

Overview of RF Genotoxicity Research

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WHAT IS GENOTOXICITY?

- **An alteration in the DNA of a cell (which may or may not be detectable using currently available methods)**
- **Provides evidence that the agent has reached the DNA molecule, either directly or through some indirect mechanism, so that damage of the DNA can occur**
- **Any such damage may or may not be repairable, and the repair process (needed for survival) may or may not result in errors in the repaired DNA which are inheritable**
- **The damage (and its repair) could occur in regions of the DNA which are never expressed (or function) in that cell, or in its daughter cells.**
- **The damage could result in a dead cell, with or without additional cell divisions occurring before the death occurs (Interphase vs. Reproductive death)**

Relevance to Human Health

- **Inherited mutations**
 - mutations in sperm and oocytes passed on to future generations
- **Initiation of cancer**
 - in the persons exposed

TYPES OF MEASURABLE GENOTOXIC DAMAGE APPLIED TO EMF STUDIES

- **DNA Single Strand Breaks (SSBs)**
- **DNA Double Strand Breaks (DSBs)**
- **Chromosome Aberrations (CAs)**
- **Micronuclei (MN)**
- **Sister Chromatid Exchanges (SCEs)**
- **DNA Base Damage**
- **DNA-DNA Crosslinks**
- **DNA Repair Synthesis (and the inhibition thereof)**
- **Phenotypic Mutation**
- **Other**

TYPES OF DNA CHANGES/DAMAGES THAT RESULT IN THE MEASURABLE ENDPOINTS

- **Breaks in DNA backbone sugar-phosphate linkages**
- **Base changes**
- **Base deletions**
- **Base insertions**
- **Frame shift mutations**
- **Small DNA sequence deletions**
- **Gene amplification**
- **Errors in DNA repair**
- **Chromosome Instability**
- **Other**

DNA Strand Breaks After RF Exposure

Freq. MHz	PW/C W Modul.	SAR W/Kg	Expos. Durat.	Cell Type or Tissue	Temp. During Expos.	Endpoint	Result	Reference
2450	CW PW 500pps 2 μ s	0.6 Whole Body; 0.5 –2.0 Brain	2 hr	Sprague-Dawley Rat: Hippocampus Total brain cells		DNA SSBs	Increased migration 2 & 4 hr post-CW exposure; Increased migration only at 4 hr post-PW exposure	Lai and Singh (1995)
2450	CW	1.2	2 hr	Sprague-Dawley Rat: Brain cells		DNA SSBs	No increase at either 2 or 4 hr post-	Malyapa et al (1998)
935.2	GSM	0.3 – 0.4	2 hr	Human blood lymphocytes	Not Stated	DNA SSBs	No SSBs immediately after exposure	Maes et al (1997)
2450	CW	0.7, 1.9	2, 4, or 24 hrs	Human U87MG glioblastoma/ C3H 10T1/2 fibroblasts	37 °C	DNA SSBs	No increase immediately and 4 hr post-exposure	Malyapa et al (1997a)
835.62 847.74	FMCW CDMA	0.6	2,4,or 24 hrs of RF exposure	Human U87MG glioblastoma/ C3H 10T1/2 fibroblasts	37 °C	DNA SSBs	No increase immediately after the 2, 4, or 24 hr exposures	Malyapa et al (1997b)
2450	PW 10 KHz 10 μ s	2.14 (mean)	2 hr	Human blood lymphocytes	36.9 °C	DNA SSBs	No increase immediately and 4 hr post-exposure	Vijalaxmi et al (2000)
847.74 835.62	CDMA FDMA	3.1 – 5.1	2,4,or 24 hrs of RF exposure	C3H 10T1/2 mouse fibroblasts	37 °C	DNA SSBs	No increase immediately after the 2, 4, or 24 hr exposures; No incr. 4 hr after the 2 hr exposure	Li et al (2001)
1900	CW	0.1, 0.26, 0.92, 2.4, and 10	2 hr	Human blood leukocytes	37 °C	DNA SSBs	No increase immediately after the 2 hr exposure	McNamee et al (2002a)
1900	PW 50 Hz, 1/3 duty factor	0.1, 0.26, 0.92, 2.4, and 10	2 hr	Human blood leukocytes	37 °C	DNA SSBs	No increase immediately after the 2 hr exposure	McNamee et al (2002b)

