-gridded polystyrene top and bottom. The boxes were positioned in an anechoic chamber on a Lucite rack in a horizontal square configuration, with the long dimension of 12 boxes parallel to the electric vector (group AC) and the long dimension of the other 12 boxes parallel to the magnetic vector (group BD). Exposures were from a truncated horn above the rack. Twenty-four similarly housed rats were sham-exposed concurrently with the RFR groups.

Temperatures within the RFR-exposure and sham-exposure chambers were not controlled; the respective mean temperatures were 25.5 ± 0.7 °C and 22.8 ± 0.2 °C. The rats were permitted to move about freely within their boxes. The authors noted that the sham-exposed rats moved around normally during the first half hour, after which they settled down and often slept, whereas the RFR-exposed rats were more active.

After treatment, the rats were allowed to deliver normally. All 24 RFR-exposed rats produced litters; the mean litter sizes (and SEs) of the AC and BD groups respectively were 9.33 ± 0.74 and 10.75 ± 0.39 pups with a range of 5-14 pups. One sham-exposed rat had not been pregnant; the mean litter size of the 23 pregnant rats was 9.78 ± 0.51 pups with a range of 4-15 pups. By t-test, the differences were not significant.

One pup each was selected from the AC, BD, and sham-exposed litters on post-partum days 2, 3, 6, 7, 8, 9, 14, and 15 for determination of body and brain weights, and the data from each group on each day were averaged. The mean body weights are shown in Table 11 (adapted from Table 4 of the paper).

TABLE 11: MEAN BODY WEIGHTS OF NEONATE RATS
[Shore et al. (1977)]

<u>POST-PARTUM DAY</u>	<u>2</u>	<u>3</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>14</u>	<u>15</u>
<u>SHAM GROUP</u>								
Body weight (g)	6.7	7.8	11.8	13.3	15.7	17.9	29.6	33.6
SE	±0.2	±0.2	±0.3	±0.6	±0.5	±0.7	±1.4	±1.8
No. of litters	12	10	12	10	12	9	12	7
<u>AC GROUP</u>								
Body weight (g)	6.6	6.8*	11.6	11.2	14.7	16.0	27.4	31.3
SE	±0.2	±0.3	±0.3	±1.3	±0.6	±1.3	±1.6	±2.5
No. of litters	6	6	6	6	5	5	5	4
<u>BD GROUP</u>								
Body weight (g)	6.5	7.1	11.7	13.9	14.6	17.9	29.3	32.9
SE	±0.2	±0.4	±0.9	±0.7	±1.3	±0.9	±2.2	±1.9
No. of litters	6	6	6	5	6	5	6	5

*p<0.05 by t-test

The only statistically significant difference in corresponding mean body weights between the RFR groups and the sham group was for the AC group on day 3. The authors remarked that although the other weight differences were not

significant, most of the means for the AC group were slightly lower than for the sham-exposed rats on corresponding days, with the reminder that the rats in the AC group had been exposed with long body axes approximately parallel to the electric vector. A similar trend was not apparent in the data for the BD group (whose long axes were approximately parallel to the magnetic vector).

The mean brain weights are displayed in Table 12 (adapted from Table 5 of the paper).

TABLE 12: MEAN BRAIN WEIGHTS OF NEONATE RATS
[Shore et al. (1977)]

<u>POST-PARTUM DAY</u>	<u>2</u>	<u>3</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>14</u>	<u>15</u>
<u>SHAM GROUP</u>								
Brain weight (mg)	282	337	530	614	696	805	1180	1272
SE	±6	±7	±8	±13	±11	±19	±19	±24
No. of litters	12	10	12	10	12	9	12	7
<u>AC GROUP</u>								
Brain weight (mg)	280	309*	511	560	667	745	1138	1232
SE	±16	±8	±10	±31	±14	±37	±20	±33
No. of litters	6	6	6	6	5	5	5	4
<u>BD GROUP</u>								
Brain weight (mg)	285	311	523	632	678	796	1156	1233
SE	±8	±11	±16	±13	±26	±18	±33	±17
No. of litters	6	6	6	5	6	5	6	5

*p<0.05 by t-test

Again except for day 3, the mean brain weights of the AC group were all nonsignificantly lower than values for the sham group on corresponding days. For day 3, the mean brain weight of the AC group was significantly lower than for the sham-exposed rats.

The authors noted that because of the planned serial sacrifices above, this study was not designed to determine postnatal mortality. However, they did indicate that the numbers of neonate deaths relative to the total numbers of neonates, summed over the 15 days of observation, were 17 of 112 (15.2%), 13 of 129 (10.1%), and 19 of 225 (8.4%) respectively for the AC, BD, and sham groups; they also displayed the ratios of the numbers of litters affected: 6 of 12, 7 of 12, and 5 of 23 litters, respectively. The authors concluded that mortality incidence was higher in the RFR groups than the sham group.

A major problem with this study was the absence of temperature control during treatment of the dams, a point recognized by the authors, with the result that the mean temperature in the RFR-exposure chamber was 2.7 °C higher than in the sham-exposure chamber. Also, the ranges of temperature with time during the various 5-hour daily treatments in the chambers were not indicated. Possible effects of such temperature differences on the findings of this study could not be assessed.

In response to a question after the oral presentation of this paper, the authors estimated, from measurements at three positions within the anechoic

chamber, that the spatial variation in power density among the 12 boxes of each RFR group was about $\pm 10\%$. A point not discussed in the paper was how large were the rat-orientation variations and therefore the RFR-absorption differences between the AC and BD groups, considering that the rats could move freely within their individual boxes. Other questioners after the oral presentation suggested that litters be culled to obtain uniform litter size, and that a group of cage-control rats could have provided additional useful information; in fact, the authors did have some cage controls, but the results therefrom were not included because their number was too small.

Smialowicz et al. (1979), in an investigation primarily of immunologic and hematologic effects, sham-exposed and exposed pregnant rats to 2.45-GHz CW RFR at 5 mW/cm² for 4 hours/day, 7 days/week from gestation day 6 through term. The SAR range was 4.7-0.7 W/kg, represented the decrease of mean SAR with increase in mean weight (with age) rather than variations among animals at any time. After birth, a group of male pups of each dam were similarly treated until age 20 days, at which time half were euthanized and the other half were treated until age 40 days and then euthanized. The dams and pups were weighed at selected intervals to determine if the RFR affected growth. There were no significant differences in mean weight between the exposed and control animals at any time. (For the immunologic and hematologic results, see the planned report on "Immunology and Hematology," when available.

Berman et al. (1981) exposed 70 time-bred CD rats in groups of eight in individual Plexiglas containers to 2.45-GHz CW RFR at 28 mW/cm² (4.2 W/kg), 22.2 °C ambient temperature, and 50% relative humidity for 100 minutes daily on gestation days 6 through 15. The individual containers were arranged in 3x3 rectangular arrays, with the central position unoccupied and the long axes parallel to the H-vector and perpendicular to the propagation direction. The mean colonic temperature at the end of each exposure period was 40.3 °C. A group of 67 rats was similarly sham-exposed. On gestation day 21, each rat was euthanized, and the live, dead, and resorbed conceptuses were counted. Each live fetus was dried, examined for external morphology, weighed, fixed, and subsequently studied for internal morphology.

There were no statistically significant differences between RFR-exposed and sham-exposed rats in: pregnancy rates; mean litter values of live, dead, resorbed, or total fetuses; or live fetal weight. The numbers of ribs and sternal ossification centers were comparable. The types and indices of major and minor terata were similar in both groups of litters. No encephaloceles (brain hernias) were seen in any of those litters. These negative results were consonant with those of Chernovetz et al. (1977), who saw no teratogenic effects from exposure to 2.45-GHz RFR at about 31 W/kg, an SAR that was lethal to about 27% of the dams.

Berman et al. (1981) surmised "that this lack of an effect may hold true at any exposure level less than that which will kill a significant number of the dams by hyperthermia (colonic temperature greater than 40 °C)". They concluded that the rat is an inappropriate model for determining whether RFR would be teratogenic to humans in exposure situations not lethal for the mothers, and suggested that the mouse is more suitable for that purpose.

The suggestion above was based on the previous findings by Berman and coworkers of consistent, significantly lower mean body weights of live fetuses from mouse dams exposed to 2.45-GHz RFR at 28.0 mW/cm² (22.2 W/kg) than from

sham-exposed dams. However, the results of some studies indicated that such growth retardation was thermally induced. Also, no retardation in growth was seen by Stavinocha et al. (1975) in mice exposed to high levels of electric and magnetic fields at 19 MHz.

In a subsequent study, Berman and Carter (1984) exposed 24 pregnant Sprague-Dawley rats dorsally to 2.45-GHz CW RFR at 40 mW/cm² (6.0 W/kg) for 100 minutes daily on gestation days 6 through 15. A group of 23 pregnant rats was similarly sham-exposed. A one-time exposure of 8 rats of similar size in early gestation for 100 minutes to that RFR level increased their mean colonic temperature from 37.6 to 39.6 °C. On day 21 of gestation, the uteri of the rats in each group were examined for pregnancy, and the numbers of live, dead, and resorbed conceptuses were tallied. Twenty-two of the 24 RFR-exposed rats and 20 of the 23 sham-exposed rats had been pregnant. On a per-litter basis, the differences between the groups in the mean numbers of live fetuses, dead/resorbed fetuses, and total implants were nonsignificant. Thus, the authors concluded that this study yielded no evidence that exposure to 2.45-GHz CW RFR at 40 mW/cm² for 100 minutes daily during organogenesis and the fetal stage is teratogenic. However, the mean weight of the live fetuses from the RFR group was found to be significantly lower than for those from the sham-exposed group [3.14 ± 0.22 g (SD) versus 3.40 ± 0.22 g, $F=13.38$, $p<0.0008$], as was the mean number of ossified sternebrae [4.8 ± 0.6 versus 5.4 ± 0.6 , $F=8.00$, $p<0.007$], an indication of RFR-induced growth retardation.

Lary et al. (1982) exposed eight groups of pregnant Sprague-Dawley rats to 27.12-MHz concurrent CW magnetic and electric fields at 55 A/m and 300 V/m in a near-field synthesizer (Greene, 1974) at 23 °C ambient temperature and 45% relative humidity. The free-space equivalent power density was about 138 mW/cm², and the SAR was 11.1 to 12.5 W/kg. Each rat was exposed individually while being restrained within a perforated cylindrical Plexiglas holder, with its frontal plane perpendicular to the magnetic field and parallel to the electric field.

One group of 16 to 28 rats each was exposed on gestation day 1, 3, 5, 7, 9, 11, 13, or 15 while colonic temperatures were monitored. Exposure of each rat was terminated when its colonic temperature reached 43.0 (± 0.1) °C (20-40 minutes duration). Colonic temperatures were also measured just preceding and following exposure. Eight control groups of 10 to 13 rats each were sham-exposed for 30 minutes, one group each on the same gestation days. A group of 29 rats maintained untreated in the animal quarters during gestation served as cage controls.

The exposure conditions were selected to deliver doses that were nearly hyperthermically lethal to the dams. In a pilot study, most of the malformed litters occurred in rats heated by RFR to 43.0 °C or higher, and no malformations were produced at less than 41.9 °C. Colonic temperatures exceeding 43.0 °C were increasingly lethal; no rat survived temperatures above 43.5 °C. In the main study, 26 (11%) of the RFR-exposed rats died of excessive hyperthermia during or shortly after exposure, and only four of these had a final temperature less than 43.0 °C. No sham-exposed or cage-control rat died during the experiment.

All rats were euthanized on gestation day 20, 2 days before parturition, to avoid cannibalization of the dead or malformed offspring by the dam. The numbers of implantations, live fetuses, and dead or resorbed conceptuses were

determined. Also, the corpora lutea of pregnancy were counted in the cage controls, as were those present during the pre-implantation period (gestation days 1, 3, and 5) of the RFR-exposed and sham-exposed groups. Each live fetus was sexed, weighed, measured for crown-rump length, and examined externally for gross malformations. One-third of the live fetuses from each litter were selected randomly, dissected, and examined for visceral abnormalities; the other fetuses were cleared and stained for skeletal examination.

The results for each group exposed to RFR on one of the preimplantation gestation days (1, 3, or 5) were compared with the combined results for the three groups sham-exposed on those gestation days, and the results for each group exposed to RFR during early organogenesis (day 7, 9, or 11) were treated similarly, as were the two groups exposed to RFR during late organogenesis (day 13 or 15). Also, to determine whether the sham-exposed rats were affected significantly by handling, transport, or restraint, their results were compared with those of the cage controls.

The results on embryotoxicity with no exposure to RFR indicated that the corresponding cage-control and the sham-exposed groups at each gestation stage did not differ significantly from one another. Specifically, the percentages of preimplantation loss and dead or resorbed conceptuses for the sham-exposed rats during the preimplantation period were higher than for the cage controls, but the differences were not statistically significant, and neither were their differences in mean fetal weight and mean crown-rump length at each of those three gestation stages.

For the rats exposed to RFR on days 1, 3, and 5, the mean fetal crown-rump lengths were each slightly lower than for the combined groups of rats sham-exposed during that gestation stage, but only the differences for days 1 and 5 were significant. The percentages of dead or resorbed conceptuses for those exposed to RFR on gestation days 7, 9, and 11 were 29%, 49%, and 18%, respectively, compared with 11% for the combined groups of rats sham-exposed on those days, but only the differences in percentages for days 7 and 9 were significant. In addition, the fetal weights and crown-rump lengths of the rats exposed to the RFR on days 7 and 9 were both significantly lower than for the combined sham groups. This was also the case for the values of those two endpoints on gestation days 13 and 15 relative to the means for the combined sham groups for that stage of gestation. Thus, maximum embryotoxicity was induced by exposure to the RFR on gestation day 9.

Regarding the occurrence of terata, the differences in percentages of external, skeletal, or visceral abnormalities between the fetuses of the cage controls and those of the sham-exposed rats were nonsignificant, with one exception: 4% of the fetuses of the rats sham-exposed during organogenesis (day 7, 9, or 11) exhibited major visceral abnormalities as compared with 0% of the cage-control fetuses, a significant difference. The percentages of fetal external abnormalities were zero for all sham groups, but significant percentages were found for the RFR groups on all days except 1 and 5, with the largest value (67%) for day 9. Significant differences between RFR- and sham groups for major skeletal abnormalities were obtained for all days except 3, 5, and 13, with the highest value (60%) again on day 9. Skeletal variations were significant for all days, with day 9 once more yielding the highest value (83%). Also, major visceral abnormalities were significant only for day 9 (65%). No significant sex-related differences were found.

Only 3 preimplantation fetuses, 5 early-organogenesis fetuses, and 1 late-organogenesis fetus of the sham groups were abnormal, and only 3 cage-control fetuses were abnormal. By contrast, more than 200 different types of abnormalities were seen in the RFR groups, most of which occurred only once. The largest variety of abnormalities (17) occurred for exposure to the RFR on gestation day 9. Microphthalmia or anophthalmia (absence of eyes or presence of vestigial eyes) with associated small, narrow cranial orbits were found in 25-39% of all viable fetuses; exencephaly and the associated defects of protruding tongue and aplasia of the upper cranial bones were evident in 17-22% of the fetuses; and other severe malformations were seen in 6-14% of the fetuses.

Lary et al. (1983a) subsequently treated five groups of rats on gestation day 9 as follows:

Group I was sham-exposed for 2.5 hours.

Group II was exposed to 27.12-MHz fields at 55 A/m and 300 V/m (SAR about 11 W/kg), which produced relatively rapid rises in colonic temperature; exposure was stopped when the temperature reached 41.0 °C (exposure duration 14-22 minutes).

For Group III, 41.0 °C was held for an additional 2 hours by on-off switching of the RFR (total exposure duration 137-144 minutes).

Exposure of Group IV was stopped when the colonic temperature reached 42.0 °C (13-33 minutes).

In Group V, 42.0 °C was maintained for an additional 15 minutes by on-off RFR switching (34-55 minutes total exposure duration).

The RFR-exposures caused relatively rapid rises in colonic temperature. The rats were euthanized on gestation day 20, at which time about two-thirds of them were found to be pregnant. No apparent differences in mating weight, exposure weight, or colonic temperature just prior to treatment were seen between the pregnant and nonpregnant rats or among the five groups of pregnant rats.

Comparing the groups successively, severity increased steadily in both the percentage of malformed fetuses and the ratio of litters affected, with by far the largest change for the prolongation of colonic temperature at 42.0 °C (Group V). Similar results were obtained for percentages of live fetuses with visceral malformations, with the largest change again occurring for prolonged exposure at 42.0 °C. The authors ascribed those teratogenic effects to the hyperthermia induced by the RFR.

As in Lary et al. (1982), the authors ascribed the observed teratogenic effects to the hyperthermia induced by the RFR, citing the study by Edwards (1978), who had demonstrated that excessive heat per se is a teratogen. Also noted by Lary et al. (1983a) was that the existence of a colonic-temperature threshold for teratogenesis in the rat is supported by the *in-vitro* results of Cockcroft and New (1975), who subjected explanted rat embryos grown in culture during gestation days 10-12 to incubation at a temperature of 40 or 41 °C (2-3 °C above normal) for 12-46 hours. Nearly all of the embryos incubated at 41 °C developed severe abnormalities, as compared with only about half of those incubated at 40 °C.

Lary et al. (1983b) exposed 34 pregnant Sprague-Dawley rats to 100-MHz CW RFR in a transverse electromagnetic (TEM) transmission cell at 25 mW/cm² for 6 hours and 40 minutes per day on gestation days 6-11 (total exposure time of 40 hours). Each rat was housed in a perforated cylindrical Plexiglas with axis oriented parallel to the electric field. The corresponding mean whole-body SAR was about 0.4 W/kg, the maximum permissible level in ANSI (1982). As controls, 32 pregnant rats were sham-exposed in a mock TEM cell. Colonic temperatures were measured immediately before and after treatment on gestation days 6 and 11. As in Lary et al. (1983a), each rat was examined for number of implantations, live fetuses, and dead or resorbed conceptuses; the fetuses were sexed, weighed, measured for crown-rump length, and examined for gross abnormalities.

The results for the various endpoints were evaluated with the t-test and tabulated. There were no significant colonic-temperature differences between RFR-exposed and sham-exposed dams just before or after the treatment periods, but both groups showed decreases in mean colonic temperature of 0.6 to 0.8 °C during treatment. There were also no significant differences between groups in numbers of litters; mean implantations per litter; percentages of dead or resorbed implantations or percentages of live fetuses with major skeletal abnormalities; or fetal mean weight, crown-rump length, sex ratio. Only 64% of the live fetuses from the RFR group had minor skeletal variations, versus 76% of the fetuses from the control group, a significant difference ($p < 0.05$). Last, there were no significant differences between the groups in the various specific kinds of external malformations or major skeletal abnormalities. Thus, the results yielded no evidence that the RFR-exposure was embryotoxic or teratogenic.

In a subsequent study, Lary et al. (1986) investigated the dose-response relationship between RFR-induced maternal increases in body temperature and the incidence of birth defects in rats. They exposed groups of pregnant rats on gestation day 9 to 27.12-MHz RFR at field strengths of 55 A/m and 300 V/m. The whole-body SAR was 10.8 W/kg. The exposures were terminated when colonic temperatures reached 41.0, 41.5, 42.0, 42.5, or 43.0 °C (exposure duration 10-40 minutes). Exposed and control dams were euthanized on gestation 20 and the uterine horns of each dam were examined for the numbers of implantations, live fetuses, and dead and absorbed conceptuses.

The numbers of the various fetal abnormalities and of fetal mortality were plotted versus colonic temperature of the dams on exposure termination (dose-response curves). The results indicated the existence of a colonic temperature threshold of 41.5 °C for birth defects and prenatal death.

Because of the high intensities of RFR used by Dietzel (1975) and Lary et al. (1982, 1983a, 1986), the relevance of their findings to possible teratogenesis in humans exposed to much lower levels of RFR in the high-frequency (HF) range might be questioned. However, Conover et al. (1980) surveyed industrial RFR plastic sealers operated (mostly by women) in the range 6-38 MHz and found that occupational exposure to the fields generated by many of the units (most at 27.12 MHz) exceeded the limits of electric and magnetic field at 27.12 MHz specified in ANSI (1974): 200 V/m and 0.5 A/m. The limits specified in ANSI (1982) were even lower: 70 V/m and 0.175 A/m. The corresponding limits in the ANSI/IEEE (1992) guidelines for controlled environments are 67.9 V/m and 0.60 A/m, averaged over any 6-minute period.

Inouye et al. (1983) concurrently exposed 8 mated female Sprague-Dawley rats within individual Styrofoam cages to 2.45-GHz RFR at 10 mW/cm² in the far field of a standard-gain horn for 3 hours daily on gestation days 4 through 21. By calorimetry, the average whole-body SAR was 1.76 W/kg. Eight mated female rats were similarly sham-exposed. Only 5 of the RFR-exposed and 7 of the sham-exposed rats were found to be pregnant. The RFR-exposed dams had a total of 50 pups (27 males and 23 females), of which 1 pup had a malformed tail. The sham-exposed dams had 92 pups (46 males and 46 females) with no malformations. The one malformation was not statistically significant.

Two days after birth, the neonates that were RFR-exposed *in utero* were separated from their dams and 24 healthy male pups were selected. Groups of 6 pups each were foster-mothered to dams that had not been RFR-exposed, and the pups were separated from the foster dams once a day, weighed, RFR-exposed at 10 mW/cm² for 3 hours from age 2 days through 40 days, and returned to foster dams on a random basis to avoid maternal effects. The pups from the sham-exposed dams were similarly treated but sham-exposed. The SARs in the brains of pups were determined from measurements with a Vitek probe of the rate of brain heating from exposures at 120 mW/cm². The mean values for 3 pups each were: 13.95 W/kg in 2-day-old ($\approx$ 10-g) pups, 19.18 W/kg in 15-day-old ($\approx$ 30-g) pups, 10.05 W/kg in 20-day-old ($\approx$ 50-g) pups, 9.72 W/kg in 30-day-old ($\approx$ 100-g) pups, and 9.52 W/kg in 40-day-old ($\approx$ 160-g) pups.

A plot of mean body weights versus age showed virtually identical values for RFR-exposed and sham-exposed pups at corresponding ages. Eye opening occurred in both groups at about the same age.

