

20-1025 (Lead); 20-1138 (Consolidated)

**UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT**

ENVIRONMENTAL HEALTH TRUST; CONSUMERS FOR SAFE CELL
PHONES; ELIZABETH BARRIS; THEODORA SCARATO

CHILDREN'S HEALTH DEFENSE; MICHELE HERTZ; PETRA BROKKEN;
DR. DAVID O. CARPENTER; DR. PAUL DART; DR. TORIL H. JELTER; DR.
ANN LEE; VIRGINIA FARVER, JENNIFER BARAN; PAUL STANLEY, M.Ed.

Petitioners

v.

FEDERAL COMMUNICATIONS COMMISSION;
UNITED STATES OF AMERICA

Respondents

Petition for Review of Order Issued by the
Federal Communications Commission

DEFERRED JOINT APPENDIX**VOLUME 8 (CORRECTED)**

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The results showed that the increase in DNA damage after exposure was associated with the increase in temperature; in this experiment, no non-thermal effects on frog erythrocytes *in vitro* were noted ([Chemeris et al., 2004](#)).

The effects of exposure to RF radiation at 835 MHz (SAR, 4 W/kg) for 48 hours were examined in assays for mutagenicity in bacteria. RF radiation was not directly mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, or in *Escherichia coli* strain WP2 *uvrA*. It significantly enhanced the mutagenicity of 4NQO in *E. coli* strain WP2 *uvrA* and of cumene hydroperoxide in *S. typhimurium* strain TA102. In a test for DNA degradation, no change in the rate of degradation (formation of DNA strand breaks) was observed with plasmid pBluescript SK(+) exposed to H₂O₂ (Fenton-type reaction) as an indicator ([Chang et al., 2005](#)).

Mutagenicity tests were conducted in different bacterial strains (*S. typhimurium* TA98, TA100, TA1535 and TA1537, and *E. coli* WP2 *uvrA*) exposed to RF radiation at 2450 MHz (SAR, 5–200 W/kg) for 30 minutes. No effects were found in any of the strains tested ([Koyama et al., 2007](#)).

[The Working Group noted that while several studies showed positive responses at high SAR values, some of these were due to thermal effects. The Working Group concluded that there was weak evidence that exposure to RF radiation is genotoxic in experimental systems in mammalian and non-mammalian cells *in vitro*.]

4.2 Effects of low-level exposure to RF radiation on the immune system

In this section, some studies that assess the effects of RF radiation on the immune system are discussed (see review by [Jauchem, 2008](#)).

4.2.1 Immunotropic effects of exposure to RF radiation in humans

[In general, occupational studies in this Section included small numbers of subjects and generally failed to control for possible confounders.]

[Dmoch & Moszczyński \(1998\)](#) measured immunoglobulin concentrations and proportions of different subsets of T lymphocytes in blood samples from 52 workers at television-retransmission and satellite-communication centres, exposed to RF radiation at 6–12 GHz. Concentrations of IgG and IgA immunoglobulins, and cell counts of total lymphocytes and T8 lymphocytes were increased, whereas the number of natural killer (NK) cells and the ratio of T-helper/T-suppressor cells were decreased, compared with the values in 30 non-exposed controls. There was no change in IgM concentrations. In an extension of this study, [Moszczyński et al. \(1999\)](#) performed a similar analysis with blood samples from radar operators. In this case, IgM concentrations were elevated and T8 lymphocyte cell-counts were decreased. The different results obtained in these two professional groups with respect to immunological parameters and blood-cell counts suggested that the effect of RF radiation on the immune system depends on the character of the exposure.

[Tuschl et al. \(1999\)](#) investigated the effects of long-term handling of various types of diathermy equipment – operating at frequencies of 27, 434, or 2450 MHz – on the immune system of medical personnel, by analysis of blood samples collected from physiotherapists operating these devices. Eighteen exposed subjects and 13 controls matched for sex and age were examined. Total leukocyte/lymphocyte counts and the proportion of leukocyte subpopulations were determined by use of flow cytometry and monoclonal antibodies to cell-surface antigens. In addition, lymphocyte activity was measured to quantify subpopulations of immunocompetent cells.

Lymphocytes were stimulated by the mitogen PHA and proliferation was measured by flow cytometry. No statistically significant differences between the exposed personnel and the controls were found. In both groups, all immune parameters were within normal ranges.

[Radon et al. \(2001\)](#) investigated the effects of RF radiation at 900 MHz (pulse frequency, 217 Hz; power density, 1 W/m²) used in modern digital wireless telecommunication (GSM standard), in eight healthy male volunteers exposed in a specifically designed, shielded experimental chamber. The circularly polarized electromagnetic field applied was transmitted by an antenna positioned 10 cm behind the head of the volunteer, who was sitting upright. In double-blind trials, each volunteer underwent a total of 20 randomly allotted 4-hour periods of exposure and sham exposure, equally distributed during day and night. The salivary concentrations of IgA – as well as those of melatonin, cortisol and neopterin – did not differ significantly between the exposed and the sham-exposed subjects.

[Yuan et al. \(2004\)](#) investigated the effect of low-intensity, 170 MHz RF radiation on immune parameters in occupationally exposed workers. Blood-sample analysis showed no marked change in IgA concentrations, whereas those of IgM and IgG were significantly increased ($P < 0.01$) in the exposed group compared with those in non-exposed controls.