Chromosome Aberrations (CAs) After RF Exposure

Freq.	PW/CW Modul.	Power Density	SAR W/Kg	Expos Durat	Cell Type	Temp During Expos	Endpoint	Result	Reference
2450	PW 25,000 pps 10 μ s	49 mW/cm ²	33.8	2 hr	CHO	37 °C to max. 40.2 °C	Chromatid and Chromosome gaps and breaks, terminal chromatid deletion., rings, dicentrics, minutes, complex rearrangements, fratgments	No increase vs Temp Control	Kerbacher et al (1990)
2450	PW 25,000 pps 10 μ s	49 mW/cm ²	33.9	2 hr	CHO	37 °C to max. 40.2 °C	Adriamycin or MMC induced: Chromatid and Chromosome gaps and breaks, terminal chromatid deletion., rings, dicentrics, minutes, complex rearrangements, fratgments	No increase vs Temp Control	Kerbacher et al (1990)
2450	CW		12.5	90 min Inter- mit.	human blood lympho- cytes	37 °C to max. 39 °C	Chromosome Aberrations	No increase	Vijalaxmi et al (1997a)
847.74	CDMA		4.9 or 5.5	24 hr	“	37 °C	Chromosome Aberrations	No increase	Vijalaxmi et al (2001a)
835.62	FDMA		4.4 or 5.0	24 hr	“	37 °C	Chromosome Aberrations	No increase	Vijalaxmi et al (2001b)
935.2	GSM CDMA		0.3 – 0.4	2 hr	“	Not stated	Chromosome Aberrations	No increase	<u>Maes et al (1997)</u>
455.7			6.5	2 hr	“	17 °C ?	Chromosome Aberrations	No increase	Maes et al (2000)
900 MHz	GSM		0.4 - 10	2 hr	“	Not stated	Chromosome Aberrations	No increase	Maes et al (2001)

Note: The papers by Garaj-Vrhovac et al (1990, 1991, 1992) are often referred to as demonstrating the induction of chromosome aberrations. The articles are extremely deficient in detail, so that one cannot understand how the experiments were done. They are therefore not presented here.

Micronucleus (MN) Formation After RF Exposure

Freq. MHz	PW/C W Modul.	SAR W/Kg	Expos. Durat.	Cell Type	Temp. during Expos.	Endpoint and Result	Reference
837 837 837 1909.8	Analog TDMA CDMA PCS	1, 5 or 10	3 or 24 hr	Human blood leukocytes and lympho- cytes	37 °C	No MN induction at 3 hr, any SAR or signal: For all signals at 10 W/Kg and 24 hr Exp., increase in MN; For TDMA and analog at 837, increase MN also at 5 W/kg	<u>Tice et al (2002)</u>
2450	CW	1.0	20 hr/dy 7 dy/wk 18 mo	Bone marrow and peripheral blood PCEs from RF exposed C3H/HeJ Mice		At termination of the animals (but not in the animals with tumors), a statistically signif. 1 in 2000 PCE increase in MN observed	<u>Vijayalaxmi et al (1997b, 1998)</u>
1748	GMSK	Max. Apprx 5 (??)	15 min	Human blood lympho- cytes	Temp. increase from 35.0 to 35.7 at end of 15 min exposure	Increased MN (No sham exposure; Incubator control only)	<u>d'Ambrosio et al (2002)</u>
2450	CW	12.5	90 min (Inter- mittent)	Human blood lympho- cytes	37 °C to max. 39 °C	No Increase in MN	<u>Vijayalaxmi et al (1997a)</u>
847.74 MHz	CDMA	4.9 or 5.5	24	“	37 °C	No Increase in MN	<u>Vijayalaxmi et al (2001a)</u>
835.62 MHz	FDMA	4.4 or 5.0	24	“		No Increase in MN	<u>Vijayalaxmi et al (2001b)</u>
835.62 847.74	FDMA CDMA	3.2 or 5.1 3.2 or 4.8	3,8,16, or 24 hrs	C3H 10T1/2 fibroblasts	37 °C	No Increase in MN	<u>Bisht et al (2002)</u>
1.9	CW	0.1, 0.26, 0.92, 2.4, or 10	2 hr	Human blood leukocytes	37 °C	No Increase in MN	<u>McNamee et al (2002a)</u>
1.9	PW 50 Hz, 1/3 duty factor	0.1, 0.26, 0.92, 2.4, or 10	2 hr	Human blood leukocytes	37 °C	No Increase in MN	<u>McNamee et al (2002b)</u>
2450	CW	12	24	PCEs from bone marrow and peripheral blood of RF Exp. Sprague- Dawley Rats		No Increase in MN	<u>Vijayalaxmi et al (2001c)</u>