At ages 15, 20, and 30 days, one group each of 6 RFR-exposed pups was euthanized and fixed with formaldehyde/glutaraldehyde by heart perfusion. Right after perfusion, each brain was removed and weighed, and the width, height, and length of the cerebral hemispheres were measured. Pups at age 40 days were similarly treated except for fixation. Instead, the right half of the brain was immersed in fixative and the left half was processed with Golgi-Cox solution for neuroanatomical examination. Specimens of the cerebrum and cerebellum from the right hemispheres were dehydrated, embedded in Paraplast, sectioned, and stained for histologic examination. Hemispheres treated with Golgi-Cox solution were sectioned, and the densities of dendritic spines in several regions of the cerebrum and of Purkinje cells in the cerebellum were determined.

At corresponding ages, no significant differences were found between RFR-exposed and sham-exposed pups in brain weights, cerebral dimensions, or histologic parameters. In the pups euthanized at age 40 days, there were no significant differences between the RFR and sham groups in dendritic-spine densities within the corresponding cerebral regions examined. Also, although the counts of Purkinje cells varied from lobule to lobule of the cerebellum, the differences in counts within the corresponding lobules did not differ significantly between the groups.

The authors noted that in Inouye et al. (1982a), a slight developmental retardation in the cerebellum was found in Japanese quail exposed *in ovo* to 2.45-GHz RFR at 5 mW/cm², but suggested that the effect may have been due to a slight temperature rise in the eggs, which had been exposed continuously to

the RFR for 12 days, i.e., much longer than the rats. They also remarked that their finding of no significant differences between the RFR-exposed and sham-exposed rats in counts of Purkinje cells was contrary to the finding by Albert et al. (1981a) of fewer Purkinje cells in RFR-exposed rats, a difference not readily explained, except possibly that the rats in the Albert et al. (1981a) study had been exposed to RFR for longer periods per day but for fewer days.

Tofani et al. (1986) divided pregnant rats into four groups. Those in group A (20 rats) were sham-exposed as controls; those in group B (20 rats) were exposed continuously to 27.12-MHz RFR at field strengths 20 V/m and 0.05 A/m (equivalent power densities 0.11 mW/cm² and 0.09 mW/cm², respectively) during gestation days 0-20; and those in groups C and D (10 rats each) were exposed continuously to the same fields during gestation days 0-6 and 6-15, respectively. For exposure, 10 rats each were co-housed in lidless plastic boxes 80 cm long, 60 cm wide, and 35 cm high (Tofani et al., 1987); two such boxes were exposed concurrently for group B, and similarly for groups C and D. The rats were exposed at a distance of 1.5 m from a radiant coil antenna (in the near field of a Siemens Diplode) fed from a 27.12-MHz generator. From Durney et al. (1978), the authors estimated the upper SAR limit to be about 0.00011 W/kg. Presumably the measurements of the fields were performed in the absence of the rats, so the relative spatial uniformity cited by the authors ("within 1 dB") probably was not indicative of the spatial (and temporal) variations of the levels with the rats present. The authors also noted that the basal metabolic rate (BMR) for such rats is 6.51 W/kg, so the SAR was insignificant relative to the BMR.

No dead fetuses were found. Total resorptions were found in half the dams of groups B and C and in 20% of the dams in group D, with none in sham-exposed group A. The values were statistically significant for groups B and C, and nonsignificant for group D, suggesting that this effect occurs during the early stage of egg development. Mean litter weights of the three RFR-exposed groups were significantly lower than for the sham group. The only significant teratologic finding was incomplete ossification of cranial bones in the three RFR-exposure groups. In view of the low RFR level, the authors characterized the effects as nonthermal and due to long-term exposure.

Lu and Michaelson (1987a) took issue with the exposure methodology used. They questioned the absence of technical details, such as a description of the means for providing food and water and for removing wastes during continuous exposures of pregnant rats. They also questioned the reality of the positive findings at an average SAR far lower than the threshold for RFR bioeffects (3-4 W/kg) that was the basis for the ANSI (1982) exposure guidelines. They also noted that the use, by Tofani et al. (1986), of Durney et al. (1978) for their SAR estimation was inappropriate because that reference applied to spheroidal models in the far field, whereas the exposures in this study were in the near field. Last, as noted by Lu and Michaelson (1987a), not discussed in the paper was whether RFR-absorbent materials were used in the exposure chamber to avoid multipath exposure, and the likelihood that the proximity of the rats to one another in the exposure boxes (spacings less than 1 wavelength) resulted in large dosimetric variations and uncertainties.

In their response, Tofani et al. (1987) clarified several of the points raised by Lu and Michaelson (1987a), but remarked that they chose to do the exposures in a room without any shielding or RFR-absorbing materials rather

than in a TEM cell within a shielded anechoic chamber available at their laboratory. As justification, they stated: "Our aim in this work is the evaluation of the biological effects due to a low-level, long-term exposure to a 27.12-MHz electromagnetic field in conditions as similar as possible to those people who usually are exposed (i.e. to near-field, multi-path radiation with distances between individuals shorter than a wavelength)." That response appears to beg the question, because the dose rates from such exposures could have varied considerably from rat to rat and with time for each rat.

Tofani et al. (1987) also remarked: "Effects due to overcrowding ought to result in the sham-exposed group too, since that group was managed in the same way." That remark appears to miss the point that overcrowding probably introduced large spatial and temporal variations in RFR-exposure levels rather than directly causing the reported effects, so overcrowding per se in the sham-exposed rats would not be expected yield those effects. In summary of the foregoing, little credence can be given to the conclusion of Tofani et al. (1987) that they had found nonthermal teratogenic effects.

Brown-Woodman and Hadley (1988) endeavored to determine whether exposure of pregnant rats on gestation day 9 to pulsed 27.12-MHz RFR is teratogenic to embryos when the exposure level is insufficient to raise the core temperature of the dam. Sets of two virgin female Sprague-Dawley rats each that had been caged overnight with one male rat were examined for indications of mating on the next morning, taken as gestation day 0, and the mated females were then randomly assigned to experimental and control groups.

Experimental groups were exposed to the RFR in either an Erbe Erbotherm 1100P or an Enraf Curapulse diathermy unit operated in the pulsed mode, and the control groups were similarly sham-exposed. The RFR applicator consisted of rigid circular electrodes 130 mm in diameter, parallel to one another and spaced 112 mm apart, to produce whole-body exposure. On gestation day 9, each rat was exposed individually without anesthesia within a perforated perspex holder, with its long axis parallel to, and centered within, the electrodes (perpendicular to the electric vector and parallel to the magnetic vector).

The incident RFR levels were stated ambiguously: That heading in Table 1 of the paper was called "MEAN POWER (W/cm²)". Presumably, the output pulse power of each diathermy unit was held constant and the pulse repetition frequency (PRF) was varied to obtain the desired values of time-averaged output power (rather than incident power density). Specifically, exposures in the Erbe unit were with 10, 20, or 30 pps, which provided time-averaged powers of 5, 10, or 15 W. The exposure durations were respectively 60, 45, or 30 minutes. Core temperatures were taken with a Yellow Springs telethermometer and a thermistor probe before treatment, and at unstated intervals during treatment. The probe was removed during exposure, to avoid artifact.

The authors estimated the whole-body SARs obtained with the Erbe unit by exposing a saline-filled phantom model of a 300-g (medium) rat at each PRF for the corresponding duration, and measuring the temperature of the saline at 5-minute intervals. By their calculation, the SARs were 2.8, 4.2, and 5.6 W/kg for the three RFR levels.

The exposures with the Enraf unit were with 15, 26, or 35 pps, yielding time-averaged powers of 6, 10.3, or 14 W. Again, the durations were 60, 45, and 30 minutes, respectively. However, unlike the results for exposure of the

the saline phantom with the Erbe unit, exposure of the phantom with the Enraf unit produced no detectable temperature rises at the five-minute measurement intervals. Two control groups were sham-exposed, one for 30 minutes and the other for 60 minutes.

The mean core-temperature rises with the Erbe unit at 5, 10, and 15 W at the end of the corresponding treatment periods were respectively 0.4, 1.3, and 0.6 °C. Those with the Enraf unit at 6, 10.3, and 14 W were 0.7, 0.8, and 0.6 °C. The temperature rises for the 30-minute and 60-minute control groups were respectively 0.5 and 0.7 °C. The authors remarked that the mean increases in temperature for the RFR-exposed rats did not differ significantly from those for the control rats, but they did not rule out local temperature rises in the former. The treated rats were euthanized on gestation day 20. The results for all of the treatments are shown in Table 13 (adapted from Table 1 of the paper).

TABLE 13: RESULTS OF EXPOSURE OF PREGNANT RATS TO 27.12 MHz RFR

[Brown-Woodman and Hadley (1988)]

<u>UNIT</u>	<u>TIME-AVERAGED POWER (W)</u>	<u>PREGNANT RATS</u>	<u>MEAN LIVE EMBRYOS PER LITTER</u>	<u>PERCENT RESORPTIONS</u>	<u>MEAN EMBRYO WEIGHT $\pm$ SD (g)</u>
ERBE	5	7	5.6	20.4	3.40 $\pm$ 0.75
	10	5	9.8	12.5	3.51 $\pm$ 0.80
	15	7	12.1	5.4	3.33 $\pm$ 0.60*
ENRAF	6	6	12.2	1.4	3.59 $\pm$ 0.52
	10.3	7	10.9	5.0	3.56 $\pm$ 0.44
	14	7	8.6	9.1	3.29 $\pm$ 0.60
30-MIN. CONTROLS		8	12.6	5.6	3.43 $\pm$ 0.54
60-MIN. CONTROLS		5	10.0	7.4	3.53 $\pm$ 0.51

*Embryo abnormal head and face; no gross malformations in all other embryos.

As is evident, the mean number of live embryos increased and the percentage of resorptions decreased with increasing power for treatment with the Erbe unit, whereas the opposite trends were obtained for treatment with the Enraf unit. Also, there appeared to be no significant differences in mean embryo weight irrespective of the level of RFR-exposure with either unit or of sham-exposure. The asterisk in the table, for exposure with the Erbe unit at 15 W for 30 minutes, signified the only embryo with abnormalities.

The authors stated: "The present study demonstrates embryo lethality without a significant increase in rectal temperature, particularly in the group irradiated for 60 min at 10 Hz [PRF] using the Erbe Erbotherm unit, when the mean increase in rectal temperature was only 0.4 °C, less than that observed in the group sham-irradiated for 60 min (0.7 °C). Longer periods of exposure at lower frequencies resulted in a greater number of implantations being resorbed than exposure for shorter durations at higher frequencies."

Thus, they gave greater credence to exposure duration than to exposure level. They also discounted the opposite trend obtained with the Enraf unit, i.e., a progressive increase (rather than decrease) in percentage resorptions with decreasing exposure duration (and increasing power level) by citing their non-detection of temperature rises in the phantom rat with that unit, implying that the actual rats had not absorbed much if any RFR.

From an engineering viewpoint, not clear is why the two diathermy units yielded such exposure differences with the same applicator. If, as indicated by the results with the saline-phantom rat, the rats indeed had not received much RFR with the Enraf unit, the aforementioned opposite trend in resorption results could be an indication of uncontrolled non-RFR factors in the study. Supporting the latter point are the mean-rectal-temperature rises apparently unrelated to RFR- or sham-exposure. Further, as noted above, only one embryo

exhibited abnormalities (in 86 embryos from the group of dams exposed with the Erbe unit for 30 minutes); none were seen in 49 embryos from the group exposed for 45 minutes or in 39 embryos from the group exposed for 60 minutes in that unit. Thus, the finding of non-thermal-RFR-induced teratogenicity in this study is questionable.

Brown-Woodman et al. (1988) used similar methods to investigate whether teratogenesis induced in rats by 27.12-MHz RFR is due to hyperthermia. As in the study above, they sham-exposed and exposed pregnant Sprague-Dawley rats on gestation 9 to the RFR, but with the applicator (two circular electrodes 130 mm in diameter, spaced 120 mm apart) powered by the Erbe Erbotherm 1100P unit in the CW mode. The measured amplitudes of the electric and magnetic fields were 33 kV/m and 0.8 A/m. From temperature measurements at 5-minute intervals in the saline-filled phantom model of a medium rat, the authors calculated the whole-body SAR to be 11.2 W/kg.

For exposure, each rat was restrained unanesthetized within a perforated cylindrical perspex holder to avoid orientation variations in whole-body SAR. The exposures were for durations necessary to reach specific rises in core temperature. When the desired core temperature was reached, a series of 1-minute bursts of the RFR were used to hold it there for an appropriate period, with core temperature measured between the bursts. Core temperature was also measured after treatment completion at 10-minute intervals for 240 minutes (recovery period).

Eighty-seven pregnant rats were exposed to the RFR and 10 pregnant rats were sham-exposed as controls. The rats were euthanized on gestation day 20; the uterine horns of each were examined for the number of implantations; and the live and dead fetuses were counted, weighed, and examined for gross malformations.

The mean resting core temperature ($\pm$ SD) of the 97 rats was 38.2 ± 0.49 °C; that of the 10 controls at the end of 30 minutes in the perspex holder was 38.3 ± 0.70 °C, indicating that the restraint did not affect core temperature. Nine of the 10 control rats produced litters. Their mean resorption rate was 4%. The resorptions were found in 2 of the 9 litters (22%), and no external malformations were seen. The mean litter size was 12.3 fetuses and their mean weight was 3.7 ± 0.60 g.

Three rats were RFR-exposed until their core temperature was raised by 5 °C and held there for a few seconds. The resorption rate was 74%, the litter sizes were small, 1 of the fetuses was dead, the mean fetal weight was 2.5 ± 0.41 g, and all of the surviving fetuses exhibited various single or multiple malformations.

Seventeen rats were RFR-exposed until their core temperature was raised by 4.5 °C. That temperature was held for 2 minutes in 5 rats, 5 minutes in 9 rats, and 10 minutes in the other 3 rats. One rat of the 2-minute group and 2 rats of the 5-minute group died, and only 3 of the 4 surviving rats in the 2-minute group and 5 of the 7 surviving rats in the 5-minute group had litters. The respective resorption rates of the three groups were 20%, 61%, and 63%, all significantly higher than for the controls; their mean litter sizes were 13.0, 2.8, and 4.0 fetuses, with 2 of the fetuses in the 2-minute group dead; the mean weights of the live fetuses were 3.1 ± 0.25 , 2.7 ± 0.62 , and $3.3 \pm$

0.74 g. Thus, the mean fetal weight changes were not unidirectional with increasing duration of temperature elevation but all were significantly lower than for the controls.

The core temperature of 27 rats was similarly raised by 4.0 °C and held there for 3, 5, 10, or 15 minutes. The 4 rats held for 3 minutes and the 10 rats held for 10 minutes survived and produced litters. However, 2 of the 8 rats held for 5 minutes and 1 of the 5 held for 15 minutes died, and only 4 of the 6 survivors in the former and 3 of the 4 survivors in the latter produced litters. The resorption rates for the 4 groups were 21%, 22%, 37%, and 98%, respectively, and the abnormal fetuses comprised 21%, 44%, 51%, and 100% of the live fetuses, both monotonic increases with duration. The mean weights of the live fetuses were 3.6 ± 0.21 , 3.1 ± 0.53 , 3.1 ± 0.73 , and 2.9 g (only 1 live fetus), a decrease trend with duration.

Core-temperature elevation by 3.5 °C for durations of 10, 15, 18, or 25 minutes (3, 4, 4, and 3 rats, respectively) yielded resorption rates of 0, 9%, 27%, and 29%, and the abnormal fetuses comprised 0, 0, 28%, and 44% of the live fetuses, clearly less severe effects than for elevations by 4.0 or 4.5 °C, even though some of the durations were longer. The mean weights of the live fetuses were 3.7 ± 0.89 , 4.2 ± 0.62 , 3.4 ± 0.52 , and 3.4 ± 0.47 g, no clear trend with duration.

For core-temperature elevation by 3.0 °C and durations of 20, 25, 30, or 50 minutes (3, 4, 4, and 5 rats, respectively), 2 of the rats held for 50 minutes died. The resorption rates of the survivors were respectively 10%, 0, 25%, and 21%; 11%, 4%, 46%, and 27% of the live fetuses were abnormal. Their mean weights were 3.3 ± 0.62 , 3.0 ± 0.41 , 3.4 ± 0.76 , and 2.8 ± 0.60 g.

Last, the core temperatures of 7 rats were elevated by 2.5 °C for 50 minutes and those of 3 rats for 60 minutes. Their resorption rates were 17% and 15%, higher than for the controls (4%), but there were no abnormal fetuses. Their mean weights were 3.1 ± 0.61 and 3.2 ± 0.65 g.

In their discussion, the authors indicated that the teratogenic and embryo-lethal effects they observed were related to both core-temperature elevation and its duration. They also noted that the types of abnormalities (microphthalmia, encephalocele, and facial defects in decreasing frequency) were essentially the same as those obtained by Germain et al. (1985) by partially immersing rats of the same strain in a heated water bath. Thus, they concluded that the teratogenic effects of RFR are due primarily to the heating therefrom, with a threshold core-temperature rise of about 2.5 °C.

In another study, Brown-Woodman et al. (1989) investigated the effects of repeated exposure to 27.12-MHz RFR on the fertility of rats. The authors exposed unanesthetized virgin female Sprague-Dawley rats for 1 hour per day, 5 days a week, for 5 weeks, a total of 25 hours. However, unlike in the studies above, groups of 5 rats each were placed within 27.5-cm x 24-cm plastic boxes, and for RFR- or sham-exposure, one such box was placed on each side of a pair of circular, 13-cm-diameter "condenser" electrodes (resembling the applicator used in the studies above), at a horizontal distance of 50 cm from the central symmetry plane of the electrodes. Thus, 10 rats were treated at a time, with the 5 rats in each group permitted limited free movement within their box.

The amplitudes of the electric and magnetic fields were measured at the center of and near the four corners of each box. The magnitudes at the two centers were 450 V/m, 0.1 A/m and 390 V/m, 0.1 A/m; those at the two corners of each box nearer the electrodes were higher and differed considerably from each other and from the values at the nearer corners of the other box. The values at the more distant corners of the two boxes were lower than those at their centers and also varied considerably among one another. However, the relationship of these values to the levels of exposure received by the rats is highly uncertain and non-uniform, because of mutual interactions and shielding among the rats in each box and the probable temporal and spatial variations of the SAR of each rat from their free movements within the boxes.

In the first of two trials, 10 rats each were RFR- and sham-exposed; in the second trial, 20 rats each were assigned to the RFR and sham groups and comprised two treatment groups. Rectal temperatures were measured right before and after treatment on 3 of the 25 treatment days chosen randomly and averaged for each rat. Box confinement of the controls (for 1 hour) produced a mean rise in rectal temperature of 0.65 ± 0.26 (SD) °C in trial 1 and 0.59 ± 0.33 °C in trial 2. The values for the RFR-exposed rats were 0.58 ± 0.24 °C and 0.64 ± 0.34 °C for trials 1 and 2, respectively. The authors noted that there were no indications of stress in the rats due to box confinement, and that the levels of RFR used were not hypothermic.

The rats were mated 3 days after the 5 weeks of treatment by cohabiting 1 RFR-exposed and 1 sham-exposed female per male for 8 days, to cover two estrus cycles. The females were examined each morning for signs of mating, taken as gestation day 0. The mated females were euthanized on gestation day 20 and their uterine horns were examined for number of implantation sites and live and dead fetuses. Also, each fetus was weighed and examined for external malformations and cleft palate. The results are shown in Table 14 (adapted from Table 1 of the paper).

TABLE 14: FERTILITY RESULTS OF EXPOSURE OF FEMALE RATS TO 27.12 MHz RFR
[Brown-Woodman et al. (1989)]

<u>TRIAL</u>	<u>TREATMENT</u>	<u>RATS MATED</u>	<u>RATS PREGNANT</u>	<u>EMBRYOS PER LITTER</u>	<u>FETAL WEIGHT (g)</u>
1	Control	10/10	9/10	12.2 ± 4.5	3.6 ± 0.51
	Exposed	8/10	6/10	13.6 ± 2.3	3.3 ± 0.31
2	Control	19/20	18/20	15.2 ± 2.4	3.5 ± 0.20
	Exposed	16/20	14/20	14.2 ± 3.4	3.5 ± 0.16

As noted by the authors, the differences in mean litter size, numbers of implantation sites, or fetal weight between the RFR-exposed and control rats that became pregnant were not significant. They also indicated that none of the fetuses exhibited any congenital malformations. However, as seen in Table 14, only 24 of the 30 RFR-exposed females had mated, as compared with 29 of the 30 control females. Moreover, of those that had mated, only 20 of the 24 RFR-exposed females became pregnant, whereas 27 of the 29 controls became pregnant. The authors performed a chi-square test, in which they combined the data for each trial in 2 x 2 tables and summed the square roots of the chi-square statistics, and determined that these differences were significant ($p < 0.05$).

The authors stated: "It would appear that breeding behaviour, hormonal cycling and/or the survivability of the eggs before implantation must be affected by the pre-breeding exposure of the rats to RF radiation." From the samples of rectal-temperature measurements just before and after the 1-hour treatments, they ruled out hyperthermia as the agent, but remarked that post-exposure measurements do not reflect such temperatures during RFR-exposure.

The authors did not provide enough data to permit evaluation of their statistical treatment of the results. Also, in the absence of adequate dosimetric data (SARs and their temporal and spatial variations), it is difficult to ascribe the differences in breeding behavior and pregnancy outcome to the RFR without independent verification.

In one of a pair of studies, Jensh et al. (1982a) exposed groups of up to 4 pregnant Wistar albino rats in individual Acrylite cages to 915-MHz CW RFR at 10 mW/cm² for 6 hours per day without food and water in an anechoic chamber on gestation days 1 to 21. The mean maternal body weight over the gestation period was 0.28 kg, from which the authors derived a mean SAR of 3.57 W/kg. For this investigation, 11 pregnant rats exposed to the RFR comprised the "experimental" group and 4 sham-exposed pregnant rats were the "concurrent-control" group. In addition, 5 rats kept in home cages (the HC group) and 10 rats kept daily for 6 hours in the anechoic chamber (the AC group) served as two "baseline-control" groups.

The rats were euthanized on gestation day 22. The weights of maternal brain, liver, kidneys, and ovaries were measured and normalized to term body weights. No statistically significant differences in organ-to-body-weight ratios were found between the HC and AC baseline control groups or between RFR-exposed and concurrent-control groups for any of the organs. However, significant differences were found between the baseline-control groups and the concurrent-control group, results ascribed to the significantly lower mean body weights of the baseline groups, which consisted of younger animals than in the RFR-exposed and concurrent-control groups. The unnormalized mean organ weights showed no significant differences among the four groups.