Induction of DNA Repair Synthesis After RF Exposure

Freq. (MHz)	PW or CW	Modul.	Power Density mW/cm ²	SAR W/Kg	Expos. Duration Hr	Cell Type	Temp. During Expos.	Endpoint	Result
350	CW		10	0.39 high	3	MRC-5 Normal human diploid fibroblasts	37 °C	DNA Repair Synthesis	None
350	PW	5000pps 10 μs	10, 5 (39 °C)	0.39 high	3	“	37 or 39 °C	“	None
850	CW		10	4.5 high	3	“	37 °C	“	None
850	PW	5000pps 10 or 100 μs	10	4.5 high	3	“	37 or 39 °C	“	None
1200	CW		10	2.7 high	3	“	37 °C	“	None
1200	PW	80000pps 3 μs	10	2.7 high	3	“	37 °C	“	None

Inhibition of UV induced DNA Repair Synthesis (by RF during Repair Period)

Freq. (MHz)	PW or CW	Modul.	Power Density mW/cm ²	SAR W/Kg	Expos. Duration Hr	Cell Type	Temp. During Expos.	Endpoint	Result
350	CW		1 or 10	0.39 high	1, 2 & 3	MRC-5 Normal human diploid fibroblasts	37 °C	Inhibition of DNA Repair Synthesis	None
350	PW	5000pps 10 μs	1, 5 or 10	0.39 high	1, 2 & 3	“	37 or 39 °C	“	None
850	CW		1 or 10	4.5 high	1 & 3	“	37 °C	“	None
850	PW	5000pps 10 or 100 μs	1 or 10	4.5 high	1, 2 & 3	“	37 or 39 °C	“	None
1200	CW		1 or 10	2.7 high	1, 2 & 3	“	37 °C	“	None
1200	PW	80000pps 3 μs	1 or 10	2.7 high	1, 2 & 3	“	37 or 39 °C	“	None

Sister chromatid exchange (SCE) After RF Exposure

Freq. MHz	PW/CW Modul.	Power Density	SAR W/Kg	Expos. Durat.	Cell Type	Temp. During Exposure	Endpoint	Result	Reference
2450	PW 25,000pps 10 μs	49 mW/cm ²	33.8	2 hr	CHO	Inc. from 37 to 39.2 °C	SCE	No Incr. vs Temp Control	Ciaravino et al (1987)
2450	PW 25,000pps 10 μs	49 mW/cm ²	33.8	2 hr	CHO	Inc. from 37 to 39.2 °C	MMC induced SCE	No Incr. vs Temp Control	Ciaravino et al (1987)
2450	PW 25,000pps 10 μs	49 mW/cm ²	33.8	2 hr	CHO	Inc. from 37 to 39.7 °C	SCE	No Incr. vs Temp Control	Ciaravino et al (1991)
2450	PW 25,000pps 10 μs	49 mW/cm ²	33.8	2 hr	CHO	Inc. from 37 to 39.7 °C	Adriamycin induced SCE	No Incr. vs Temp Control	Ciaravino et al (1991)
2450	PW 50 Hz		75	30 or 120 min	Human blood lymphocytes	36 °C (?-High SAR) (Uniformity "Guaranteed")	SCE	No Incr.	Maes et al (1993)
954	GSM	5 cm from base station antenna	Calc. 1.5	2 hr	Human blood	17 °C	SCE	No Inc.	Maes et al (1996)
935.2	GSM (CMDA) CW		0.3 – 0.4	2 hr	Human blood	Not Stated	SCE	No Inc.	Maes et al (1997)
455.7		5 cm from car phone antenna	6.5	2 hr	Human blood	17 °C ?	SCE	No Inc.	Maes et al (2000)
900	GSM		2, 3.5	2 hr	Human blood	Not Stated	SCE	No Inc.	Maes et al (2001)