There were no statistically significant differences in mean litter size or mean 21-day-old fetal weight among the four groups. Only one fetus, in the AC baseline group, was abnormal. The resorption rates for the HC and AC baseline groups were 7.1% and 12%, respectively. For the RFR-exposed group, the resorption rate was 4.4%. In the concurrent-control group, an entire litter of 13 fetuses was resorbed by one of the rats; inclusion of those resorptions yielded a rate of 25.5%.

Not clear were the differences in treatment between the baseline-AC and the concurrent-control (sham-exposed) groups. In addition, the significant difference in mean body weights between these two groups tended to confound comparisons between them of the various biological endpoints studied. Thus, only the comparisons between the RFR-exposed and sham-exposed groups seem pertinent. The results for the latter two groups showed no statistically significant differences in any of the biological endpoints measured. These negative findings are consonant with those of Chernovetz et al. (1977) and Berman et al. (1981) at 2.45 GHz, and of Lary and coworkers and Brown-Woodman et al. (1988) at 27.12 MHz, which showed that much higher SARs are necessary for teratogenic effects in rats.

Jensh et al. (1982b), the companion study of this pair, was directed toward determining possible behavioral changes in similarly exposed rats. (For a discussion of those behavioral results, see the report on "Behavior" when available.) In addition, at age 90 days, half of the initial (Fla) offspring of the exposed and unexposed dams were killed and examined for histopathology. The remaining offspring were bred in four groups: control male to control female, control male to RFR-exposed female, RFR-exposed male to control female, and RFR-exposed male to RFR-exposed female. The resulting litters (F2) were examined prenatally for teratogenesis. In addition, the original females were rebred 40 days after delivery of the Fla offspring (but not reexposed to the RFR) and the resulting fetuses (Flb) were examined for teratogenesis.

The results for the initial pregnancy showed no significant differences in maternal weight, weight gain, or Fla mean litter size. Only one abnormal neonate, in the AC group, was found. The weekly mean weights of the RFR-exposed Fla neonates were significantly larger than for the concurrent-control neonates through age 24 days, after which the differences were not significant. Some significant weight differences were also seen at various ages among the baseline (HC and AC) groups and the concurrent-control group. Necropsies of the Fla litters at 90 days showed no significant differences between the RFR-exposed and concurrent-control groups in organ weights or organ/body weight ratios.

The second breeding of the original females yielded no significant differences in mean maternal weight or litter size between the RFR- and concurrent-control groups, and no abnormal offspring were evident. Also, subsequent necropsies of those mothers showed no significant differences in mean organ weights or organ/body weight ratios. In the cross breeding of Fla males and females to obtain F2 fetuses, there were no significant RFR-related differences in mean maternal weight, percentage of resorptions, fetal weight, or litter size.

The finding of significantly larger perinatal mean weekly weights for the RFR-exposed Fla neonate Wistar albino rats than for concurrent controls is opposite to that found by Berman et al. (1981) in CD rats exposed to 2.45-GHz RFR at 28 mW/cm² (4.2 W/kg). This and a minor behavioral effect found by Jensh et al. (1982b) both appear to indicate that prenatal exposure of rats to relatively low levels of RFR may be beneficial, but such findings require independent verification.

Jensh et al. (1983a, 1983b) were another pair of studies, but with 2.45-GHz RFR. In Jensh et al. (1983a), preliminary experiments with exposures at up to 30 mW/cm², 20 mW/cm² was found to be the highest RFR level that did not produce significant increases in colonic temperature in near-term pregnant rats. They then exposed 11 pregnant rats in groups of up to 4 each daily for 6 hours/day throughout gestation at 20 mW/cm². From Durney et al. (1978), the authors estimated that the mean SARs during gestation days 0-1, 7-8, and 20 were about 5.2, 4.8, and 3.6 W/kg, respectively. Three concurrent-control (sham-exposed) rats, 10 AC rats, and 5 HC rats served for comparisons. All of the rats were euthanized on gestation day 22, the numbers and positions of all live and dead fetuses were noted, and the fetuses were examined for abnormalities. No RFR-induced significant differences were found in mean

maternal weight gain during pregnancy, term maternal organ weights (brain, liver, kidneys, ovaries), term fetal weight, resorption rate, or abnormality rate, which led the authors to conclude that protracted exposure of the dams throughout gestation to 2.45-GHz RFR at 20 mW/cm² (5.2-3.6 W/kg) is not embryotoxic.

In Jensh et al. (1983b), 12 RFR-exposed, 8 concurrent-control, and 59 baseline-control pregnant rats were similarly treated, but allowed to come to term. The differences among the groups for initial or term maternal weight or weight gain during pregnancy were not significant. Comparative ranking of the growth rates of the Fla offspring during corresponding periods up to age 87 days indicated that the RFR group had the highest growth rate, followed in succession by the AC, concurrent-control, and HC groups, but the differences were not statistically significant. A linear-regression analysis of those weight data also showed nonsignificance. No significant differences were found among groups in the results of cross-breeding Fla offspring or in the results of teratologic examination of dams rebred 10 days after weaning the Fla offspring or of the resulting F2 offspring.

In the first of still another pair of studies, Jensh (1984a) exposed 10 pregnant rats (and 1 rat later found to be not pregnant) for 6 hours/day throughout gestation to 6-GHz RFR at 35 mW/cm² from above, which did not increase colonic temperature significantly. From Durney et al. (1978), the author estimated the mean SAR to be 7.28 W/kg. Ten concurrent-control rats, 10 AC rats, and 5 HC rats served for comparison. On gestation day 22, half of the dams in each group were decapitated, and the rest of the dams were subjected to postnatal analysis. (In addition to the teratologic endpoints assessed in the previous studies, the authors analyzed peripheral blood samples from the dams on gestation day 22; for those results, see the report on "Immunology and Hematology" when available.)

No significant differences were seen in any of the teratologic endpoints studied except for mean fetal weight at term, which was significantly lower for the RFR group than for the concurrent-control (sham) group. However, so was the difference between the sham and AC groups and between the HC and AC groups, which could indicate that lower mean fetal weight of the RFR group may not have been RFR-induced.

Another point of conjecture is whether teratogenic effects would be expected for exposure from above to 6-GHz RFR at 35 mW/cm² (estimated whole-body SAR of 7.28 W/kg). At this frequency, the penetration depth for muscle is about 0.7 cm, compared with about 2.4 cm at 915 MHz and 1.7 cm at 2.45 GHz. Therefore, the local SARs in the uteri may have been much lower at 6 GHz even though the whole-body SAR was considerably larger than in the earlier studies. In this context, it may be misleading to compare whole-body SARs for the three frequencies, and the author did not do so.

In Jensh (1984b), the companion study, Fla offspring at age 90 days were bred within and across groups as before, and teratologic evaluations were completed on 659 F2 term fetuses. The original dams were then rebred 10 days after weaning the Fla pups, and teratologic evaluations were completed on 263 Flb offspring. Organ weight analyses were done on 17 of the original dams and on 181 Fla adult offspring.

The difference in mean maternal weights of the RFR and the sham groups on gestation day 0 of the first breeding was nonsignificant ($p > 0.05$, t-test). On gestation day 21, the mean maternal weight for the RFR group was smaller ($p < 0.02$) than for the sham group: the mean weight gains were 42.1% and 45.2% respectively for the RFR and sham dams. However, the mean weight gain of the HC group was 45.8%, which was close to that of the sham group, but the mean for the baseline AC group was 42.8% or close to that of the RFR group. The mean litter size for the RFR dams was 9.55 fetuses, as compared with 12.00 for the sham group. The mean litter sizes for the HC and AC groups were 12.40 and 11.20, respectively.

Examination of the Fla pups on postnatal day 3 revealed that 3 pups from one RFR-exposed dam had cataracts (unilateral in 2 pups and bilateral in 1 pup), 1 pup from a sham-exposed dam had bilateral cataracts, and 1 pup from an AC dam had a unilateral cataract. No other abnormalities were evident.

The mean weights of 68 RFR-exposed and 63 sham-exposed pups on postnatal day 3 were 9.1 and 9.9 g, respectively, a significant difference ($p < 0.01$). In the subsequent weekly weighings, the weight differences were successively less significant, becoming nonsignificant ($p > 0.05$) at about 38 days of age. On day 3, however, the mean weight for 111 AC pups was only 8.1 g and it remained significantly lower than for the RFR-exposed pups throughout the subsequent weekly weighings (to age 87 days).

The results of breeding the adult Fla rats were that the mean maternal weight increase during gestation of (*in-utero*) RFR-exposed females bred with RFR-exposed males (32.7%) was significantly less than for colony-control females bred with RFR-exposed males (44.7%) or for RFR-exposed females bred with colony-control males (37.0%) or for sham-exposed females bred with sham-exposed males (39.5%). Also significant was the weight-increase difference between the colony-control females mated with RFR-exposed males (44.7%) and RFR-exposed females mated with colony-control males (37.0%).

No results were presented on breeding of colony-control rats with either colony-control rats or sham-exposed rats of either sex; however, the author stated: "The group in which only the mother was irradiated (irradiated female x colony control male) did not significantly differ ($P > 0.05$) in weight gain from the colony control female x sham male group but did differ significantly ($P < 0.05$) from the colony control female x irradiated male group as well as the sham female x sham male group ($P < 0.01$)." [Reviewer note: by t-test, the last difference, 37.0% versus 39.5%, was not significant.]

Regarding the F2 offspring, the author stated: "Mean litter sizes differed significantly only between the irradiated female x irradiated male and the sham female x sham male groups ($P < 0.05$). Both the litter size and the resorption rate varied inversely with the exposure groups. That is, the highest resorption rate (8.7%) and the smallest litter size (12.2) occurred in the irradiated female x irradiated male group, the two irradiated x colony control groups were intermediate, and the sham female x sham male group was the lowest in resorption rate (4.5%) and largest in litter size (14.8). Correlation coefficient analyses revealed a significant direct correlation between maternal weight gain and mean litter size ($P < 0.05$) in all groups." [Reviewer note: t-tests of the tabulated data in the paper indicated that the differences among the four groups in mean F2 litter size and mean fetal weight were not significant ($p > 0.05$).]

Mean organ-to-body weight ratios of RFR-exposed and sham-exposed adult Fla males differed significantly ($p < 0.05$) only for the left kidney and the right testis, with the mean values larger for the RFR group. However, the values for both groups were significantly larger ($p < 0.01$) than for the baseline HC and AC groups. For the RFR-exposed and sham-exposed females, the only significant ratio difference was for the liver ($p < 0.02$), but again the values for both groups were significantly larger ($p < 0.001$) than for the HC and AC groups.

Perhaps the most important finding of this study was the absence of any terata in Fla, Flb, and F2 offspring from prolonged exposure of rats (8 hours per day throughout their first pregnancy) to 6-GHz RFR at 35 mW/cm² (whole-body SAR about 7 W/kg). This finding is consonant with the results of Berman et al. (1981) on pregnant rats exposed to 2.45-GHz RFR for 100 minutes daily at 28 mW/cm² (whole-body SAR 4.2 W/kg) on gestation days 6 through 15. (The few cataracts seen in Fla offspring appear to be unrelated to RFR-exposure.)

Merritt et al. (1984) exposed 10 pregnant Sprague-Dawley rats, each unrestrained in a cylindrical Plexiglas cage within a circular-waveguide system (Guy et al., 1979), to circularly polarized pulsed 2.45-GHz RFR (8- μ s pulses at 830 pps) for 24 hours/day. The exposures were started on gestation day 2 and terminated on gestation day 18.

Power absorption was determined from measurements of forward, reflected, and transmitted powers without and with the rat present. From Durney et al. (1980), p. 60, the estimated incident average power density of circularly polarized RFR corresponding to 0.4 W/kg in a prolate-spheroidal model of a medium rat exposed end-on was 2 mW/cm². Based on this estimate and on power measurements on rat carcasses of different masses, the input power was varied to maintain the SAR constant at 0.4 W/kg [the basis for the ANSI (1982) and ANSI/IEEE (1992) exposure guidelines] for each dam as its mass increased during the exposure period.

Ten similarly housed rats were concurrently sham-exposed. All 20 of the waveguides were in a room held at 24 ± 2 °C and 50-60% relative humidity. Water and food were provided freely during exposure via a bottle and food-pellet holder decoupled from each cage and waveguide by quarter-wavelength chokes to minimize external power losses.

All 20 rats were pregnant when they arrived on gestation day 2. They were weighed, immediately placed randomly in the 10 RFR-exposure and 10 sham-exposure waveguides, and treated. They were reweighed every fourth day. On gestation day 18, they were euthanized and the fetuses were removed. After each fetus was weighed, its brain was dissected out, weighed, homogenized, and assayed for RNA, DNA, and protein. The last three endpoints were shown in terms of both mg/brain and μ g/mg of brain tissue (which, together with fetal and brain weight, totaled 8 endpoints). The difference between the groups for each of the 8 endpoints was nonsignificant ($p > 0.05$).

To determine the effects of exposure to the RFR on brain development, a linear regression of mean litter brain weight on mean litter body weight was calculated for the sham group and plotted. The mean values for the RFR group were plotted on the same graph and found to be scattered about the regression

line. The criterion used by the authors as an indication of microencephalous litters was a regression line two SEs below the regression line for the sham group, based on the study by Edwards (1969). All of the mean values for the RFR group were above the criterion line, indicating that no RFR-exposed litter was microencephalous.

It is interesting to note that all of the negative findings above were for rats. By contrast as noted previously, RFR-induced teratogenesis (growth retardation) in the mouse and hamster was reported, for example by Berman et al. (1982a, 1982b). This effect appears to have been thermally induced, a conclusion supported by the results of Inouye et al. (1982b) and Nawrot et al. (1981). These differences in response among the three species of rodents may be an indication that none is a satisfactory surrogate for humans with regard to possible RFR teratogenesis.

3.3 NONHUMAN PRIMATES

Kaplan et al. (1982), in a study designed primarily for seeking possible effects of chronic exposure to RFR on mother-offspring behavioral patterns and the EEG, exposed 33 female squirrel monkeys near the beginning of the second trimester of pregnancy to 2.45-GHz RFR in multimode, mode-stirred microwave cavities (Heynick et al., 1977) at whole-body SARs of 0.034, 0.34, or 3.4 W/kg (plane-wave equivalent to 0.1, 1, and 10 mW/cm², respectively) for 3 hours/day, 5 days/week, until parturition. Eight pregnant monkeys were sham-exposed in the cavities for the same periods. After parturition, 18 of the RFR-exposed dams and their offspring were exposed to the RFR for 6 more months; then the offspring were exposed without the dams for still another 6 months. (For the results of the EEG and behavioral aspects of the study, see the reports on "The Nervous System" and "Behavior" when available.)

Two of the dams exposed at 3.4 W/kg (10 mW/cm²) and one dam exposed at 0.34 W/kg (1 mW/cm²) died, all within a day or two after parturition. Those dams comprised less than 10% of the total number exposed, but the authors remarked that similar deaths had not occurred in more than 250 pregnancies recorded during the five previous years in their squirrel-monkey colony.

All of the 8 control dams produced live births, and none of the infants died subsequently. The numbers of dams RFR-exposed only during gestation that had live births were: 4 of 5 in the 0.034-W/kg group, 6 of 6 in the 0.34-W/kg group, and 4 of 4 in the 3.4-W/kg group. Two of the 4 infants in the 0.034-W/kg group, none of the 6 infants in the 0.34-W/kg group, and 1 of the 4 infants in the 3.4-W/kg group died later (totaling 3 deaths in 14 infants). Of the dams exposed during gestation and additionally post-parturition with infants, 5 of 6 in the 0.034-W/kg group, 6 of 6 in the 0.34-W/kg group, and 5 of 6 in the 3.4-W/kg group had live births. None of the 5 infants in the 0.034-W/kg group, 2 of the 6 infants in the 0.34-W/kg group, and 4 of the 5 infants in the 3.4-W/kg group died later (totaling 6 deaths in 16 infants). Thus, the percentages of live births among the various RFR groups were similar irrespective of RFR level, but unexpectedly the numbers of infant deaths were not comparable, as discussed below.

The offspring were weighed weekly for the first 8 weeks of age, and then monthly until they were 1 year old. There were no significant differences in mean weights of the RFR and sham groups at any corresponding age.

Of the 14 infants RFR-exposed only prenatally, the 2 exposed at 0.034 W/kg died at ages 32 and 83 days, and the 1 exposed at 3.4 W/kg died at age 4 days. Of the 16 exposed both prenatally and postnatally, the 2 exposed at 0.34 W/kg died at ages 38 and 49 days, and the 4 exposed at 3.4 W/kg died at ages 58, 78, 143, and 177 days. The annual mortality rate during the first year of life for the 5 previous years of the colony averaged 20-25%, so the numbers of infant deaths at 0.034 and 0.34 W/kg were not atypical; however, the 4 deaths of the 5 infants in the 3.4-W/kg group exposed prenatally and postnatally were much larger than the normal mortality rate, and appeared to be a direct result of exposure to that level of RFR. As noted above, none of the 8 sham-exposed infants died during the study, which was also atypical for the colony, and comparison of the sham group with the 3.4-W/kg group by the Fisher exact probability test showed that the difference was statistically significant ($p < 0.01$).

In all but one case, the infant deaths occurred without warning; each infant was found in its home cage in the morning. Necropsies had not been planned, and therefore were not performed on any of the adults, and were done on only 4 of the 9 dead infants. Because of autolysis, the cause of death could not be determined in any of those cases. However, as stated in a note added in proof to Kaplan et al. (1982), a followup study was done, with infant mortality as the major endpoint.

The exposure regimen was similar, but the numbers of dams were increased to provide greater statistical validity. Specifically, 31 dams were exposed in the microwave cavities used previously to 2.45-GHz RFR at 3.4 W/kg for 3 hours per day, 7 days a week, beginning in the first trimester of pregnancy, and 34 dams were sham-exposed. Following parturition, dams were similarly treated with their offspring for 6 months, after which offspring were treated alone through age 9 months. The authors did not provide any data, but stated that the differences between RFR-exposed and control groups in the numbers of abortions, stillbirths, live births, or infants that subsequently died were not significant.

3.4 SUMMARY

The findings of the various studies on RFR-teratogenesis in mammalian species are summarized in Tables 15A-15I. Regarding mice, Bollinger et al. (1974) found no effects of exposure of pregnant C3H/He mice to 25-kHz electric and magnetic fields of 15 kV/m and 7.5 A/m on growth, reproductive ability, or metabolism of the neonates, and saw no pathologic effects of exposure of 4-day-old pups to those fields. Stavinoha et al. (1975, 1976), using 10.5-, 19.27-, and 26.6-MHz pulsed RFR in a TEM line or 19-MHz CW at 5.8 kV/m in a near-field synthesizer, found no significant differences in the growth of 4-day-old mice relative to controls, or differences in cyclic-AMP in the adult mice whose brains were rapidly inactivated immediately after exposure to 19-MHz CW fields at 8 kV/m plus 55 A/m.

Rugh et al. (1974, 1975) exposed female CF-1 mice to 2.45-GHz RFR at 138 mW/cm² (123 W/kg) for 2-5 minutes, and derived a total-dose of 11 cal/g for dam lethality. They then exposed mice at 123 mW/cm² (110 W/kg), representing sublethal doses for the dams. Analysis of their data revealed a teratogenic total-dose threshold of about 3 cal/g despite a remark by the authors about the absence of such a threshold.

TABLE 15A: TERATOGENESIS IN MAMMALS

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Bollinger et al. (1974)	C3H/He pregnant mice 4-day old pups	25 kHz	15 kv/m E-field plus 7.5 A/m H-field* or 10 kv/m E-field plus 5.3 A/m H-field**	Not determined	1 hr/day, 5 days per week, 50 hours total	No effects on growth, reproductive ability, or metabolism for neonates from RFR-exposed and sham-exposed dams.	*Full power: 59.5 + 2.12 W/cm ² equivalent plane wave power densities, set to obtain 3-°C rectal-temperature rise in mouse carcasses in 1 hour. **Half power: 29.8 + 1.06 W/cm ² . Chromosomes were unaffected. No incidence of C3H/He-mouse mammary tumors up to age 98 days.
Stavinoha et al. (1975)	4-day-old mice	Pulses at 10.5, 19.27, 26.6 MHz 19 MHz CW	*5.8 kv/m **8 kv/m plus 55 A/m	Not determined	20 min 40 min per day on 5 days	Weight graphs of exposed and control mice up to age 21 days showed no significant differences. No significant growth differences among RFR, thermal-control, and cage-control groups to age 21 days.	*Exposures were done in a TEM line (Mitchell, 1970); pulse duration and duty cycle were not stated. **Parallel E & H fields in a near-field synthesizer (Greene, 1974); 1.5-°C rectal-temperature rise in RFR and thermal-control groups.
Stavinoha et al. (1976)	Adult mice	19 MHz CW	8 kv/m plus 55 A/m	Not determined	40 min per day on 5 days	No significant cyclic-AMP differences among RFR, thermal-control, and cage-control groups.	Brain assays were done after brain-enzyme inactivation with high-intensity RFR of short (300 milliseconds) duration.
Rugh et al. (1974, 1975)	CF-1 female mice	2.45 GHz	138 mW/cm ² (lethality); 123 mW/cm ² (sublethal)	123 W/kg 110 W/kg	Various 2-5 min on gestation day 8.5*	11 cal/g total dose for lethality. Sublethal total-dose range 3-8 cal/g; teratogenic threshold dose about 3 cal/g.	Exposures were done in a waveguide with controlled ambients. 110 W/kg was just below dam lethality. *Gestation day 8.5 is most sensitive to effects of ionizing radiation.
Chernovetz et al. (1975)	pregnant C3H/HeJ mice	2.45 GHz	Exposures were done in a microwave cavity.	38 W/kg	10 min	RFR and sham groups had comparable percentages of normal fetuses, abnormal fetuses, and pup survival to weaning.	In contrast with Rugh et al. (1974, 1975), a sublethal threshold was not found. Cortisone, a teratogen, was used as a positive control.
Berman et al. (1978)	Arrays of pregnant CD-1 mice	2.45 GHz	3.4, 13.6, 14.0, 28 mW/cm ²	2.0, 8.1, 8.3, 22.2 W/kg	100 min a day on gestation days 1-17	27 of 318 RFR-exposed litters had 1 or more abnormal fetuses versus 12 of 366 sham-exposed litters.	The counts of litters with abnormal fetuses were without regard to RFR level; the validity of the statistical treatment was questioned.

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Berman et al. (1982a)	Arrays of pregnant CD-1 mice	2.45 GHz	28 mW/cm ²	Array mean: 16.5 ± 4.5 (SD) W/kg	100 min a day on gestation days 6-17	On gestation day 18, no significant differences between RFR and sham dams in live, dead, and resorbed fetus counts.* Ossification of sternal centers delayed; lower weights for RFR-exposed fetuses than for sham-exposed fetuses.** Weights of 7-day-old RFR-exposed pups 10% lower than for sham-exposed pups.	*Finding at variance with Berman et al. (1978) **Finding consonant with Berman et al. (1978). Growth retardation was permanent.
Berman et al. (1984)	Arrays of pregnant CD-1 mice	2.45 GHz	28 mW/cm ²	Array mean: 16.5 W/kg	100 min a day on gestation days 6-17	Significantly lower body and brain weights (by 10%) for neonates from RFR-exposed dams; no differences in ability to concentrate urine or in tolerance to ouabain.	Initial brain weight deficits persisted; effect ascribed by the authors to heat stress (at 16.5 W/kg).
Berman et al. (1982b)	Syrian hamsters	2.45 GHz	20 or 30 mW/cm ²	6 or 9 W/kg	100 min a day on gestation days 6-14	No significant effects at lower RFR level (0.4-°C rectal-temperature rise); higher fetal resorptions, lower fetal body weights, and delayed skeletal maturity at higher RFR level (1.6-°C rectal-temperature rise).	Comment by authors: Hamster fetus may be more susceptible to RFR than the mouse.
Nawrot et al. (1981)	Arrays of handled and non-handled pregnant CD-1 mice	2.45 GHz	5, 21, or 30 mW/cm ²	6.7, 28.1, or 40.2 W/kg; respective rises in rectal temperature: 0, 1, 2.3 °C	8 hr per day on gestation days 1-6, 6-15, or 1-15	Smaller weight gains in handled groups relative to nonhandled groups irrespective of RFR- or sham-exposure; handling thus the primary factor. Differences in numbers of pregnancies, maternal weight gains, and fetal weights for nonhandled-RFR- and sham-exposed dams nonsignificant.	Comparisons with dams treated at temperatures that yielded the rectal temperature rises obtained at the two higher RFR levels also showed that handling was important, but heat as well. The authors concluded that the threshold for teratogenic effects in CD-1 mice is about 30 mW/cm ² (40.2 W/kg).

TABLE 15B: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Nawrot et al. (1985)	Arrays of handled and non-handled pregnant CD-1 mice	2.45 GHz	30 mW/cm ²	40.2 W/kg	8 hr daily on gestation days 1-6 or 6-15	For treatment on days 1-6, pregnancy rate of RFR groups was lower than for other groups. For treatment on days 1-6 or 6-15, maternal weight gains for the handled groups were lower than for corresponding non-handled groups.	As in Nawrot et al. (1981), handling was the primary factor, but combining the data from both studies indicated that the effect was not due to that factor alone, with the RFR contribution ascribed to higher local temperatures in the uterine region.
Inouye et al. (1982b)	Arrays of female CD-1 mice	2.45 GHz	9 or 19 mW/cm ²	11.7 or 24.7 W/kg	3 hr on gestation day 2 or day 3	On gestation day 4, no significant differences were seen between RFR and sham groups in any endpoint. Conventional heating at 38 °C (2.2-°C rectal-temperature rise) resulted in stunted development.	At 11.7 & 24.7 W/kg, rectal-temperature rises were 0 and 1 °C. Endpoints included embryo counts, abnormalities, and developmental stage. The negative results are consonant with the ~30 mW/cm ² threshold found by Nawrot et al. (1981).
Chiang and Yao (1987)	Pregnant mice & their pups	3 GHz pulsed (1.2-µs pulses at 937 pps)	8 mW/cm ² (average)	3.0-3.5 W/kg for dams; not estimated for pups	5 hr/day for dams during gestation and pups at ages 3-20 days	Histochemical changes in the brains of pups (seen by fluorescence spectrophotometry) were ascribed primarily to postnatal RFR-exposure.	The results were not detailed enough for an independent statistical analysis; no discussion or data were presented on the incidences of terata.
Dietzel (1975)	Pregnant rats	27.12 MHz	55, 70, or 100 W*	*SAR was not measured; the RFR levels and durations were selected to attain 39, 40.5, or 42 °C rectally.	Each rat was given a single exposure of up to 10 min on one day during gestation days 1-16	The major abnormalities seen were neurocranial malformations, kinked or short tails and hand defects, and cleft palate. The highest incidences were for exposure on days 13, 14; they correlated with rectal temperature, showing that the effects were due to heating.	In a separate experiment, heating of tumors to 42 °C with 461-MHz RFR was found to lower the DNA-synthesis rate more effectively than tumor treatment with X-rays.

TABLE 15C: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Chernovetz et al. (1977)	Pregnant rats	2.45 GHz IR at 47 °C*	In microwave cavity; power density not determined	31 W/kg	20 min on one day during gestation days 10 to 17	Living fetus counts per dam were significantly lower for the RFR group than the IR and sham groups. Fetal masses of the RFR and IR groups were significantly lower than for the sham group. Structural abnormalities were not seen in any fetal group, but brain-chemistry differences were found in RFR and IR fetuses.	*For the same rise in colonic temperature as with the RFR (3.5 °C) Effects were clearly thermal, but validity of the findings may be questioned because of the small numbers of rats studied (recognized by the authors), which necessitated averaging the data in each group over the 10- to 17-day gestation period.
Shore et al. (1977)	Mated female Sprague-Dawley rats	2.45 GHz	10 mW/cm ²	Not determined	5 hr daily on gestation days 3-19	The differences in mean litter size among the RFR and sham groups were nonsignificant. Selected from each litter was one pup each on post-partum days 2-15 to determine body and brain weights. The differences among corresponding groups were not significant except for day 3.	Temperatures within the RFR-exposure and sham-exposure chambers were not controlled; the mean temperature in the RFR chamber was 2.7 °C higher than in the sham chamber. Also, rat orientation relative to the electric or magnetic vector may have varied during RFR-exposure. These points render questionable the findings of this study.
Smialowicz et al. (1979)	Pregnant rats	2.45 GHz	5 mW/cm ²	4.7-0.7*	Dams: 4 hr/day, 7 days/week from day 6. Pups: to ages 20 or 40 days.	The differences in mean weight at corresponding ages between RFR and sham groups of dams or pups were not significant.	This study was primarily on seeking immunologic and hematologic effects. *SAR decrease due to increase of dam weight with age.
Berman et al. (1981)	Arrays of CD female rats	2.45 GHz	28 mW/cm ²	4.2 W/kg	100 min daily on gestation days 6-15	Differences between RFR and sham groups in any of the endpoints were nonsignificant; no brain hernias or other terata were seen.	The RFR level was sublethal; the colonic temperature was 40.3 °C. Endpoints included: counts of live, dead, resorbed fetuses, terata; litter weights; morphology.

TABLE 15D: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Berman and Carter (1984)	Pregnant Sprague-Dawley rats	2.45 GHz	40 mW/cm ²	6.0 W/kg	100 min daily on gestation days 6-15	The differences between groups in mean numbers of live fetuses, dead or resorbed fetuses, and total implants were not significant. The mean weight of live fetuses from the RFR-exposed dams was significantly lower than for the sham-exposed dams, as was the mean number of ossified sternebrae.	A single exposure of rats in early gestation for 100 min at that RFR level raised their mean colonic temperature from 37.6 to 39.6 °C. The lower mean live fetus weight and smaller number of ossified sternebrae was taken as an indication of RFR-induced growth retardation.
Lary et al. (1982)	Pregnant Sprague-Dawley rats	27.12-MHz ExH fields	55 A/m plus 300 V/m in a near-field synthesizer (Greene, 1974)	11.1 to 12.5 W/kg	20-40 min once on gestation day 1, 3, 5, 7, 9, 11, 13, or 15*	On day 20, significantly higher effects were seen in RFR groups than in sham groups and cage controls treated on corresponding days, with highest embryotoxicity for exposure on day 9.	*Durations were to attain 43.0 °C colonic temperature, found to be sublethal in a pilot study, in which malformations were not seen below 41.9 °C. The teratogenic effects were clearly thermal.
Lary et al. (1983a)	Pregnant Sprague-Dawley rats	27.12 MHz	Same as in Lary et al. (1982)	~11 W/kg	Exposure solely on gestation day 9*	The severity of the teratogenic effects increased with colonic temperature and duration of maintenance at each temperature.	Treatment groups were: 1) 14-22 min to attain colonic temperature 41.0 °C, 2) held at 41.0 °C for +2 hr, 3) 13-33 min to reach 42.0 °C, 4) held at 42.0 °C for +15 min.
Lary et al. (1983b)	Pregnant Sprague-Dawley rats	100 MHz	25 mW/cm ² in a TEM cell	~0.4 W/kg	6 hr & 40 min per day on gestation days 6-11	No significant differences were seen between RFR-exposed and sham-exposed groups in any of the tabulated teratogenic endpoints. Only 64% of live fetuses from the RFR group had skeletal variations vs 76% from the sham group (p<0.05).	There were no significant differences in colonic temperature between RFR and sham groups just before or after the treatment periods, but both groups showed drops in colonic temperature of 0.6 to 0.8 °C during treatment. The results provided no evidence that the RFR was embryotoxic or teratogenic.
Lary et al. (1986)	Pregnant Sprague-Dawley rats	27.12 MHz	Same as in Lary et al. (1982)	10.8 W/kg	10-40 min on gestation day 9*	The dose-response curve indicated a 41.5 °C temperature threshold for birth defects and prenatal death.	*Duration to reach 41.0, 41.5, 42.0, 42.5, or 43.0 °C. The RFR levels used were much higher than the ANSI/IEEE (1992) limits for controlled environments.

TABLE 15E: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Inouye et al. (1983)	Mated female Sprague-Dawley rats and pups	2.45 GHz	10 mW/cm ²	1.76 W/kg for dams. Brain SARs for the pups mostly decreased with age; range 19-10 W/kg for ages 15-40 days.	3 hr/day on days 4-21 for dams; 3 hr daily at ages 2-40 days for pups	One of 50 RFR-exposed neonates had a malformed tail (not significant). Differences between the RFR and sham pups at corresponding ages in brain weights, cerebral dimensions, histologic endpoints were all not significant. Also, the Purkinje-cell counts in the corresponding cerebellar lobules did not differ significantly between the groups.	Only 5 of 8 RFR-exposed and 7 of 8 sham-exposed rats were found to be pregnant, which diminishes the credibility of the findings. The authors remarked that their finding of no significant differences between the RFR-exposed and sham-exposed rats in counts of Purkinje cells was contrary to the finding by Albert et al. (1981a) of fewer Purkinje cells in RFR-exposed rats.
Tofani et al. (1986)	Pregnant rats	27.12 MHz	20 V/m + 0.05 A/m with a radiant coil antenna in the near field of a Siemens Dipole	Upper limit -0.00011 W/kg (authors' estimate from Durney et al., 1978)	24 hr per day on gestation days 0-20, 0-6, or 6-15	No dead fetuses were found. Total resorptions occurred in half of the dams exposed on days 0-20 or days 0-6, in 20% exposed on days 6-15, and none in the sham-exposed dams. The litter weights were lower in the RFR groups, and incomplete ossification had occurred.	The findings were disputed by Lu & Michaelson (1987a) for lack of details on exposure methodology such as: whether shielding or RFR-absorbing materials were used, how the rats were fed and their wastes were removed, adequacy of the SAR estimate, and spatial SAR variations. In a response by Tofani et al. (1987), they clarified several points, but not key issues such as the probable spatial and time SAR variations among the rats. Little credence can be given to their finding of nonthermal teratogenic effects.
Brown-Woodman and Hadley (1988)	Pregnant Sprague-Dawley rats	Pulsed 27.12 MHz	5, 10, 15 W (average) with a special whole-body applicator and an Erbe diathermy unit; 6, 10.3, or 14 W with that applicator and an Enraf Curapulse	2.8, 4.2, or 5.6 W/kg with the Erbe; no temperature rise obtained with the Enraf unit, hence no SAR determination	Rats were exposed singly for 60, 45, or 30 min on gestation day 9 with either type of diathermy unit.	With the Erbe unit, the numbers of live embryos rose and the resorptions fell with increasing RFR level, whereas opposite trends were observed with the Enraf unit. No significant differences were seen in mean embryo weight irrespective of the RFR-exposure level with either unit or of sham-exposure.	The SARs were determined with saline phantoms. Not clear is why the two diathermy units yielded such differences with the same applicator. The findings are questionable, especially because with the Erbe, only 1 of 86 embryos exposed for 30 min, and none of 49 of embryos exposed for 45 min or of 39 embryos for 60 min exhibited abnormalities. The presence of uncontrolled non-RFR factors was likely.

TABLE 15F: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Brown-Woodman et al. (1988)	Pregnant Sprague-Dawley rats; 87 for RFR-exposure and 10 for sham-exposure	27.12 MHz CW	33 kV/m + 0.8 A/m with the same applicator, and with the Erbe unit in the CW mode	11.2 W/kg by measurements on saline phantoms	Durations chosen to raise and hold core temps by 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 °C	Core temperatures raised by 2.5 °C and held for 50 or 60 min yielded resorption rates of 17% and 15%, higher than for the controls (4%), but yielded no abnormal fetuses. The severity of teratogenic effects rose with the larger core-temperature increments.	The authors concluded that the observed teratogenic effects of RFR were due primarily to the heating therefrom, with a threshold core-temperature rise of about 2.5 °C.
Brown-Woodman et al. (1989)	Virgin rats; 5 each in 2 plastic boxes treated concurrently	27.12 MHz	450 V/m + 0.1 A/m between a pair of parallel "condenser" electrodes	Not discussed	1 hr/day, 5 days a week for 5 weeks; 25 hours total time	Rats were mated 3 days after treatment for 8 days. On gestation day 20, no teratogenic effects were found, but fewer RFR-exposed rats had mated and fewer of those became pregnant.	Spatial and time variations of exposure level within each of the 2 boxes were large and uncertain. In the absence of adequate dosimetric data, it is difficult to ascribe the differences seen in breeding behavior and pregnancy outcome to the RFR without independent verification.
Jensh et al. (1982a)	Pregnant Wistar albino rats	915 MHz	10 mW/cm ²	4 W/kg	6 hours per day on gestation days 1-21	On gestation day 22, no significant differences were seen between the RFR and sham groups in weights of maternal brain, liver, kidneys, or ovaries, or in litter sizes or fetal weights.	The findings were consonant with those of Chernovetz et al. (1977) and Berman et al. (1981) at 2.45 GHz, and with Lary and coworkers and Brown-Woodman et al. (1988) at 27.12 MHz, indicating that much higher SARs are necessary for teratogenic effects in rats.
Jensh et al. (1982b)	Pregnant Wistar albino rats	915 MHz	10 mW/cm ²	W/kg ⁴	6 hours per day on gestation days 1-21	The weights of RFR-exposed pups of the first dam breeding (F1a) were significantly higher than of sham-exposed pups, but no significant teratogenic effects were seen in those F1a pups, pups of the second dam breeding (F1b), or pups of the next generation (F2).	This was a companion study to Jensh et al. (1982a), directed primarily toward seeking behavioral effects. The finding of larger perinatal weights for the RFR-exposed F1a neonate Wistar albino rats than for concurrent controls is opposite to that found by Berman et al. (1981) in CD rats exposed to 2.45-GHz RFR at 28 mW/cm ² (4.2 W/kg). This effect by Jensh et al. (1982b) appears to indicate that prenatal exposure of rats to relatively low RFR levels may be beneficial (subject to independent verification).

TABLE 15G: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Jensh et al. (1983a)	Pregnant Wistar albino rats	2.45 GHz	20 mW/cm ²	5.2, 4.8, 3.6 W/kg**, authors' estimate from Durney et al. (1978)	6 hours per day through entire gestation period	On gestation day 22, no differences were seen between RFR-exposed and sham-exposed dams in any of the dam endpoints, and no terata were evident in the fetuses.	The authors concluded that protracted exposure of the dams throughout gestation to 2.45-GHz RFR at 20 mW/cm ² is not embryotoxic. **the highest level for no rise in colonic temperature in near-term rats. **For days 0-1, 7-8, 20.
Jensh et al. (1983b)	Pregnant Wistar albino rats	2.45 GHz	20 mW/cm ²	See Jensh et al. (1983a)	6 hours per day through entire gestation period	Again, no significant differences were seen between RFR-exposed and sham-exposed dams in any dam endpoints. F1a pups from RFR-exposed dams had nonsignificantly higher growth rates than controls. Cross-breeding of F1a rats yielded no significant differences among groups of F2 pups.	This was a companion study to Jensh et al. (1983a), in which the dams were allowed to come to term. No teratogenic effects were seen in F1a or F2 offspring, or in dams rebred 10 days after weaning the F1a offspring or in the resulting F2 offspring.
Jensh (1984a)	Pregnant Wistar albino rats	6 GHz	35 mW/cm ²	7.28 W/kg, authors' estimate from Durney et al. (1978)	6 hours per day through entire gestation period	No teratogenic effects were seen, but the mean fetal weight at term was significantly lower for the RFR group than the sham group. The latter effect may not have been RFR-related because of fetal-weight differences among control groups.	Teratogenic effects at 6 GHz may not be expected, because the penetration depth in muscle (0.7 cm) is much smaller than at 2.45 GHz (1.7 cm) or 915 MHz (2.4 cm), so local SARs in the uteri may have been much lower than at 6 GHz even though the whole-body SARs were much higher than in the earlier studies.
Jensh (1984b)	Pregnant Wistar albino rats (from breeding of adult F1a rats studied in Jensh, 1984a)	6 GHz	35 mW/cm ²	See Jensh (1984a)	6 hours per day through entire gestation period	The mean weight gain of RFR-exposed F1a dams was significantly lower than for sham-exposed dams, but there were also comparable differences among control groups. Mean litter size for RFR dams was 9.55 fetuses, versus 12.00 for sham dams. At age 3 days, the mean weight of RFR F2 pups was smaller than for sham F2 pups, but the difference became successively smaller with age.	This was a companion study to Jensh (1984a), directed primarily toward seeking immunologic effects. No terata were evident in F1a, F1b, or F2 pups, a finding consonant with the results of Berman et al. (1981) on rats exposed to 2.45-GHz RFR for 100 minutes daily at 28 mW/cm ² (whole-body SAR 4.2 W/kg) on gestation days 6 through 15.

TABLE 15H: TERATOGENESIS IN MAMMALS (CONTINUED)

Authors	Subjects	RFR Freq.	Intensity	SAR	Duration	Effects	Notes
Merritt et al. (1984)	Pregnant Sprague-Dawley rats	2.45 GHz, pulsed (9- μ s pulses at 830 pps)	In circular waveguides: 2 mW/cm ² average, estimated from Durney et al. (1980)	Input power was varied to maintain whole-body SAR constant at 0.4 W/kg with dam age	24 hours per day during gestation days 2-18	On gestation day 18, no significant differences were seen between RFR and sham groups in fetal body or brain weights, or in assays of brain RNA, DNA, or protein. Also, no litter was microencephalous.	The circular waveguides (Guy et al., 1979) provided circularly polarized RFR. Power absorption was determined from measurements of forward, reflected, and transmitted powers without and with the rat present.
Kaplan et al. (1982)	Pregnant squirrel monkeys Dams+kids Kids only	2.45 GHz	0.1, 1, or 10 mW/cm ² , plane-wave equivalent in multimode microwave cavities (Heynick et al., 1977)	0.034 0.34, or 3.4 W/kg, determined with saline phantoms	3 hr/day, 5 days/wk in second trimester to term Six more months 6 months additional	Two dams exposed at 3.4 W/kg and 1 dam exposed at 0.34 W/kg died after parturition, versus none in more than 250 pregnancies in the monkey colony. The percentages of live births among the various RFR groups were similar irrespective of the RFR level. However, 9 of all 30 infants exposed at the several RFR levels unexpectedly died, and atypically, none of the 8 sham-exposed infants died, for a difference that was significant ($p < 0.01$).	This was primarily a study of mother-infant behavior, and of EEGs. Because of autolysis, the cause of the infant deaths could not be determined. However, as stated in a note added in proof to Kaplan et al. (1982), they performed a followup study, with infant mortality as the primary endpoint. The exposures were only at 3.4 W/kg, but the regimen was otherwise similar, and the numbers of dams were increased to provide greater statistical validity. No data were given, but the authors stated that the differences between RFR-exposed and control groups in the numbers of abortions, stillbirths, live births, or infants that subsequently died were not significant.

TABLE 151: TERATOGENESIS IN MAMMALS (CONCLUDED)

Chernovetz et al. (1975) exposed one group each of pregnant C3H/HeJ mice on gestation days 11, 12, 13, and 14 to 2.45-GHz RFR in a microwave cavity at about 38 W/kg for 10 minutes. The energy absorbed was 22.8 J/g or 5.44 cal/g, which they had found to be just sublethal. Examinations on gestation day 19 showed no significant differences between RFR-exposed and sham-exposed groups in percentages of normal fetuses or fetuses with structural abnormalities, and no dependence on gestation day of treatment. With similar treatments only on gestation day 14 and with the dams permitted to come to term, there were also no significant differences ($p > 0.1$) in pup survival to weaning. By contrast, injection of cortisone (a teratogen) as a positive control with and without RFR-exposure or sham-exposure yielded significantly higher percentages of abnormal fetuses and lower survival of pups.

Berman et al. (1978) exposed arrays of pregnant CD-1 mice to 2.45-GHz RFR at 3.4, 13.6, 14.0, or 28 mW/cm² (2.0, 8.1, 8.3, or 22.2 W/kg) for 100 minutes a day on gestation days 1-17. Their uteri were examined on gestation day 18. For most of the 10 specific fetal anomalies seen, the numbers of litters affected were too small for statistical treatment, or no RFR-related pattern was apparent. In total, however, 27 of 318 litters (8.5%) of RFR-exposed dams (irrespective of RFR level) had one or more abnormal fetuses versus 12 of 366 litters (3.3%) of sham-exposed dams. The validity of thus analyzing the numbers of litters rather than the numbers of fetuses affected, adding them without regard to RFR level, and ascribing the findings to RFR-exposure is open to question. Moreover, the spatial ranges of power density over the mouse arrays were relatively large, making it even more difficult to discern a clear dose-response relationship. An important finding was that the mean live fetal weights of the litters exposed at 28.0 mW/cm² (22.2 W/kg) were significantly lower than for the sham-exposed litters, but the corresponding differences at the lower RFR levels were not significant.