Phenotypic Mutation after RF Exposure

Freq. (MHz)	PW or CW	Modul.	Power Density mW/cm	Specific Absorption Rate W/Kg	Expos. Durat. hr	Cell Type:	Temp. During Expos.	Endpoint	Result
2450	PW	25,000pps 10 μ s	48.8	30 (1989)	4	L5178Y Mouse Leukemia	Increased up to 39.9 $^{\circ}$ C	Mutation at TK +/- Locus	None
2450	PW	“	48.8	30 (1989)	4	“	“	Increase in MMC induced mutation	None
2450	PW	“	65 or 87	40 or 40.8 (1990)	4	“	Increased up to 39.5 $^{\circ}$ C	Mutation at TK +/- Locus	None
2450	PW	“	65 or 87	40 or 40.8 (1990)	4	“	“	Increase in proflavin induced mutation	None
1000		TDMA		0.27 (whole body avg.) with 2 (brain avg. (2002)	90 m/dy 5 dy/wk 4 wks	Big Blue Mouse		Independent mutations of the <i>lacI</i> transgene in the brain	None

Genotoxic Agents Are Typically Lethal: Colony Formation and Apoptosis After RF Exposure

Freq. MHz	PW/CW/Modul.	Power Density	SAR W/Kg	Exposure Duration	Cell Type	Temp. During Expos.	Endpoint	Result	Reference
434-460896		135 W/cm ³		30m	CHO, RI-mouse fibro-sarcoma cells	12-46 °C	Colony Formation	Killing due to heating	Sapareto et al (1982)
2450	CW			Increas. times (intermit.)	CHO cells	At 44 °C	Colony Formation	Killing due to heating	Livingston et al (1979)
2450	PW 120pps 83 μs		4.4	24 hr	C3H 10T1/2	37.2 °C	Colony Formation	50% P.E.	BK & H- (1985)
2450	“		4.4	24 hr	C3H 10T1/2	37.2 °C	Colony Formation	No-Killing	BK & H- (1989)
2450	120 Hz		0.1, 1, 4.4	24	C3H 10T1/2	37.2 °C	Colony Formation	No Killing	BK & H- (1991)
7700		0.5 mW/cm ²		15, 30 and 60 min	V79 Chinese Hamster cells	Temp in membrane with cells “not known) P.148	Colony Formation	Inc. Killing with increasing power density	G-V et al- (1991)
1500	TDMA		0.67 2.0	90 m/dy 5 dy/wk 4 wks	Big Blue Mice		Apoptosis (Terminal end labeling)	None	Takahashi et al (2002)

Dye Exclusion, Staining and Functional Activity After RF Exposure (as indicators of cell death)

Freq. MHz	PW/CW/Modul.	SAR W/Kg	Exposure Duration	Cell Type or animal exposed	Temp. During Expos.	Endpoint	Result	Ref.
2450		Ranging up to 50	2 hr	CTLL-2 cytolytic T-lymphocytes	37 °C	Dye-Exclusion	No killing	Cleary et al (1996)
837 837 1909.8 837	TDMA CDMA PCS Analog	1 - 10	3 or 24 hr	Human blood leukocytes and lymphocytes	37 °C	Special Staining	No killing	Tice et al (2002)
2450	PW 8 Hz Square-wave	0.4 decreasing to 0.15	21.55 hr/day 25 mo.	Sprague-Dawley rats		155 Clinical Parameters (Immunolog. Hormonal; Metabolic, etc)	No alterations over lifetime vs sham	Chou et al (1992)
435		0.3 – 0.35	22 h/dy 7 dy/wk 6 mo	Sprague-Dawley rats		Blood, hormonal, cardiovascular other	No alterations over lifetime vs sham	Toler et al (1988)

CONCLUSION:

- The overwhelming weight of the existing scientific evidence supports the hypothesis that, for a wide variety of RF frequencies and modulations, at exposure levels slightly above, at, or below current international guidelines, radiofrequency field exposure is not genotoxic.

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