Berman et al. (1982a) similarly exposed pregnant mice at 28.0 mW/cm² for 100 minutes daily on gestation days 6 through 17, but with a different array configuration; the mean SAR for the array was 16.5 ± 4.5 (SD) W/kg. The uteri of some dams were examined on day 18, and other dams were allowed to come to term. For those examined on day 18, the various endpoints were found to be comparable for the RFR-exposed and sham-exposed mice, findings at variance with those of their previous study (Berman et al., 1978). However, the mean body weight of the live fetuses in the RFR group was significantly smaller (by 10%) than of the live fetuses in the sham group, a finding consonant with their previous results. In addition, ossification of sternal centers was significantly delayed in the RFR-exposed fetuses. For the mice permitted to come to term, the mean body weight of the RFR-exposed pups at age 7 days was significantly smaller (by 10%) than for the sham-exposed pups. The survival rates of the RFR and sham groups were comparable, but the growth retardation was permanent.

In a followup study, Berman et al. (1984) exposed pregnant CD-1 mice to 2.45-GHz RFR at 28 mW/cm² (16.5 W/kg) as before, and found that the neonates had significantly lower body and brain weights than the neonates from sham-exposed mice. The initial brain-weight deficits persisted. The effect was ascribed by the authors to heat stress. There were no differences in ability of the neonates to concentrate urine or in tolerance to ouabain (a medication used in humans to treat congestive heart failure and other heart disorders).

Berman et al. (1982b) also exposed arrays of Syrian hamsters to 2.45-GHz RFR at 20 or 30 mW/cm² (6 or 9 W/kg) for 100 minutes per day on gestation days 6-14. Exposure at 20 mW/cm², for which rectal temperatures were about 0.4 °C higher than for sham-exposed hamsters, produced no significant changes in fetal survival, body weight, skeletal maturity, or incidence of terata. However, exposure at 30 mW/cm², which raised rectal temperatures by about 1.6 °C, caused significantly higher fetal resorptions, lower fetal body weights, and delayed skeletal maturity. The authors, citing Berman et al. (1978, 1982a), stated: "It appears that the hamster fetus may be more susceptible to microwave radiation than the mouse."

Nawrot et al. (1981) exposed pregnant CD-1 mice to 2.45-GHz CW RFR daily for two 4-hour exposures at 5, 21, or 30 mW/cm² (6.7, 28.1, or 40.2 W/kg) on gestation days 1-15, 1-6, or 6-15. Other groups were sham-exposed. Still others were sham-exposed at 30 or 31 °C respectively to attain the same rises in colonic temperature as those for the two higher RFR levels. Two groups were given each treatment, one group characterized as "handled" and the other as "nonhandled". Handled mice were transferred to Styrofoam cages for RFR-, sham-, or heat-exposure with no food or water available for the two treatment periods, and at the other times were housed in polycarbonate shoe-box-type cages with food and water available. Non-handled groups were housed in shoe-box-type cages with food and water available for the entire 24-hour period, and were sham-exposed or heated concurrently with the handled groups. On day 18, the dams were killed, and implantation sites, resorptions, dead fetuses, and live fetuses were counted. Fetuses were sexed, weighed, and examined for malformations.

In one experiment, one handled group was exposed at 5 mW/cm² (6.7 W/kg) on gestation days 1-15, and one handled and one nonhandled group were sham-exposed. The pregnancy rates, maternal weight gains, and average fetal weights for both handled groups (RFR- and sham-exposed) were significantly lower than for the nonhandled sham-exposed group, showing that handling was the primary factor in the differences. The results for the other endpoints did not differ significantly among the three groups.

Next, one handled group was exposed at 21 mW/cm² (28.1 W/kg) and 22 °C ambient temperature, which caused a rectal-temperature rise of about 1 °C; one handled group was heated in ambient temperature 30 °C to obtain the same rectal-temperature rise; and one handled group was sham-exposed at 22 °C. In addition, one nonhandled group was sham-exposed at 22 °C, and another was heated in ambient temperature 30 °C. All groups were treated on gestation days 1-6. The same procedure was also used for other handled and nonhandled groups, but on gestation days 6-15. For treatment on days 1-6, significantly smaller maternal weight gains were observed in the handled RFR-exposed, sham-exposed, and heated groups than in the nonhandled heated and sham-exposed groups. For those treated on days 6-15, the maternal weight gain was smaller for the nonhandled-heated group as well, and the largest decrease was for the handled-heated group. Thus, handling was again an important factor, but heating was as well. The other endpoints were not significantly affected.

A third experiment was similar to the second, but with treatment at 30 mW/cm² (40.2 W/kg) or at 31 °C, the latter to attain the same increase of 2.3 °C in rectal temperature as with the RFR. Treatment on days 1-6 yielded a significant decrease in pregnancy rate for the handled-RFR and the handled-

sham-exposed groups relative to the nonhandled-sham-exposed and nonhandled-heated groups. The dams in all three handled groups gained significantly less weight than those in the nonhandled groups. The handled-RFR group had fewer implantation sites per litter than the other groups, but only the difference relative to the nonhandled-sham-exposed group was significant. Fetal weight was smaller in the handled-RFR group than in the handled- and nonhandled-sham-exposed groups, but was comparable to that of the handled-heated group. No increases in external, visceral, or skeletal malformations were seen in any group. For treatment on days 6-15, the dams of all handled groups gained less weight than those in the nonhandled groups, and the mean percentage of malformed fetuses per litter was larger for the handled-RFR group than any other group, with cleft palate the predominant malformation. Thus, handling was again an important factor in causing lower weight gains of dams, but heating was as well. The authors concluded that the threshold for teratogenic effects in CD-1 mice is about 30 mW/cm² (40.2 W/kg).

Nawrot et al. (1985) did experiments similar to their last one above, and compared groups of handled and nonhandled sham-exposed mice, a nonhandled heated group, and a cage-control group (maintained in animal quarters during pregnancy). On day 18: the implantation sites were counted; the conceptus at each site was classed as resorbed, dead, or alive; and the live and dead fetuses were sexed, weighed, and examined for external anomalies. All live and dead fetuses were examined for skeletal alterations. Stunted fetuses and fetuses with external anomalies were examined for visceral anomalies. For handled dams treated during gestation days 6-15, during which most prenatal brain development occurs, fetal brains were examined for histopathology and assayed for cholinesterase activity.

The mean pregnancy rate of the dams exposed to the RFR on days 1-6 was significantly lower than for the other groups treated on days 1-6. The mean maternal weight gains for the handled groups (RFR-exposed, sham-exposed, heated) were significantly lower than for the corresponding nonhandled groups (sham-exposed, heated, cage-control). The mean fetal weights were lower for all three handled groups than the nonhandled groups, but the differences were significant only for the sham-exposed and heated groups. Highest incidence of external malformations (cleft palate, open eyes) occurred for the handled-sham-exposed group, but none of the differences among groups was significant.

For the treatments on days 6-15, the mean maternal weight gains were also smaller in the handled than the nonhandled groups, and the mean fetal weights were smaller for the handled-RFR-exposed and handled-heated groups than for the other groups, but the difference was larger for the handled-heated group. There were no significant differences in the other teratologic endpoints among the groups. The mean cholinesterase activities assayed in the fetuses from the three handled groups did not differ significantly from one another. A few fetal abnormalities were found, but none was related to the differences in treatment.

The authors suggested that the lower mean pregnancy rate in the group exposed to RFR on days 1-6 may have been due to preimplantation death and/or early postimplantation litter resorption, and that the absence of this effect in those exposed on days 6-15 may indicate that embryos in the earlier stage of gestation are more susceptible to the RFR. On the other hand, the authors noted that the decrease in mean pregnancy rate observed for mice exposed at 30

mW/cm² on days 1-6 in the previous study resulted from handling, but that combining the data from both studies indicates that the effect was not due to handling alone. They ascribed the RFR contribution to this effect to higher local temperatures in the uterine region, because they had found that colonic temperature during RFR-exposure rose twice as fast than during treatment at the elevated temperature used to attain the same final colonic temperature.

Inouye et al. (1982b) mated CD-1 mice, and then exposed arrays of them for 3 hours on either gestation day 2 (during the 2-cell stage) or day 3 (during the 4- to 8-cell stages) to far-field 2.45-GHz CW RFR at 9 or 19 mW/cm² (11.7 or 24.7 W/kg) at 22 °C ambient temperature. Also, one group was exposed at 38 °C ambient temperature without RFR. No colonic-temperature increase was obtained at 9 mW/cm², 1 °C increase occurred at 19 mW/cm², and at least 2.2 °C occurred for the 38-°C heat treatment. On gestation day 4, the embryos were counted, examined for abnormalities, and classified by developmental stage as: morula (9 or more blastomeres but no blastocoelic cavity), early blastocyst (small blastocoelic cavity), or blastocyst (large blastocoelic cavity). Abnormal embryos were defined as underdeveloped (less than 9 blastomeres) and as fragmented and/or collapsed embryos.

No statistically significant differences were found in the number of fertilized mice, the number of embryos per mouse, or the percentage of abnormal embryos (total and per dam) among all of the groups. In addition, there were no significant differences in embryonic development or in abnormal embryos between RFR-exposed groups (at either power density) and sham-exposed groups for either treatment day. However, the heat treatment at 38 °C caused stunted embryonic development, i.e., significant increases in the number of morulae and decreases in the numbers of blastocysts compared with the numbers for sham-exposed mice on corresponding treatment days.

Direct comparisons of the results of this study with those of Nawrot et al. (1981) are difficult because in the latter investigation, the dams were exposed for 8 hours a day over gestation days 1-6 or 6-15 (in contrast with a single 3-hour exposure on day 2 or 3), and the fetuses were examined at a much later stage of gestation (day 18 versus day 4). Moreover, the frequent handling of the dams was a significant factor. Nevertheless, the negative findings of Inouye et al. (1982b) are consonant with the 30-mW/cm² threshold found by Nawrot et al. (1981). Also, fetal stunting occurred in both studies from exposure of the dams to elevated ambient temperatures without RFR.

Chiang and Yao (1987) exposed pregnant mice to pulsed 3-GHz RFR (1.2-μs pulses at 937 pps) at 8 mW/cm² (SARs in the range 3.0-3.5 W/kg) for 5 hours daily throughout gestation. The authors noted that no core-temperature rises had occurred after exposure. The exposures were continued for half the pups (RR group) from day 3 to day 20 after birth (SARs not estimated). The other pups were sham-exposed (RC group). Other pregnant mice were similarly sham-exposed, and half those pups were exposed to the RFR (CR group) and the other half were sham-exposed (CC group).

On day 2 after treatment (age 22 days), medial-sagittal sections of brain from 10 pups in each group were assayed for succinate dehydrogenase (SDH), monoamine oxidase (MAO), and catecholamines (CA) by fluorescence spectrophotometry. Also assayed was SDH in the liver. The results were presented as bar graphs of relative fluorescence (with error bars) for the four groups.

For hypothalamic SDH, the mean relative fluorescence was highest in the CC group and successively lower for the RC, CR, and RR groups. The levels of SDH in the liver were about twice those in the hypothalamus, but showed a similar succession of decreases. The succession of patterns for constituents CA and MAO (in the hypothalamus) were also similar. Differences between each pair of groups for each constituent were compared by analysis of variance. Most of them were stated to be significant at less than the 1% level.

The authors ascribed the decreases of SDH in the hypothalamus to either prenatal or postnatal exposure to the RFR, and the decreases of SDH in the liver and of CA and MAO in the hypothalamus primarily to postnatal exposure. They also remarked that such histochemical tests may be more sensitive and reliable indexes for determining the effects of RFR on development than those usually used.

Presumably because this paper was a "short communication," the authors did not present any data on, or discuss the incidences of terata in any of the groups, or the importance of their positive histochemical findings with regard to RFR-induced teratogenesis. Also, the results presented were not in enough detail to do an independent statistical analyses of the findings.

Various RFR-teratogenesis studies were also done with rats. Dietzel (1975) singly exposed pregnant rats once between gestation days 1 and 16 to 27.12-MHz RFR in the abdomen with a diathermy machine and applicator at 55, 70, or 100 W. In lieu of any other dosimetry, each rat was removed when its rectal temperature reached 39, 40.5, or 42 °C (duration up to 10 minutes). On day 20, the fetuses were removed, counted, weighed, and examined for external malformations. Also, embryos in resorption and corpora lutea were counted, and the preimplantation losses were calculated by subtracting the numbers of mature and resorbed fetuses from the number of corpora lutea.

Typical predominant abnormalities were neurocranial malformations from exposure on days 9 and 10, kinked or short tails and "hand" defects for days 13 and 14, and cleft palate for day 15. The maximum numbers of abnormalities occurred for exposure on days 13 and 14, and they correlated well with rectal temperature, showing that the abnormalities resulted from heating by the RFR.

Chernovetz et al. (1977) exposed 26 pregnant rats for 20 minutes on one day during days 10-17 of gestation to 2.45-GHz RFR in a multimode microwave cavity at a mean SAR of 31 W/kg, an ambient temperature 22 °C, and relative humidity 50%. Twenty-six pregnant rats were exposed to infrared radiation (IR) in an incubator held at 47 ($\pm$ 7) °C and 10-15% relative humidity, to attain a colonic-temperature rise of 3.5 °C, the same as with the RFR. As controls, 12 rats were sham-exposed in the microwave cavity. Three of the total of 64 rats died after exposure to the IR, 7 died after exposure to the RFR, and none died in the control group.

On day 19, the numbers of implantations and resorptions were counted in the 54 surviving dams, each fetus was examined for abnormalities, and its mass and viability were determined. The percentages of living fetuses per dam were about 98% each for the control and IR groups and 87% for the RFR group, a statistically significant difference. The mean fetal masses for the IR and RFR groups were both significantly lower than for the controls. No structural

abnormalities were evident in any of the 468 formed fetuses, all of which were alive when taken, but severe edema and hemorrhagic signs were endemic in the IR and RFR groups.

Twenty brains each from control, IR, and RFR fetuses were assayed for norepinephrine (NE) and dopamine (DA) in four groups of five pooled brains for each treatment. The mean NE level of the RFR group was significantly lower than for the controls, but only marginally lower than for the IR group. The DA levels ranked similarly, but the differences were not significant.

The authors regarded the results as evidence that a brief but highly thermalizing exposure to 2.45-MHz RFR or to IR to attain equal colonic-temperature rises can have effects both comparable and different. A problem with this study was the small number of rats used (a point recognized by the authors), which necessitated averaging the data in each group over the 10-day to 17-day gestation period, a procedure open to question both biologically and statistically. Perhaps a minor point was the use of the sham-RFR rats as controls for the IR group instead of a separate set of sham-IR controls, in view of the relative-humidity/ambient-temperature differences. Because of such problems, the validity of either the positive or negative results of this investigation is difficult to assess.

Shore et al. (1977) exposed 24 mated female Sprague-Dawley rats in individual boxes to 2.45-GHz RFR at 10 mW/cm² in an anechoic chamber for 5 hours daily on gestation days 3 through 19. Half the boxes were placed with their long axes parallel to the electric vector (group AC), and the other half with long axes parallel to the magnetic vector (group BD). Twenty-four similarly housed rats were sham-exposed concurrently with the RFR groups. Temperatures within the RFR-exposure and sham-exposure chambers were not controlled; the respective mean temperatures were 25.5 ± 0.7 °C and 22.8 ± 0.2 °C. The rats were permitted to move about freely within their boxes.

After treatment, all 24 RFR-exposed rats produced litters; the mean litter sizes of the AC and BD groups respectively were 9.33 and 10.75 pups. One sham-exposed rat had not been pregnant; the mean litter size of the 23 pregnant rats was 9.78 pups. The differences were not significant.

One pup each was selected from the AC, BD, and sham-exposed litters on post-partum days 2, 3, 6, 7, 8, 9, 14, and 15 for determination of body and brain weights, and the data from each group on each day were averaged. The only statistically significant difference in corresponding mean body weights between the RFR groups and the sham group was for the AC group on day 3. The authors noted that although the weight differences on the other days were not significant, most of the means for the AC group (body axes roughly parallel to the electric vector) were slightly lower than for the sham-exposed rats on each day. A similar trend was not seen for the BD group (body axes roughly parallel to the magnetic vector). For day 3, the mean brain weight of the AC group was significantly lower than for the sham-exposed rats. On the other days, the mean brain weights of the AC group were all nonsignificantly lower than values for the sham group.

A major problem with this study was the absence of temperature control during treatment, a point recognized by the authors; the mean temperature in the RFR-exposure chamber was 2.7 °C higher than in the sham-exposure chamber.

Also, the ranges of temperature with time during the various 5-hour daily treatments were not indicated. Possible consequences of such temperature differences on the findings of this study could not be assessed.

Smialowicz et al. (1979), in an investigation primarily of immunologic and hematologic effects, exposed pregnant rats to 2.45-GHz CW RFR at 5 mW/cm² for 4 hours a day, 7 days a week from gestation day 6 through term. The SAR range was 4.7-0.7 W/kg, represented the decrease of mean SAR with increase in mean weight (with age) rather than variations among animals at any time. A group of male pups of each dam were similarly treated until age 20 days, at which time half were euthanized and the other half were treated until age 40 days and then euthanized. The dams and pups were weighed at intervals to determine if the RFR had affected growth. No significant differences were seen in mean weight between the exposed and control animals at any time.

Berman et al. (1981) exposed arrays of CD rats in individual Plexiglas containers to 2.45-GHz CW RFR at 28 mW/cm² (4.2 W/kg), 22.2 °C ambient temperature, and 50% relative humidity for 100 minutes daily on gestation days 6 through 15. The long axes the containers were parallel to the H-vector and perpendicular to the propagation direction. The mean colonic temperature at exposure end of each period was 40.3 °C. On gestation day 21, each rat was euthanized, and the live, dead, and resorbed conceptuses were counted. Each live fetus was dried, examined for external morphology, weighed, fixed, and subsequently studied for internal morphology.

There were no statistically significant differences between RFR-exposed and sham-exposed rats in: pregnancy rates; mean litter values of live, dead, resorbed, or total fetuses; or live fetal weight. The numbers of ribs and sternal ossification centers were comparable. The types and indices of major and minor terata were similar in both groups of litters. No encephaloceles (brain hernias) were seen in any of those litters. These negative results were consonant with those of Chernovetz et al. (1977), who saw no teratogenic effects from exposure to 2.45-GHz RFR at about 31 W/kg, an SAR that was lethal to about 27% of the dams. Berman et al. (1981) concluded that the rat is an inappropriate model for determining whether RFR would be teratogenic to humans in exposure situations not lethal for the mothers, and suggested that the mouse is more suitable for that purpose.

In a subsequent study, Berman and Carter (1984) exposed 24 pregnant Sprague-Dawley rats to 2.45-GHz CW RFR at 40 mW/cm² (6.0 W/kg) for 100 minutes daily on gestation days 6 through 15. Exposure of rats in early gestation for 100 minutes at 40 mW/cm² increased the mean colonic temperature from 37.6 to 39.6 °C. On gestation day 21, the numbers of live, dead, and resorbed conceptuses were tallied. On a per-litter basis, the differences between RFR and sham groups in mean numbers of live fetuses, dead/resorbed fetuses, and total implants were nonsignificant. Thus, the authors concluded that exposure to 2.45-GHz CW RFR at 40 mW/cm² for 100 minutes daily during organogenesis and the fetal stage is not teratogenic. However, the mean weight of the live fetuses from the RFR group was found to be significantly lower than for those from the sham-exposed group, as was the mean number of ossified sternebrae, an indication of RFR-induced growth retardation.

Lary et al. (1982) exposed pregnant Sprague-Dawley rats individually to concurrent 27.12-MHz CW magnetic and electric fields at 55 A/m and 300 V/m (equivalent power density 138 mW/cm², SAR 11.1-12.5 W/kg). One group was

exposed on gestation day 1, 3, 5, 7, 9, 11, 13, or 15. Exposure of each rat was terminated when its colonic temperature reached 43.0 °C (20-40 minutes duration). On the same gestation days, one group each was sham-exposed for 30 minutes, and another group was maintained in the animal quarters without treatment as cage controls. The exposure conditions were selected to deliver doses that were nearly hyperthermically lethal to the dams.

In a pilot study, most of the malformed litters occurred in rats heated by RFR to 43.0 °C or higher, and no malformations were produced at less than 41.9 °C. Colonic temperatures exceeding 43.0 °C were increasingly lethal. In the main study, 26 (11%) of the RFR-exposed rats died of hyperthermia during or shortly after exposure, and only four of them had a final temperature less than 43.0 °C. No sham-exposed or cage-control rat died during the experiment.

On gestation day 20, the numbers of implantations, live fetuses, and dead or resorbed conceptuses were determined. Also, the corpora lutea of pregnancy were counted in the cage controls, as were those present during the pre-implantation period (gestation days 1, 3, and 5) of the RFR-exposed and sham-exposed groups. Each live fetus was sexed, weighed, measured for crown-rump length, and examined externally for gross malformations. One-third of the live fetuses from each litter were selected randomly, dissected, and examined for visceral abnormalities; the other fetuses were cleared and stained for skeletal examination.

The results for each group exposed to RFR preimplantation gestation days (1, 3, or 5) were compared with the combined results for the three groups sham-exposed on those gestation days, and the results for each group exposed to RFR during early organogenesis (day 7, 9, or 11) were treated similarly, as were the two groups exposed to RFR during late organogenesis (day 13 or 15). Also, to determine whether the sham-exposed rats were affected significantly by handling, transport, or restraint, their results were compared with those of the cage controls.

A comparison of the results on embryotoxicity on gestation day 1, 3, or 5 indicated no significant differences between corresponding cage-control and the sham-exposed groups. Neither were the differences significant in mean fetal weight or mean crown-rump length. For the rats exposed to RFR on those days, the mean fetal crown-rump lengths were slightly lower than for the sham-exposed rats, but only the differences for days 1 and 5 were significant.

The percentages of dead or resorbed conceptuses for those exposed to RFR on gestation days 7, 9, or 11 were 29%, 49%, and 18%, respectively, compared with 11% for the rats sham-exposed on those days, but only the differences in percentages for days 7 and 9 were significant. Also, the fetal weights and crown-rump lengths of the rats RFR-exposed on days 7 or 9 were significantly lower than for the sham groups, as was also the case for those exposed on gestation days 13 or 15. Thus, maximum embryotoxicity occurred from exposure to the RFR on gestation day 9.

Regarding terata incidences, the differences in percentages of external, skeletal, or visceral abnormalities between the fetuses of the cage controls and those of the sham-exposed rats were nonsignificant, with one exception: 4% of the fetuses of the rats sham-exposed during organogenesis (day 7, 9, or 11) had major visceral abnormalities as compared with 0% of the cage-control

fetuses. The percentages of fetal external abnormalities were zero for all sham groups, but significant percentages were found in the RFR groups for all days except 1 and 5, with the largest value (67%) for day 9. Significant differences between RFR and sham groups for major skeletal abnormalities were seen for all days except 3, 5, and 13, with the highest value (60%) again on day 9. Skeletal variations were significant for all days, with day 9 once more yielding the highest value (83%). Major visceral abnormalities were significant only for day 9 (65%).

Only 3 preimplantation fetuses, 5 early-organogenesis fetuses, and 1 late-organogenesis fetus of the sham groups were abnormal, and only 3 cage-control fetuses were abnormal. By contrast, more than 200 different types of abnormalities were seen in the RFR groups, most of which occurred only once. The largest variety of abnormalities (17) occurred for exposure to the RFR on gestation day 9. Microphthalmia or anophthalmia (absence of eyes or presence of vestigial eyes) with associated small, narrow cranial orbits were found in 25-39% of all viable fetuses, exencephaly and related defects of protruding tongue and aplasia of the upper cranial bones were evident in 17-22% of the fetuses, and other severe malformations were seen in 6-14% of the fetuses.

Lary et al. (1983a) treated five groups of rats on gestation day 9 as follows: One group was sham-exposed for 2.5 hours. Another was exposed to 27.12-MHz fields at 55 A/m and 300 V/m (SAR about 11 W/kg), which produced relatively rapid rises in colonic temperature; exposure was stopped when the temperature reached 41.0 °C (exposure duration 14-22 minutes). For a third group, 41.0 °C was held for an additional 2 hours (total exposure duration 137-144 minutes). Exposure of a fourth group was stopped when the colonic temperature reached 42.0 °C (13-33 minutes). In a fifth group, 42.0 °C was maintained for an additional 15 minutes (total exposure 34-55 minutes).

The RFR-exposures caused relatively rapid rises in colonic temperature. In successive comparisons of the groups on gestation day 20, the severity increased steadily in both the percentage of malformed fetuses and the ratio of litters affected, with by far the largest change for the prolongation of colonic temperature at 42.0 °C (fifth group). Similar results were obtained for percentages of live fetuses with visceral malformations, with the largest change again occurring for prolonged exposure at 42.0 °C. Those teratogenic effects were ascribed to the hyperthermia induced by the RFR.

Lary et al. (1983b) exposed pregnant Sprague-Dawley rats to 100-MHz CW RFR at 25 mW/cm² (0.4 W/kg) for 6 hours and 40 minutes per day on gestation days 6-11 (total exposure time of 40 hours). Colonic temperatures were measured just before and after treatment on gestation days 6 and 11. As in Lary et al. (1983a), each rat was examined for number of implantations, live fetuses, and dead or resorbed conceptuses; the fetuses were sexed, weighed, measured for crown-rump length, and examined for gross abnormalities. RFR-exposed and sham-exposed dams showed decreases in mean colonic temperature of 0.6 to 0.8 °C during treatment. No significant differences were found in numbers of litters; mean implantations per litter; percentages of dead or resorbed implantations or percentages of live fetuses with major skeletal abnormalities; or fetal mean weight, crown-rump length, sex ratio. Only 64% of the live fetuses from the RFR group had minor skeletal variations, versus 76% of the fetuses from the control group, a significant difference ($p < 0.05$). Also, there were no significant differences between the groups in the various

specific kinds of external malformations or major skeletal abnormalities. Thus, the results yielded no evidence that RFR-exposure at the maximum level permitted by ANSI/IEEE (1994) was embryotoxic or teratogenic.

Lary et al. (1986) investigated the dose-response relationship between RFR-induced maternal increases in body temperature and the incidence of birth defects in rats. They exposed groups of pregnant rats on gestation day 9 to 27.12-MHz RFR at 55 A/m and 300 V/m (10.8 W/kg). Exposures were terminated when colonic temperatures reached 41.0, 41.5, 42.0, 42.5, or 43.0 °C (10-40 minutes duration). Exposed and control dams were euthanized and the uterine horns of each dam were examined for the numbers of implantations, live fetuses, and dead and absorbed conceptuses. The numbers of the various fetal abnormalities and dead fetuses found on gestation 20 were plotted versus the colonic temperature of the dams at exposure end (dose-response curves). The results yielded a colonic-temperature threshold of 41.5 °C for birth defects and prenatal death.

Because of the high intensities of RFR used by Dietzel (1975) and Lary et al. (1982, 1983a, 1986), the relevance of their findings to possible teratogenesis in humans exposed to much lower levels of RFR in the high-frequency (HF) range might be questioned. However, Conover et al. (1980) surveyed industrial RFR plastic sealers operated (mostly by women) in the range 6-38 MHz and found that occupational exposure to the fields generated by many of the units (most at 27.12 MHz) exceeded the limits of electric and magnetic field at 27.12 MHz specified in ANSI (1974): 200 V/m and 0.5 A/m. The limits specified in ANSI (1982) were even lower: 70 V/m and 0.175 A/m. The corresponding limits in the ANSI/IEEE (1992) guidelines for controlled environments are 67.9 V/m and 0.60 A/m, averaged over any 6-minute period.

Inouye et al. (1983) exposed mated 8 female Sprague-Dawley rats within individual cages to 2.45-GHz RFR at 10 mW/cm for 3 hours daily on gestation days 4 through 21. By calorimetry, the average whole-body SAR was 1.76 W/kg. Eight mated female rats were sham-exposed. Only 5 of the RFR-exposed and 7 of the sham-exposed rats were found to be pregnant. The RFR-exposed dams had a total of 50 pups (27 males and 23 females), of which 1 pup had a malformed tail. The sham-exposed dams had 92 pups (46 males and 46 females) with no malformations. The single malformation was not statistically significant.

Two days after birth, the neonates RFR-exposed *in utero* were separated from their dams and 24 healthy male pups were selected. Groups of 6 pups each were foster-mothered to dams that had not been RFR-exposed, and the pups were separated from the foster dams once a day, weighed, RFR-exposed at 10 mW/cm² for 3 hours from age 2 days through 40 days. The pups from the sham-exposed dams were similarly treated but sham-exposed. The SARs in the brains of pups were determined from measurements of the rate of brain heating from exposures at 120 mW/cm². The mean values were: 13.95 W/kg in 2-day-old pups, 19.18 W/kg in 15-day-old pups, 10.05 W/kg in 20-day-old pups, 9.72 W/kg in 30-day-old pups, and 9.52 W/kg in 40-day-old pups. At corresponding ages, the mean body weights of RFR-exposed and sham-exposed pups were virtually identical. Eye opening occurred in both groups at about the same age.

The brains of one group each of 6 RFR-exposed pups at ages 15, 20, and 30 days were removed, fixed, and weighed, and the width, height, and length of the cerebral hemispheres were measured. Pups at age 40 days were similarly

treated except for fixation. Instead, the right hemispheres were immersed in fixative, and sections of cerebrum and cerebellum were prepared for histologic examination. The left halves were prepared and sectioned for neuroanatomical examination, and the densities of dendritic spines in several regions of the cerebrum and of Purkinje cells in the cerebellum were determined.

At corresponding ages, no significant differences were found between RFR-exposed and sham-exposed pups in brain weights, cerebral dimensions, or histologic parameters. In the pups euthanized at age 40 days, there were no significant differences between the RFR and sham groups in dendritic-spine densities within the corresponding cerebral regions examined. Also, although the counts of Purkinje cells varied from lobule to lobule of the cerebellum, the differences in counts within the corresponding lobules did not differ significantly between the groups. The authors remarked that their finding of no significant differences between RFR-exposed and sham-exposed rats in counts of Purkinje cells was contrary to a finding by Albert et al. (1981a) of fewer Purkinje cells in RFR-exposed rats, a difference not readily explained, except possibly that the rats in the Albert et al. (1981a) study had been exposed to RFR for longer periods per day but for fewer days.

Tofani et al. (1986) treated four groups of pregnant rats. Group A was sham-exposed; group B was exposed continuously to 27.12-MHz RFR at 20 V/m and 0.05 A/m during gestation days 0-20; groups C and D respectively were exposed to the same fields during gestation days 0-6 and 6-15. For exposure, 10 rats each were co-housed in large plastic boxes; two such boxes, comprising group B, were exposed concurrently. Groups C and D were treated similarly. The exposures were done in the near field of a Siemens Diplode fed from a 27.12-MHz generator. The authors used Durney et al. (1978), and estimated that the upper SAR limit was about 0.00011 W/kg, a level insignificant relative to the the basal metabolic rate for such rats (6.51 W/kg).

No dead fetuses were found. Total resorptions were found in half the dams of groups B and C and in 20% of the dams in group D, with none in sham-exposed group A. The values were statistically significant for groups B and C, and nonsignificant for group D, suggesting that this effect occurs during the early stage of egg development. Mean litter weights of the three RFR-exposed groups were significantly lower than for the sham group. The only significant teratologic finding was incomplete ossification of cranial bones in the three RFR-exposure groups. In view of the low RFR level, the authors characterized the effects as nonthermal and due to long-term exposure.

Lu and Michaelson (1987a) took issue with the exposure methodology used and questioned the absence of technical details, such as a description of the means for providing food and water and for removing wastes during continuous exposures of pregnant rats. They noted that use of Durney et al. (1978) for their SAR estimation was inappropriate. They noted that not discussed in the paper was whether RFR-absorbent materials were used in the chamber to avoid multipath exposure, and that the proximity of the rats to one another in the exposure boxes probably resulted in large and uncertain dosimetric variations.

In their response, Tofani et al. (1987) clarified several of the points raised by Lu and Michaelson (1987a), but remarked that they chose to do the exposures in a room without any shielding or RFR-absorbing materials. They stated: "Our aim in this work is the evaluation of the biological effects due

to a low-level, long-term exposure to a 27.12-MHz electromagnetic field in conditions as similar as possible to those people who usually are exposed (i.e. to near-field, multi-path radiation with distances between individuals shorter than a wavelength)." That response begs the question, because the dose rates from such exposures could have varied considerably from rat to rat and with time for each rat. They also stated: "Effects due to overcrowding ought to result in the sham-exposed group too, since that group was managed in the same way." That remark appears to miss the point that rat overcrowding probably introduced large spatial and temporal variations in RFR-exposure levels rather than directly causing the reported effects, so overcrowding per se in the sham-exposed rats would not be expected yield those effects. Thus, little if any credence can be given to their conclusion that they had found nonthermal teratogenic effects.

Brown-Woodman and Hadley (1988) sought whether exposure of pregnant rats on gestation day 9 to pulsed 27.12-MHz RFR at levels too low to raise core temperature is teratogenic to embryos. Mated female Sprague-Dawley rats were exposed individually to the RFR between a pair of circular electrodes, using an Erbe Erbotherm 1100P or an Enraf Curapulse diathermy unit operated in the pulsed mode as the source. The long axis of the rat holder was perpendicular to the electric vector and parallel to the magnetic vector. Exposures in the Erbe unit were with 10, 20, or 30 pps, which provided time-averaged powers of 5, 10, or 15 W, with durations respectively 60, 45, and 30 minutes. Core temperatures were taken with a Yellow Springs telethermometer and a thermistor probe before treatment, and at unstated intervals during treatment. The probe was removed during exposure, to avoid artifact. From temperature-versus-time measurements in a saline-filled rat phantom exposed at each pulse repetition frequency and its corresponding duration, the whole-body SARs were 2.8, 4.2, and 5.6 W/kg, respectively.

Exposures with the Enraf unit were with 15, 26, or 35 pps, which yielded 6, 10.3, or 14 W. The durations were also 60, 45, and 30 minutes. However, for unknown reasons, exposure of the phantom with the Enraf unit produced no detectable temperature rises. Two control groups were sham-exposed, one for 30 minutes and the other for 60 minutes.

In rats, the mean core-temperature rises with the Erbe unit at 5, 10, and 15 W at the end of the corresponding treatment periods were respectively 0.4, 1.3, and 0.6 °C. Those with the Enraf unit at 6, 10.3, and 14 W were 0.7, 0.8, and 0.6 °C. The temperature rises for the 30-minute and 60-minute control groups were respectively 0.5 and 0.7 °C. The authors remarked that the mean temperature increases in the RFR-exposed rats did not significantly differ from those for the control rats, but did not rule out local temperature rises in the former.

The mean number of live embryos on gestation day 20 increased and the percentage of resorptions decreased with increasing power for treatment with the Erbe unit, whereas the opposite trends were obtained for treatment with the Enraf unit. Also, there appeared to be no significant differences in mean embryo weight irrespective of the level of RFR-exposure with either unit or of sham-exposure. Only one embryo had abnormalities, from the group exposed with the Erbe unit at 15 W for 30 minutes (5.6 W/kg).

The authors stated: "The present study demonstrates embryoletality without a significant increase in rectal temperature, particularly in the

group irradiated for 60 min at 10 Hz [PRF] using the Erbe Erbotherm unit, when the mean increase in rectal temperature was only 0.4 °C, less than that observed in the group sham-irradiated for 60 min (0.7 °C). Longer periods of exposure at lower frequencies resulted in a greater number of implantations being resorbed than exposure for shorter durations at higher frequencies."

Thus, they gave greater credence to exposure duration than to exposure level. They also discounted the opposite trend obtained with the Enraf unit, i.e., a progressive increase (rather than decrease) in percentage resorptions with decreasing exposure duration (and increasing power level) by citing their non-detection of temperature rises in the phantom rat with that unit, implying that the actual rats had not absorbed much if any RFR.

Unclear is why the two diathermy units yielded such exposure differences with the same applicator. If the rats indeed had not received much RFR with the Enraf unit, the aforementioned opposite trend in resorption results could be an indication of uncontrolled non-RFR factors. Supporting the latter point are the mean-rectal-temperature rises apparently unrelated to RFR- or sham-exposure. Further, as noted above, only one embryo (of 86 from the dams exposed with the Erbe unit for 30 minutes) exhibited abnormalities; none were seen in 49 embryos from the group exposed for 45 minutes or in 39 embryos from the group exposed for 60 minutes in that unit. Thus, the authors' finding of non-thermal-RFR-induced teratogenicity in this study is questionable.

Brown-Woodman et al. (1988) used similar methods to investigate whether teratogenesis induced in rats by 27.12-MHz RFR is due to hyperthermia. As before, they exposed pregnant Sprague-Dawley rats on gestation 9 to the RFR, but with the Erbe unit in the CW mode. The amplitudes of the electric and magnetic fields were 33 kV/m and 0.8 A/m. The whole-body SAR was 11.2 W/kg. The exposure durations were those needed to reach specific core-temperature rises, at which time 1-minute bursts were used to hold it there for specific durations. Eighty-seven pregnant rats were exposed to the RFR and 10 pregnant rats were sham-exposed. On gestation day 20, each rat was examined for the number of implantations, and the live and dead fetuses were counted, weighed, and examined for gross malformations.

Nine of the 10 sham-exposed rats produced litters. The mean resorption rate was 4%; the resorptions were found in 2 of the 9 litters (22%), and no external malformations were seen. The mean litter size was 12.3 fetuses and their mean weight was 3.7 ± 0.60 g.

Three rats were RFR-exposed until their core temperature was raised by 5 °C and held for a few seconds. The resorption rate was 74%, the litter sizes were small, 1 of the fetuses was dead, the mean fetal weight was 2.5 ± 0.41 g, and all surviving fetuses had various single or multiple malformations.

Seventeen rats were RFR-exposed until their core temperature was raised by 4.5 °C. That temperature was held for 2 minutes in 5 rats, 5 minutes in 9 rats, and 10 minutes in the other 3 rats. One rat of the 2-minute group and 2 rats of the 5-minute group died, and only 3 of the 4 surviving rats in the 2-minute group and 5 of the 7 surviving rats in the 5-minute group had litters. The respective resorption rates of the three groups were all significantly higher than for the controls; their mean litter sizes were 13.0, 2.8, and 4.0 fetuses, with 2 of the fetuses in the 2-minute group dead; the mean weights of

the live fetuses were 3.1, 2.7, and 3.3 g. Thus, the changes in mean fetal weight were not unidirectional with increasing temperature-elevation duration but all were significantly lower than for the controls.

In similar experiments with successively lower core-temperature rises for various durations, the severity of the effects decreased. In the last of those experiments, the core temperatures of 7 rats were elevated by 2.5 °C for 50 minutes and those of 3 rats for 60 minutes. Their resorption rates were 17% and 15%, higher than for the controls (4%), but there were no abnormal fetuses. Their mean weights were 3.1 and 3.2 g, slightly lower than for the sham-exposed rats (3.7 g).

The authors remarked that their observed teratogenic and embryolethal effects were related to both core-temperature elevation and its duration. They also noted that the abnormalities (microphthalmia, encephalocele, and facial defects in decreasing frequency) were essentially the same as those obtained by Germain et al. (1985) by partially immersing rats of the same strain in a heated water bath. Thus, they concluded that the teratogenic effects of RFR are due primarily to the heating therefrom, with a threshold core-temperature rise of about 2.5 °C.

In a fertility study, Brown-Woodman et al. (1989) exposed virgin female Sprague-Dawley rats to 27.12-MHz RFR for 1 hour per day, 5 days a week, for 5 weeks, a total of 25 hours. Groups of 5 rats each were placed within plastic boxes, and one box was placed on each side of a pair of circular electrodes (resembling the applicator used in the studies above). Measurements of the electric and magnetic fields indicated large spatial variations. Thus, the levels of exposure received by the rats is highly uncertain and non-uniform, because of mutual interactions and shielding among the rats in each box and the probable temporal and spatial variations of the SAR of each rat from their free movements within the boxes.

Rectal temperatures were measured right before and after treatment. Box confinement of sham-exposed rats for 1 hour produced a mean rise in rectal temperature of about 0.6 °C, as did RFR-exposure. The rats were mated 3 days after treatment. On gestation day 20, the mated females were examined for numbers of implantation sites and live and dead fetuses. Also, each fetus was weighed and examined for external malformations and cleft palate.

There were no significant differences in mean litter size, numbers of implantation sites, or fetal weight between the RFR-exposed and control rats that became pregnant. None of the fetuses had any congenital malformations. However, only 24 of the 30 RFR-exposed females had mated, as compared with 29 of the 30 control females. Moreover, of those that had mated, only 20 of the 24 RFR-exposed females became pregnant, whereas 27 of the 29 controls became pregnant.

By chi-square test, the authors found that the differences above were significant ($p < 0.05$), and they ruled out hyperthermia as the agent. However, they did not provide enough data to permit evaluation of their statistical treatment of the results. Also, in the absence of adequate dosimetric data (SARs and their temporal and spatial variations), it is difficult to ascribe the differences in breeding behavior and pregnancy outcome to the RFR without independent verification.

Jensh et al. (1982a) exposed groups of pregnant Wistar albino rats in individual Acrylite cages to 915-MHz CW RFR at 10 mW/cm² for 6 hours per day without food and water in an anechoic chamber on gestation days 1 to 21. The mean maternal body weight over the gestation period was 0.28 kg, from which the authors derived a mean SAR of 3.57 W/kg. For this study, 11 pregnant rats exposed to the RFR comprised the "experimental" group and 4 sham-exposed pregnant rats were the "concurrent-control" group. In addition, 5 rats kept in home cages (the HC group) and 10 rats kept daily for 6 hours in the anechoic chamber (the AC group) served as two "baseline-control" groups.

On gestation day 22, the weights of maternal brain, liver, kidneys, and ovaries were measured and normalized to term body weights. No statistically significant differences in organ-to-body-weight ratios were found between the HC and AC baseline control groups or between the RFR-exposed and concurrent-control groups for any of the organs. However, significant differences were found between the baseline-control groups and the concurrent-control group, results ascribed to the significantly lower mean body weights of the baseline groups, consisting of younger animals. The unnormalized mean organ weights showed no significant differences among the four groups. Also, there were no significant differences in mean litter size or mean fetal weight among the four groups. Only one fetus, in the AC baseline group, was abnormal. These negative findings are consonant with those of Chernovetz et al. (1977) and Berman et al. (1981) at 2.45 GHz, and of Lary and coworkers and Brown-Woodman et al. (1988) at 27.12 MHz, which showed that much higher SARs are necessary for teratogenic effects in rats.

Jensh et al. (1982b), a companion study, was directed toward determining possible behavioral changes in similarly exposed rats. At age 90 days, half of the initial (Fla) offspring of the exposed and unexposed dams were killed and examined for histopathology. The remaining offspring were cross-bred in four groups, and the resulting litters (F2) were examined prenatally for teratogenesis. In addition, the original females were rebred 40 days after delivery of Fla offspring (but not reexposed to the RFR) and the resulting fetuses (Flb) were examined for teratogenesis.

The results for the initial pregnancy showed no significant differences in maternal weight, weight gain, or Fla mean litter size. Only one abnormal neonate, in the AC group, was found. The weekly mean weights of the RFR-exposed Fla neonates were significantly larger than for the concurrent-control neonates through age 24 days, after which the differences were not significant. Some significant weight differences were also seen at various ages among the baseline (HC and AC) groups and the concurrent-control group. Necropsies of the Fla litters at 90 days showed no significant differences between the RFR-exposed and concurrent-control groups in organ weights or organ/body weight ratios. The second breeding of the original dams yielded no significant differences between the RFR- and concurrent-control groups in any of the endpoints, and no abnormal offspring were evident. In the cross breeding of Fla males and females to obtain F2 fetuses, no significant RFR-related differences were seen in maternal weight, resorption percentages, fetal weight, or litter size.

The second breeding of the original females yielded no significant differences in mean maternal weight or litter size between the RFR- and concurrent-control groups, and no abnormal offspring were evident. Also,

subsequent necropsies of those mothers showed no significant differences in mean organ weights or organ/body weight ratios. In the cross breeding of Fla males and females to obtain F2 fetuses, there were no significant RFR-related differences in mean maternal weight, percentage of resorptions, fetal weight, or litter size.

The finding of significantly larger perinatal mean weekly weights for the RFR-exposed Fla neonate Wistar albino rats than for concurrent controls is opposite to that found by Berman et al. (1981) in CD rats exposed to 2.45-GHz RFR at 28 mW/cm² (4.2 W/kg). This and a minor behavioral effect found by Jensh et al. (1982b) both appear to indicate that prenatal exposure of rats to relatively low levels of RFR may be beneficial, but such findings require independent verification.

Jensh et al. (1983a, 1983b) were another pair of studies, but with 2.45-GHz RFR. In Jensh et al. (1983a), preliminary experiments with exposures at up to 30 mW/cm², 20 mW/cm² was found to be the highest RFR level that did not produce significant increases in colonic temperature in near-term pregnant rats. They then sham-exposed and exposed groups of pregnant rats daily for 6 hours per day throughout gestation at 20 mW/cm², with HC and AC groups as baseline controls. The estimated mean SARs during gestation days 0-1, 7-8, and 20 were about 5.2, 4.8, and 3.6 W/kg, respectively. No significant RFR-related differences were found in mean maternal weight gain during pregnancy, term maternal organ weights (brain, liver, kidneys, ovaries), term fetal weight, resorption rate, or abnormality rate.

In Jensh et al. (1983b), groups of RFR-exposed, concurrent-control, and baseline-control pregnant rats were similarly treated, but allowed to come to term. The differences among the groups for initial or term maternal weight or weight gain during pregnancy were not significant. Comparative ranking of the growth rates of the Fla offspring during corresponding periods up to age 87 days indicated that the RFR group had the highest growth rate, followed in succession by the AC, concurrent-control, and HC groups, but the differences were not statistically significant. No significant differences were found among groups in the results of cross-breeding Fla offspring or in the results of teratologic examination of dams rebred 10 days after weaning the Fla offspring or of the resulting F2 offspring.

In the first of still another pair of studies, Jensh (1984a) exposed pregnant rats from above for 6 hours per day to 6-GHz RFR at 35 mW/cm² (estimated mean SAR 7.28 W/kg), which did not increase colonic temperature significantly. On gestation day 22, half the exposed and control dams were decapitated, and the rest of the dams were given postnatal analysis. No significant differences were seen in any of the teratologic endpoints studied except for mean fetal weight at term, which was significantly lower for the RFR group than the concurrent-control (sham) group. However, so was the difference between the sham and AC groups and between the HC and AC groups, which could indicate that lower mean fetal weight of the RFR group may not have been RFR-induced.

Another point of conjecture is whether teratogenic effects would be expected for exposure from above to 6-GHz RFR at 35 mW/cm², a frequency at which the penetration depth for muscle is about 0.7 cm, compared with about 2.4 cm at 915 MHz and 1.7 cm at 2.45 GHz. Therefore, the local SARs in the uteri may have been much lower at 6 GHz even though the whole-body SAR was considerably larger than in the earlier studies.

In Jensh (1984b), the companion study, Fla offspring at age 90 days were bred within and across groups as before, and teratologic evaluations were done on the F2 term fetuses. The original dams were then rebred 10 days after weaning the Fla pups, and teratologic evaluations were done on the Flb offspring. The difference in mean maternal weight of the RFR and sham groups on gestation day 0 of the first breeding was nonsignificant. On day 21, the mean maternal weight for the RFR group was smaller ($p < 0.02$) than for the sham group: the mean weight gains were 42.1% and 45.2%, respectively. However, the mean weight gain of the HC group was 45.8%, which was close to that of the sham group, but the mean for the baseline AC group was 42.8% or close to that of the RFR group. The mean litter size for the RFR group was 9.55 fetuses, compared with 12.00 for the sham group. The sizes for the HC and AC groups were 12.40 and 11.20, respectively.

The mean weights of the RFR-exposed and sham-exposed pups on postnatal day 3 were 9.1 and 9.9 g, respectively, a significant difference ($p < 0.01$). In the subsequent weekly weighings, the weight differences were successively less significant, becoming nonsignificant ($p > 0.05$) at about 38 days of age. On day 3, however, the mean weight for AC pups was only 8.1 g and it remained significantly lower than for the RFR-exposed pups throughout the subsequent weekly weighings (to age 87 days). On postnatal day 3, cataracts were found in 3 Fla pups from one RFR-exposed dam, 1 pup from a sham-exposed dam, and 1 pup from an AC dam. No other abnormalities were evident.

In the cross-breeding of Fla rats previously treated *in-utero*, the mean maternal weight increase of RFR-exposed females bred with RFR-exposed males was significantly less than for colony-control females bred with RFR-exposed males or for RFR-exposed females bred with colony-control males or for sham-exposed females bred with sham-exposed males. Also, the difference in weight-increase between colony-control females mated with RFR-exposed males and RFR-exposed females mated with colony-control males was significant. Regarding the F2 offspring, independent t-tests of the data tabulated in the paper indicated that the differences among the four groups in mean F2 litter size and mean fetal weight were not significant ($p > 0.05$).

Perhaps the most important finding of this study was the absence of any terata in Fla, Flb, and F2 offspring from prolonged exposure of rats (8 hours per day throughout their first pregnancy) to 6-GHz RFR at 35 mW/cm² (whole-body SAR about 7 W/kg). This finding is consonant with the results of Berman et al. (1981) on pregnant rats exposed to 2.45-GHz RFR for 100 minutes daily at 28 mW/cm² (whole-body SAR 4.2 W/kg) on gestation days 6 through 15. The few cataracts seen in Fla offspring appear to be unrelated to RFR-exposure.

Merritt et al. (1984) concurrently exposed 10 pregnant Sprague-Dawley rats, each in a special circular waveguide, for 24 hours a day starting on gestation day 2 and ending on day 18, to circularly polarized pulsed 2.45-GHz RFR (8- μ s pulses at 830 pps) maintained at 0.4 W/kg as the mass of each dam increased with time. Ten similarly housed rats were sham-exposed. All 20 of the waveguides were in a room held at 24 ± 2 °C and 50-60% relative humidity.

On gestation day 18, the rats were euthanized and the fetuses were weighed, and each brain was weighed, homogenized, and assayed for RNA, DNA, and protein. The last three endpoints were shown in terms of both mg/brain

and $\mu\text{g}/\text{mg}$ of brain tissue (which, together with fetal and brain weight, totaled 8 endpoints). The difference between the groups for each of the 8 endpoints was nonsignificant ($p>0.05$).

Based on a linear regression analysis of mean litter brain weight on mean litter body weight and use of the criterion for microencephalous litters by Edwards (1969), no RFR-exposed litter was microencephalous.

Kaplan et al. (1982) sought possible effects of chronic exposure to RFR on mother-offspring behavioral patterns and the EEG in squirrel monkeys. They exposed 33 pregnant squirrel monkeys near the start of the second trimester to 2.45-GHz RFR in multimode microwave cavities at 0.034, 0.34, or 3.4 W/kg for 3 hours a day, 5 days a week, until parturition. Eight other pregnant monkeys were sham-exposed in the cavities for the same periods. After parturition, 18 of the RFR-exposed dams and their offspring were exposed to the RFR for 6 more months; then the offspring were exposed without the dams for still another 6 months. Two of the dams exposed at 3.4 W/kg and one dam exposed at 0.34 W/kg died, all within a day or two after parturition. Those dams comprised less than 10% of the total number exposed, but the authors remarked that similar deaths had not occurred in more than 250 pregnancies recorded during the five previous years in their squirrel-monkey colony. However, the percentages of live births among the various RFR groups were similar irrespective of RFR level, but unexpectedly the numbers of infant deaths were not comparable. All 8 control dams had live births, and none of the infants died subsequently.

The offspring were weighed weekly for the first 8 weeks of age, and then monthly until they were 1 year old. There were no significant differences in mean weights of the RFR and sham groups at any corresponding age.

The annual mortality rate during the first year of life for the 5 previous years of the colony averaged 20-25%, so the numbers of infant deaths at 0.034 and 0.34 W/kg were not atypical. However, the 4 deaths of the 5 infants in the 3.4-W/kg group exposed prenatally and postnatally were much larger than the normal mortality rate, and appeared to be a direct result of exposure to that level of RFR. As noted above, none of the 8 sham-exposed infants died during the study, which was also atypical for the colony, and comparison of the sham group with the 3.4-W/kg group by the Fisher exact probability test showed that the difference was statistically significant.

In all but one case, the infant deaths occurred without warning; each infant was found in its home cage in the morning. Necropsies had not been planned, and therefore were not performed on any of the adults, and were done on only 4 of the 9 dead infants. Because of autolysis, the cause of death could not be determined in any of those cases. However, as stated in a note added in proof to Kaplan et al. (1982), a followup study was done, with infant mortality as the major endpoint.

The exposure regimen was similar, but the numbers of dams were increased to provide greater statistical validity. Specifically, 31 dams were exposed in the microwave cavities used previously to 2.45-GHz RFR at 3.4 W/kg for 3 hours per day, 7 days a week, beginning in the first trimester of pregnancy, and 34 dams were sham-exposed. Following parturition, dams were similarly treated with their offspring for 6 months, after which offspring were treated alone through age 9 months. The authors did not provide any data, but stated

that the differences between RFR-exposed and control groups in the numbers of abortions, stillbirths, live births, or infants that subsequently died were not significant.

3.5 CONCLUSIONS ON NONHUMAN MAMMALS

It is interesting to note that all of the negative findings above were for rats. By contrast as noted previously, RFR-induced teratogenesis (growth retardation) in the mouse and hamster was reported, for example by Berman et al. (1982a, 1982b). This effect appears to have been thermally induced, a conclusion supported by the results of Inouye et al. (1982b) and Nawrot et al. (1981). These differences in response among the three species of rodents may be an indication that none is a satisfactory surrogate for humans with regard to possible RFR teratogenesis.

4 EPIDEMIOLOGIC STUDIES OF RFR AND CONGENITAL ANOMALIES

This section is wholly reproduced from a not-yet-published report entitled "Human Exposure to RFR: A Comprehensive Review Pertinent to Air Force Operations" (by the authors of the present report) that also discusses other papers on human exposure to RFR besides congenital anomalies.

Two studies were done that sought a possible relationship between the occurrence of Down's syndrome ("mongolism") and presumed exposure of the fathers to RFR from radars during military service. In the first study, Sigler et al. (1965) examined the data, derived from Baltimore hospital records and interviews with parents, on 216 Caucasian children with Down's syndrome. The case children were matched with 216 control children for hospital of birth (or birth at home), sex, and birthdate (within 6 months), and nearly all were matched for maternal age (within 1 year) at time of birth. Parents were also matched for birthplace, residence, and hospital treatment.

The exposure histories of the mothers were categorized as: diagnostic radiation excluding fluoroscopy, fluoroscopic examinations, radiation for therapy, and occupational contact. One statistically significant finding was that the percentage of case mothers that had received fluoroscopy before the birth of the case child was significantly higher than for the control mothers. The percentage of case mothers who had received at least one therapeutic radiation exposure (mostly for skin ailments) and the percentage of case mothers who had worked in a professional or technical capacity in medical fields were also significantly higher than for the control mothers.

The difference in the percentages of case and control fathers that had served in the military was nonsignificant, but a higher percentage of case fathers reported close association with radars as technicians or operators than the control fathers. The authors thus ascribed the higher incidence of Down's syndrome primarily to greater exposure of the case mothers to ionizing radiation, but concluded: "The only truly puzzling association is the suggested relationship between Mongolism and paternal radar exposure."

In the second study, Cohen et al. (1977) reexamined the data in the first study, denoted as the "Original Series," together with the data on 128 additional matched pairs denoted as the "Current Series". They concluded that the findings for the Current Series did not confirm the suggestions that the fathers of the children with Down's syndrome previously did have excess radar exposure or a larger proportion of military experience.

Peacock et al. (1971) endeavored to assess whether the incidence of birth defects in Alabama could be associated with proximity of military bases. They examined a state-wide file of birth certificates by counties and found an overall rate of 10.3 newborns with anomalies per thousand births, a rate that was comparable to those in other registries. However, a more detailed study of the data showed that there were 17 anomalies per thousand births for the military personnel in the six-county area surrounding Fort Rucker, whereas the anomaly rate for civilian births was only 6.8 per thousand.

Subsequently, Peacock et al. (1973) reassessed the premise, but with data spanning four years rather than the 17 months examined previously. Also, the data were corrected and rendered more accurate than previously, and a more precise test of the reliability of inferences was performed that did not rely on the questionable use of a normal approximation. After accounting for "non-radar" factors, the authors repeated the analyses for the Fort Rucker area and specifically for Lyster Hospital (within Fort Rucker). In addition, as a "control" test, they compared the fetal death anomaly rates in the military hospitals at Fort Rucker and Eglin Air Force Base (which they designated as "radar bases") with those of three military hospitals in bases with minimal radar networks.

The results of the retests confirmed that the total anomaly rate and the rates for several specific anomalies were abnormally high at Lyster Hospital. Also, the numbers of fetal deaths for Lyster hospital and the hospital at Eglin Air Force Base were comparable and "constitute evidence that the problem may be associated with radar".

Burdeshaw and Schaffer (1977) reexamined the original Alabama birth records, but compared the data for Coffee and Dale Counties (within which Fort Rucker is located) with the data from each of the other 65 counties in Alabama on a score and rank basis instead of the statewide averages. They found little evidence that the incidence of congenital anomalies in the Fort Rucker area was unusually high. The overall rate at Lyster Hospital was well within the expectations for hospitals having characteristics similar to those of Lyster. When the addresses of mothers of anomalous infants were plotted on county road maps, no significant clustering was found, notably in the vicinity of presumed radar sites. The increased incidence of congenital anomalies at Lyster Hospital was found to be attributable to a higher than normal reporting rate of one physician who apparently included "birth defects" not considered such by other physicians.

Thus, these negative findings superseded those of the two studies by Peacock et al. (1971, 1973).

Källén et al. (1982) hypothesized that physiotherapists (in Sweden) were likely to have been exposed occupationally more than the general population to various agents (chemicals, drugs, X-rays, RFR). To test this surmise, they did a cohort study on 2,043 infants born during years 1973 to 1978 to 2,018 women who were registered as physiotherapists during their pregnancies. By crosslinking files in two major computer-based registers, the authors were able to identify infants of mothers registered as physiotherapists at delivery time. They then analyzed this cohort for perinatal mortality and the presence of malformations by comparing the data with information on all deliveries in the Swedish Medical Birth Register.

The results showed that for all endpoints, the expectation values for the total cohort were statistically better than, or comparable to, those for the general population. The authors noted that this excellent outcome could have been the result of a "healthy worker" effect, so they hypothesized that if hazardous exposure had occurred, it should be more common among the few females who had dead or malformed infants than among those who had normal babies. Accordingly, they did a case-control study within the cohort, in which they selected 37 infants who had major malformations or those that did not but had died perinatally. Each malformed or dead infant was compared with two normal infants matched for maternal age, parity, and season of delivery (to compensate for work seasonality). Exposures for case and control mothers were estimated from the answers to a questionnaire that asked (in part):

"Did you, during the pregnancy, work with or in close proximity to the following:

Shortwave equipment: daily/often/seldom/never
Microwave equipment: daily/often/seldom/never
Ultrasonic equipment: daily/often/seldom/never
X-Ray equipment: daily/often/seldom/never
Electrostimulator: daily/often/seldom/never

"Did you use hexachlorophene-containing soap (e.g., Phisoex):
daily/often/seldom/never"

On careful review and interpretation of the results, the authors concluded that the physiotherapists as a group had a slightly better-than-expected outcome for perinatal deaths and major malformations than did the general Swedish population for the same period. They did report that the use of shortwave equipment was higher among those who gave birth to a malformed or perinatally dead infant. However, it is noteworthy that those results would change from borderline significance to nonsignificance if one or two answers to the questionnaire were based on faulty recall.

Thus, the Källén et al. (1982) study actually yielded fewer dead or malformed infants of physiotherapists presumed to have been occupationally exposed to various agents than in the general population. The data base for the cohort part of the study was large, yielding statistically credible negative findings. However, the use of a questionnaire in the case-control part renders questionable the finding of a possible weak association of malformed or perinatally dead infants with the use of shortwave equipment.

Taskinen et al. (1990) did a study of all registered physiotherapists in Finland who had become pregnant during the study period, to determine whether their occupational exposure to various patient-treatment modalities, including RFR, is associated with spontaneous abortion or congenital malformations in their offspring. The subjects were those who had been treated for spontaneous abortion during 1973-1983 or had a malformed child during 1973-1982.

Data were obtained on ultrasound exposure, exposure to shortwaves, and physical exertion from the responses to questionnaires mailed to 1329 female physiotherapists. Selected initially were three age-matched controls ($\pm$ 18 months) for each abortion case and five controls for each malformation case.

One pregnancy per woman was randomly chosen for study. Traced were 1020 of 1047 women (275 cases and 745 controls) for the spontaneous-abortion aspect, and responses were obtained from 247 cases and 693 controls. After removal of unrecorded pregnancies, the final spontaneous-abortion populations were 204 cases and 483 controls. Similarly traced were 309 of 314 physiotherapists for the congenital-malformation aspect (51 cases and 258 controls), of whom 47 and 227 responded. The final congenital-malformation populations were 46 cases and 187 controls.

For assessing exposures of the therapists, the authors classified the equipment used in treating patients by mode of action: They characterized the intermittent or continuous use of electromagnetic shortwave equipment, usually at 27.12 MHz, as "deep heat therapy" because of the deep penetration of such waves into tissues. [Note: the wavelength equivalent of 27.12 MHz is 1106.19 cm, not 12.2 cm mentioned by the authors.] Ultrasound exposure at frequencies in the range 0.5-3 MHz was analyzed separately because the therapist usually holds the ultrasound applicator in her hand throughout the treatment session. Various electric-current treatments for pain (listed as transcutaneous nerve stimulation, diadynamic currents, electrogalvanic stimulation, interference current, laser?) and for activation of muscles were grouped together, as were the various types of equipment that produce superficial heat ("hydrocollator" packages, infrared, ultraviolet). Exposure duration was defined as the amount of time the therapist handled the operating equipment while standing close to it (at distances of 1 meter or closer).

The authors used linear logistic regression for individually matched data, and evaluated significance in terms of odds ratios (ORs) relative to estimates based on a normal distribution. The 95% confidence intervals (CIs) were calculated from the standard errors of the estimates. Significance for homogeneity of the ORs relative to pregnancy duration was determined by using a dummy variable to separate the cases with gestation times of 10 weeks or shorter from those with gestation times exceeding 10 weeks, and including the interaction of that variable with the exposure variable in the logistic model.

From the data gathered, ultrasound exposure was most often reported (115 cases and 256 controls). Analysis showed that handling ultrasound equipment for at least 20 hours per week increased the risk of spontaneous abortion significantly ($p < 0.05$): OR = 3.4; CI = 1.2-9.0, but those subpopulations were small (9 cases and 8 controls). Also, exposures for less than 20 hours a week (106 cases and 248 controls) yielded ORs slightly exceeding 1.0 but with CIs that spanned 1.0. Administering electric therapies for at least 5 hours per week also showed a significant increase of spontaneous-abortion risk: OR = 2.0; CI = 1.0-3.9. Physical exertion by the therapists was the only other factor that showed a significant increase ($p < 0.05$) of spontaneous-abortion risk. Specifically, heavy lifting (weights exceeding 10 kg) and/or transfer of patients 50 or more times a week yielded an OR of 3.5 and CI of 1.1-9.0. The extent of massage or mobilization therapy given by therapists had no influence on spontaneous-abortion risk.

For deep-heat therapy overall and spontaneous abortion, the OR for 1-4 hours a week was 1.2 with a CI of 0.8-1.9, but was 1.6 with a CI of 1.0-2.7 for 5 or more hours a week (not labeled significant by the authors). As shown, this treatment class consisted of shortwaves and microwaves, but the authors did not provide any information about the microwave frequencies or any

other details regarding such exposures. The ORs for each modality exceeded 1.0, but the CIs spanned 1.0 for both 1-4 hours per week and 5 or more hours per week of usage.

From the analysis by pregnancy duration, heavy lifting during pregnancy durations of 10 weeks or shorter was the only factor that contributed to a significant risk for spontaneous abortion: OR = 3.8 ($p < 0.05$, no CI shown). On the other hand, for pregnancy durations exceeding 10 weeks, significant risks were indicated for using deep-heat-therapy equipment (including those emitting shortwaves) for 5 or more hours a week (OR = 2.6, $p < 0.01$), and specifically for shortwaves (OR = 2.5, $p < 0.01$). Similarly, the results for ultrasound and for infrared heating for 10 or more hours a week were respectively: OR = 3.4, $p < 0.01$ and OR = 1.7, $p < 0.05$. As discussed below, the authors regarded these results and the absence of significant risk increases for pregnancy durations 10 weeks or shorter as indicative of a dose-response relationship. Heavy lifting was a significant factor again, but for both ranges of pregnancy duration ($p < 0.05$).

The homogeneity analysis of the ORs with respect to the two pregnancy-duration ranges yielded $p < 0.05$ for the deep-heat therapies as a class, $p < 0.05$ specifically for shortwaves, and $p < 0.01$ for the ultrasound therapy. However, a univariate analysis of possible confounding factors showed that spontaneous abortion was significantly associated with failures of the contraceptive devices used by the women (OR = 2.0, CI = 1.0-3.7; $p < 0.05$), as were previous spontaneous or induced abortions (OR = 1.8, CI = 1.0-3.1; $p < 0.05$).

The results for congenital malformations (46 cases and 187 age-matched controls) showed a significant increase in risk for administering deep-heat therapy: OR = 2.4, CI = 1.0-5.3; $p < 0.05$ for 1-4 hours per week but not for 5 or more hours a week: OR = 0.9, CI = 0.3-2.7. Specifically for shortwaves, the results for 1-4 hours per week were significant (OR = 2.7, CI = 1.2-6.1; $p < 0.05$), but were nonsignificant for 5 or more hours a week (OR = 1.0, CI = 0.3-3.1). The authors suggested that bias due to selective recall cannot be excluded in this part of the study but they discounted such bias in the spontaneous-abortion part.

The only other modality that indicated a significant risk increase of congenital malformations was for transcutaneous nerve stimulation for more than 5 hours a week (OR = 4.7, CI = 1.2-18.7, $p < 0.05$). No significant risk increase was seen for congenital malformations from the use of microwaves (OR = 0.5, CI = 0.1-3.9).

The authors concluded: "The results of this study suggest that heavy physical exertion is a risk factor for spontaneous abortion. The effect of shortwaves and ultrasound on the 'late' spontaneous abortions was significant and increased in a dose related manner. On the other hand, in the multivariate analyses neither the effects of ultrasound nor shortwaves reached statistical significance. Therefore, the finding has to be interpreted cautiously. The finding of an association between the exposure to shortwaves and congenital malformations does not justify conclusions of a causal relationship."

The authors are rightly cautious in interpreting their findings; as in other studies, responses to questionnaires are often unreliable. Based on the high and similar response rates for the cases and controls in the spontaneous-

abortion part of the study, the authors remarked that selective participation was not likely. However, they suggested that selective reporting or recall bias could be excluded as well in that part of the study because of "dose-response relationships, effects of gestational length, differences in results between spontaneous abortions and malformations (because bias should affect them in the same way), and uniformity of effects between the two periods analyzed". In the absence of any data on exposure levels and their variations with time and patient-treatment site, the authors' use of the term "dose" as in "dose-response relationships" is meaningless quantitatively, and their remarks about the other points in the quotation above are obscure at best. Thus, at least with regard to RFR, little if any credence can be given to either the positive or negative findings of this study.

Larsen et al. (1991), noting a small cluster of four malformed newborns of Danish physiotherapists exposed to RFR during pregnancy [Larsen (1991)], conducted a study to determine possible reproductive hazards among female physiotherapists from RFR-exposure. The subjects were members of the Union of Danish Physiotherapists (UDP) born after 1932 and registered with the UDP in 1978 or later who delivered or miscarried between 1978 and 1985. They were identified by linkage of the UDP file to the Danish register of births and medical registers of abortions. The information gathered consisted of all spontaneous abortions treated in hospitals and all deliveries during that period, and included data on induced abortions, gestation durations, births, birthweights, gender, perinatal deaths, places of birth, and mothers' ages. Twins and induced abortions were excluded from the study.

One of the authors interviewed the subjects by telephone about exposure to RFR during pregnancy and about confounding factors without prior knowledge of the outcome of the pregnancies. The only pregnancy-outcome datum obtained from the interviews was the "time to pregnancy" (the time from the last use of contraception to first recognition of pregnancy). However, information was gathered on some potential confounders, notably the consumption of medicine, tobacco, and alcohol during pregnancy, and serious acute or chronic diseases during pregnancy.

The cases studied consisted of five overlapping groups: (i) spontaneous abortion before the 29th week, (ii) subfecundity (waiting time to pregnancy exceeding six months), (iii) low birthweight (<2500 g), (iv) prematurity (birth before the 38th week), and (v) stillbirth or death within the first year. The reference group for the first case group consisted of a random sample of all births, and the reference group for the other four case groups was the same sample minus any actual cases.

Exposures during the first month of pregnancy were assessed based on two categories: (1) from the main work tasks during the day: manual physiotherapy, electrotherapy (ultrasound, short-wave diathermy), administrative work, and teaching; (2) characterizing the exposure to high-frequency electromagnetic radiation (use of different types of electrodes, time spent in the short-wave room, frequency of short-wave use in the clinic, and direct versus indirect exposure, with indirect exposure defined as for a woman within 1 meter from a diathermy unit operated by a colleague). The emission from the electrodes were scored as: 0 for circuplade- or no exposure, 1 for dipole exposure, and 10 for plate-electrode exposure. Independently of the data analysis, a time-weighted exposure index was formed *a priori* from the product of the score for

the electrodes used, frequency of short-wave use, and total time spent in the short-wave room. The index was divided arbitrarily into three categories: 0 for no exposure, 1 for low exposure, and 2 for high exposure.

The major positive finding was an unexpected low ratio of boys to girls for those physiotherapists exposed to high-frequency radiation. Specifically, there were 107 boys and 71 girls born to physiotherapists in category 0; the OR was said to be 1.0 relative to the reference sample (a nonsignificant difference). However, 11 boys and 23 girls were born to the category-1 physiotherapists; the OR was 3.2 with a CI of 1.5-7.1. Also, 4 boys and 13 girls were born to the physiotherapists in category 2; the OR was 4.9 with a CI of 1.6-7.9. The latter two ORs were significant. The authors noted that there was a difference in the male/female gender ratio between the study base ($52.6/47.4 = 1.11$) and the general population ($51.4/48.6 = 1.06$), but that the decrease in gender ratio would still be significant.

The results for spontaneous abortions, subfecundity, stillbirth or death within one year, prematurity, and low birthweight yielded ORs nonsignificantly different from 1.0. The possible confounding factors cited above apparently did not contribute to the findings of this study.

It is noteworthy that the data on gender ratio indicated sensitivity to the type of electrodes used: the OR was 2.1 with a CI of 0.6-7.5 for exposure with diode electrodes, and 2.8 with a CI of 1.5-5.5 for plate electrodes. Also, the type of exposure was important: the OR for direct exposure solely was 2.2 with a CI of 0.9-5.6, but was 2.8 with a CI of 1.0-8.5 for indirect exposure.

The statistical treatments of the data in this study were extensive, but as with other epidemiologic studies, the absence of measurements of the actual RFR levels to which the physiotherapists were exposed and the vague estimates of exposure durations vitiate the credibility of the single positive finding, as well as the negative findings. In addition, as remarked by the authors, the results are based on sparse data and must be interpreted with caution.

Ouellet-Hellstrom and Stewart (1993) mailed questionnaires to 42,403 female physical therapists in 1989 whose names were obtained from the American Physical Therapy Association, to assess for possible effects of occupational use of microwave and shortwave diathermy at conception time, and specifically whether an excess risk of miscarriage was associated with exposure to RF and microwave radiation just before conception or during the first trimester of pregnancy. Information was sought on infertility, use of oral contraceptives, smoking during pregnancy, and outcome of all pregnancies, the latter including questions on any birth conditions diagnosed during the first 5 years of life and any cancers ever diagnosed. Also sought was information about the age and race of the women. Complete information was requested only from women who had ever tried to or did become pregnant.

Questions regarding occupational exposures included: a complete work history (employer, date of employment, position held), use of therapeutic treatment modalities in general, and use of various modalities and chemicals during the first two trimesters of pregnancy. For each reported occupation, precoded responses were used to elicit information on the frequency of usage of specific treatment modalities (infrared radiation, whirlpool, Hubbard tank,

electrical stimulation, transcutaneous nerve stimulation, microwave diathermy, shortwave diathermy, and ultrasound). Other questions asked were on the use of electric blankets, the father's occupation, and any health conditions ever diagnosed in the mother.

To ascertain possible response bias and the reasons for nonresponse, an attempt was made to interview a sample of 500 nonrespondents by telephone for data similar to those from the respondents. Also sought was a brief history of their pregnancies, including the total number, the number of live births, the years of first and last births, and the number of pregnancies incurred while working; and the mother's race and date of birth. Of those 500, 259 were reached and agreed to provide data, and 187 of them were regarded as eligible.

A nested case-control design was used. The authors noted that because of resource constraints, only the questionnaires of respondents who reported ever using microwave or shortwave diathermy (6,684 or 57% of the respondents) were completely edited and processed. Also noted was that "ever exposed" does not imply exposure only just prior to or during any one pregnancy, but meant that all women who had ever used such diathermy were included.

All recognized first-trimester miscarriages (except ectopic pregnancies) reported by those 6,684 respondents were defined as case pregnancies (1,791 of 14,989 pregnancies). Excluded were 38 cases for which the mother's date of birth and date of conception or last menstrual period were missing, leaving a total of 1,753 case pregnancies. These cases were matched with 1,753 control pregnancies, selected from all pregnancies irrespective of pregnancy outcome (excluding ectopic pregnancies). The overall mean difference in maternal age at birth between cases and controls was 1.9 ± 5.6 (SD) months and the mean difference between them in the time interval between conception and interview was 4.4 ± 7.2 months. The authors remarked that some mothers contributed one case pregnancy only and others one control pregnancy only, but that others contributed one case and one control pregnancy, two case pregnancies, two control pregnancies, three or more case pregnancies, or three or more control pregnancies.

Case and control therapists who had not worked during the 6 months prior to and during the first trimester were classified as unexposed. Therapists of each group were classified as exposed if they had been working and reported using microwave or shortwave diathermy during that time interval. The authors noted that most of the therapists had reported using more than one treatment modality on the same job. Specifically, more than 78% of those who had used microwave diathermy and 64% of those who had used shortwave diathermy had reported using at least four other modalities, rendering it impossible to stratify the analyses by the use of a single modality.

The unconditional odds ratios for an association of miscarriage risk and reported exposure to microwave diathermy are shown in Table 16 (adapted from Table 3 of the paper), stratified with respect to the number of reported exposures per month. Of the 1,759 pregnancies in each group, there were 209 cases (11.9%) and 167 controls (9.5%) who had any exposure.

**TABLE 16: UNCONDITIONAL ODDS RATIOS FOR AN ASSOCIATION OF MISCARRIAGE RISK AND
REPORTED EXPOSURE TO MICROWAVE DIATHERMY**
[Ouellet-Hellstrom and Stewart (1993)]

<u>No. of exposures per month</u>	<u>Case pregnancies</u>	<u>Control pregnancies</u>	<u>OR (95% CI)</u>
<u>All Pregnancies</u>			
0	1,459	1,494	1.00
<5	88	86	1.05 (0.77-1.43)
5-20	72	49	1.50 (1.04-2.17)
>20	45	29	1.59 (0.99-2.55)*
Total no. exposed†	209	167	1.28 (1.02-1.59)
<u>No Prior Fetal Loss</u>			
0	1,102	1,258	1.00
<5	71	76	1.07 (0.78-1.49)
5-20	58	47	1.41 (0.95-2.09)
>20	34	25	1.55 (0.92-2.61)**
Total no. exposed†	167	151	1.26 (1.00-1.59)

†All exposed women, including those who reported using microwave diathermy at the time of pregnancy but did not report their level of exposure. Exposure status was unknown for 85 cases and 95 controls.

*Chi² test for trend: $p < 0.005$.

**Chi² test for trend: $p < 0.01$.

The authors remarked that for all pregnancies, the OR increased with the number of exposures and that by the chi² test, the trend was statistically significant. However, the 95% CI for the most exposure durations (more than 20 hours a month) encompassed 1.00, rendering that OR value nonsignificant. In addition, the CI for the cases and controls with less than 5 hours a month encompassed 1.00 as well. For the cases and controls with no previous fetal loss (Table 16), the total OR was 1.26 but all of the CIs encompassed 1.00. The results for exposure to shortwave diathermy were similarly shown in the paper. All of those CIs encompassed 1.00 and the authors found no significant trend with increasing number of exposures. Thus, the authors concluded that the women were at increased risk of miscarriage from reported use of microwave diathermy six months prior to and during the first trimester of pregnancy, but not from shortwave diathermy.

The positive findings of this study are dubious, because the percentages of exposed cases and controls were too small yield much statistical power. Also, no estimates were presented regarding the levels of exposure to the RFR from either of the diathermy modalities. Third, as the authors stated, the use of other modalities by the therapists could not be stratified adequately. This conclusion applies as well to any of the negative findings in this study.

4.1 SUMMARY

The findings of the various studies on RFR and congenital anomalies are summarized in Tables 17A-17C.

Authors	Effects Sought or Examined	Exposure Modality	Effects Reported	Notes & Comments
Sigler et al. (1965)	Down's syndrome in children of mothers nonoccupationally exposed to ionizing radiation, and those with occupational fluoroscopic exposure in medical practice.	Exposure of mothers to ionizing radiation and radar exposure of fathers.	The percentage of case mothers who had received fluoroscopy before childbirth was significantly higher than control mothers, but the percentage of case fathers who reported close association with radars was also significantly higher than control fathers.	See Cohen et al. (1977) below.
Cohen et al. (1977)	Down's syndrome. See Sigler et al. (1965).	Radar exposure of fathers.	This study of the larger data base found no association of Down's syndrome with radar exposure of fathers.	These authors augmented the number of matched case-control pairs in Sigler et al. (1965).
Peacock et al. (1971)	Birth defects. The authors examined Alabama-wide birth records by county over a period of 17 months.	Proximity to military bases.	The authors found a higher percentage of newborns with anomalies for the military personnel in the 6 counties surrounding Fort Rucker than for the civilians.	See Burdeshaw and Schaffer (1977) below.
Peacock et al. (1973)	Birth defects. The authors used more accurate data spanning 4 years, and used better statistical treatment.	Proximity to military bases. The authors compared data for military hospitals at Fort Rucker and Eglin AFB with non-radar bases.	Abnormally high anomaly rates were found at Lyster Hospital (within Fort Rucker) and the military hospital at Eglin AFB; the authors associated this finding with radar exposure.	See Burdeshaw and Schaffer (1977) below.
Burdeshaw and Schaffer (1977)	Birth defects. These authors reexamined the original Alabama birth records but compared the data for the 2 counties encompassing Fort Rucker with the other 65 Alabama counties on a score and rank basis rather than by statewide averages.	Proximity to military bases.	The overall anomaly rate was found to be within expectations for hospitals like Lyster; no significant clustering of anomalies was found in the vicinity of the presumed radar sites.	The reported higher incidence of congenital anomalies at Lyster Hospital was found to be attributable to a higher than normal reporting rate of one physician who apparently included "birth defects" not characterized as such by other physicians.

TABLE 17A: RFR AND CONGENITAL ANOMALIES

Authors	Effects Sought or Examined	Exposure Modality	Effects Reported	Notes & Comments
Källén et al. (1982)	Perinatal mortality and birth defects in infants of female physiotherapists in Sweden.	Occupational exposure of physiotherapists to various treatment modalities.	For the total cohort, the expectation values for all of the endpoints were statistically better or comparable to those for the general population, a finding the authors hypothesized as a "healthy worker" effect. In a case-control study within the cohort, the authors matched two normal infants with each dead or malformed infant, and estimated the exposures of the mothers to various occupational modalities from their responses to a questionnaire. The only possible association with RFR-exposure was authors' report that the use of shortwave equipment was higher by mothers of a dead or malformed infant.	The shortwave-equipment finding was of borderline statistical significance. However, use of responses to a questionnaire is questionable because of self-selection by the respondents. Thus, the finding above is of doubtful validity.
Taskinen et al. (1990)	Spontaneous abortions or birth defects in infants of Finnish physiotherapists.	Patient treatments with ultrasound (0.5-3 MHz); "deep-heat therapy" (including "shortwaves" [27.12 MHz] and "microwaves" [not characterized]); electric-current modalities; and physical exertion.	Significant increases of spontaneous-abortion risk were found for: ultrasound use more than 20 hours a week, electric-current therapies more than 5 hours a week, and heavy lifting or frequent transfers of patients. No significant risk increase of spontaneous abortion was found for deep-heat therapies (shortwaves or microwaves). Regarding congenital malformations, a significant risk increase was reported for deep-heat therapies for 1-4 hours per week but not for 5 or more hours a week, results likely due to selective recall bias.	Statistical treatment of the response data was reasonably extensive, but absent were any data on exposure levels to the various treatment modalities and their variations with time and patient-treatment site. Thus, at least with regard to RFR, little if any credence can be given to either the positive or negative findings of this study.
Larsen et al. (1991)	Possible reproductive hazards among female physiotherapists in the Union of Danish Physiotherapists from RFR-exposure.	Exposures to short-wave diathermy (and to ultrasound and the performance of other duties) during the first pregnancy month were assessed, and an a priori diathermy-exposure index was formed.	Data for 1978-1985 on spontaneous abortions, gestation durations, low birth weights, premature births, stillbirths, gender, and deaths within 1 year were analyzed. Twins and induced abortions were excluded from the study. The odds ratios for "subfertility" (waiting time to pregnancy more than six months), spontaneous abortion, stillbirth or death within 1 year, premature birth, and low birth weight did not differ significantly from 1.0. The sole positive finding was a low ratio of boys to girls for those presumed exposed to RFR from diathermy.	As with other epidemiologic studies, lack of measurements of the RFR-exposure levels and vague estimates of exposure durations diminish the credibility of the single positive finding, as well as of the negative findings. Moreover, as noted by the authors, the results are based on sparse data and must be interpreted with caution.

TABLE 17B: RFR AND CONGENITAL ANOMALIES (CONTINUED)

Authors	Effects Sought or Examined	Exposure Modality	Effects Reported	Notes & Comments
Ouellet-Hellstrom and Stewart (1993)	Possible reproductive hazards among female physiotherapists listed in 1989 by the American Physical Therapy Association from occupational use of microwave or shortwave diathermy.	Exposures from treating patients with microwave or shortwave diathermy of frequencies not stated and from use of other modalities and chemicals, just before or during the first trimester of pregnancy.	Tabulated were the odds ratios (ORs) and 95% confidence intervals (CIs) for an association of miscarriage risk and exposure to microwave and shortwave diathermy. For microwaves, 209 of 1,759 (11.9%) case pregnancies and 167 of 1,759 (9.5%) control pregnancies had any exposure. Those data were shown in terms of <5, 5-20, and >20 exposures a month. The respective ORs and CIs were 1.07 (0.77-1.43), 1.41 (1.04-2.17), and 1.55 (0.99-2.55), for overall values of 1.28 (1.02-1.59). The authors stated that by the chi-square test, the trend in OR increase with exposure was significant ($p < 0.005$). However, the CI for the most exposure durations (more than 20 hours a month) encompassed 1.00, rendering that OR value nonsignificant. Similar results were displayed for 167/1102 cases and 151/1258 controls who had no prior fetal losses. For shortwaves, all of the CIs spanned 1.00, with no significant trend with increasing exposure. Thus, the authors concluded that women were at higher miscarriage risk from administering microwave diathermy during their first trimester of pregnancy, but not from shortwave diathermy.	Of 6,684 respondents to mailed questionnaires, 1,753 case pregnancies were selected from those who had first-trimester miscarriages. Those cases were matched with 1,753 control pregnancies selected from all pregnancies irrespective of outcome. Some of the women selected had reported only 1 case pregnancy and others only 1 control pregnancy, but still others contributed 1 each case and control pregnancy, 2 case pregnancies, 2 control pregnancies, 3 or more case pregnancies, or 3 or more control pregnancies. The positive findings of this study are dubious, because the percentages of exposed cases and controls were too small to yield much statistical power. Second, the authors gave no estimations on RFR-exposure levels for either of the diathermy modalities. Third, as the authors stated, the use of other modalities could not be stratified adequately. This conclusion applies as well to any of the negative findings in this study.

TABLE 17C: RFR AND CONGENITAL ANOMALIES (CONCLUDED)

4.2 CONCLUSIONS ON HUMAN EXPOSURE TO RFR

Although Sigler et al. (1965) had reported finding an association of Down's syndrome in children with RFR-exposure of the fathers, a study by Cohen et al. (1977) of a larger data base did not confirm that association. Peacock et al. (1971, 1973) had reported the incidence of a higher percentage of neonates with anomalies for military personnel at "radar" bases than at non-radar bases, but a more encompassing study and use of a better statistical treatment by Burdeshaw and Schaffer (1977) failed to confirm that finding.

It is noteworthy that in a study by Källén et al. (1982) of infants of Swedish physiotherapists, the authors had found better outcomes on all of the endpoints for their exposed cohort than their controls, which they ascribed to a "healthy worker" effect. On the other hand, they also noted that the use of shortwave equipment was higher by mothers of a dead or malformed infant, but that finding was of borderline statistical significance and otherwise open to serious question. Taskinen et al. (1990) sought possible increases in risk of spontaneous abortion or congenital abnormalities for physiotherapists who treated patients with various modalities, including "shortwaves" (27.12 MHz) and "microwaves" (frequencies or other characteristics not indicated). The findings were mixed, but little if any credence can be accorded to either the negative or positive findings because of lack of quantitative exposure data and the likelihood of recall bias in the responses to questionnaires. A study by Larsen et al. (1991) of pregnancy outcomes of Danish physiotherapists yielded only one positive finding, a lower than expected ratio of neonate boys to girls, but the data were sparse and the descriptions of the exposures to short-wave (diathermy) RFR were vague. Ouellet-Hellstrom and Stewart (1993) studied pregnancy outcomes of physiotherapists, listed in 1989 by the American Physical Therapy Association, who treated patients with microwave or shortwave diathermy (or other modalities) just before or during the first trimester of pregnancy of the therapists. The authors reported a trend toward increasing risk of miscarriage with frequency of microwave-diathermy use, but no such trend for shortwave-diathermy use. However, both the positive and negative findings of this study are dubious, because of the small numbers of cases involved, the absence of any information on the RFR frequencies or exposure levels, and the inability to separate the effects of the various modalities from one another. It is noteworthy that the findings of Ouellet-Hellstrom and Stewart (1993) of a significant trend of increasing risk for those who used microwave diathermy and no such trend for shortwave diathermy are opposite to the findings of Källén et al. (1982).

Thus, collectively those studies provide no scientifically credible evidence that chronic exposure of mothers during pregnancy or of fathers to RFR at levels at or below the ANSI/IEEE (1992) maximum exposure guidelines would cause any anomalies in their offspring.

5 OVERALL CONCLUSIONS

Most of the teratogenic investigations with animals were done with RFR levels well in excess of the ANSI/IEEE (1992) maximum exposure guidelines. Taken collectively, those studies indicate that teratogenic effects can occur in both nonmammalian and mammalian subjects from RFR exposure only at levels that produce significant bodily temperature rises. For mammals, increases in maternal body temperature that exceed specific thresholds (for each species)

are necessary for causing teratogenic effects; such temperature increases would not occur for exposure to RFR at or below those ANSI/IEEE (1992) guidelines. It is noteworthy that mice appear to be more susceptible than rats to RFR-teratogenic effects, but because of such major differences in experimental findings among the two rodent species, neither one may be adequate surrogates for humans in investigating RFR teratogenesis.

None of the epidemiologic studies of possible congenital anomalies provide credible evidence that chronic exposure of mothers during pregnancy or of potential fathers to RFR at levels at or below the ANSI/IEEE (1992) maximum exposure guidelines would cause any anomalies in their offspring.

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