[Kimata \(2005\)](#) exposed 15 patients with atopic eczema dermatitis syndrome (AEDS) to RF radiation from a mobile phone (SAR, 1.62 W/kg) for 30 minutes. A second group of 15 patients was sham-exposed. In a repeat experiment 2 weeks later, the groups were switched with respect to exposure/sham-exposure. Before and after each study, mononuclear cells were stimulated with latex, the allergen to which the patients were sensitive. The production of latex-specific immunoglobulin E (IgE) was significantly increased ($P < 0.01$) after exposure to RF radiation.

[The Working Group noted that studies of humans exposed to RF radiation provided weak evidence for effects on the humoral immune system.]

4.2.2 Immunotropic effects of exposure to RF radiation in experimental animals: studies in vivo

See [Table 4.8](#)

(a) Mouse

[Smiałowicz et al. \(1983\)](#) exposed male CBA/J mice to 2450 MHz continuous-wave RF radiation (power density, 5, 15, 30 mW/cm²; SAR, 3.5, 10.5, 21 W/kg, respectively) for 90 minutes per day for 2 or 9 days, and studied the effects on the activity of NK cells and the mitogen-induced response of lymphocytes. There was no consistent difference in the mitogen response of spleen cells from irradiated mice and sham-irradiated mice, while a significant suppression of NK activity was seen at the highest exposure intensity. NK activity returned to normal within 24 hours after exposure.

[Veyret et al. \(1991\)](#) exposed BALB/c mice to pulsed-wave RF radiation at 9400 MHz (1 μ s pulses at 1000/second), both with and without amplitude modulation (AM) by a sinusoid signal at discrete frequencies between 14 and 41 MHz. Mice were immunized with sheep erythrocytes and exposed to RF radiation (30 μ W/cm²; whole-body SAR, 0.015 W/kg) for 10 hours per day, for 5 days. The antibody response to sheep erythrocytes was measured by the plaque-forming assay. In the absence of AM, there was not much change in immune responsiveness. Exposure to RF radiation with AM at 21 or 32 MHz led to significant enhancement of the response, while there was a decrease in the number of plaque-forming cells with AM at 14, 36, or 41 MHz.

[Elekes et al. \(1996\)](#) studied the effects of continuous-wave (CW) or amplitude-modulated (AM) RF radiation at 2450 MHz in male

Table 4.8 Immunotropic effects of exposure to radiofrequency radiation in experimental animals *in vivo*

Experimental system	Exposure conditions	Results	Reference
CBA/J mice	2450 MHz PW; SAR, 3.5, 10.5 and 21 W/kg; 1.5 h/d for 2, 3, 9 d	No increase in mitogenic response of splenic lymphocytes	Smialowicz et al. (1983)
BALB/c mice	9400 MHz PW; AM; 30 μ W/cm ² ; whole-body SAR, ~0.015 W/kg; 10 h/d for 5 d	Significant increase in numbers of PFC at AM frequencies 21 and 32 MHz; significant decrease at 14, 36, 41 MHz.	Veyret et al. (1991)
BALB/c mice	2450 MHz CW or AM (50 Hz square wave); SAR, 0.14 W/kg; 3 h/d for 6 d	Increase in the number of antibody-producing cells in the spleen of male mice; no effect in female mice.	Elekes et al. (1996)
C57BL/6 mice	900 MHz (GSM); SAR, 1 or 2 W/kg; 2 h/d for 1, 2, 4 wk	No substantial effect on T- and B-cell compartments. Transient increase of interferon- γ after 1 week of exposure, not at 2 or 4 wk	Gatta et al. (2003)
Mice [strain not given]	42 GHz; 105 μ W/cm ² ; 20 min/d for 1–14 d	Strong effect on indices of non-specific immunity. Phagocytic activity of neutrophils was suppressed by 45–50% within 2–3 h after a single exposure, remained suppressed for 1 d, and was restored to normal during 3 d. Blood leukocytes were increased after exposure for 5 d.	Kolomytseva et al. (2002)
NMR1 mice, exposed in the far-field zone of horn antenna	42 GHz; 150 μ W/cm ² ; 20 min (single exposure), 20 min/d for 5 or 20 successive days, before or after immunization	No effect of single exposure or five repeat exposures. Daily exposure for 20 d before immunization with SRBC resulted in significant reductions in thymic and renal cellularity	Lushnikov et al. (2001)
C57BL/6 mice	900 MHz (GSM); whole-body average SAR, 2 W/kg; 2 h/d for 4 wk	No changes in frequencies of various B cell types or in IgM/IgG serum levels. Production of IgM/IgG by B cells from exposed mice, challenged <i>in vitro</i> with lipopolysaccharides, was comparable to that in controls	Nasta et al. (2006)
NMR1 mice	1.8–81.5 GHz; 1 μ W/cm ² ; 5 h	Increased production of TNF in peritoneal macrophages and splenic T lymphocytes. Increased mitogenic response in T lymphocytes.	Novoselova & Fesenko (1998) , Novoselova et al. (1999)
NMR1 mice	8.15–18 GHz; 1 μ W/cm ² ; 5 h –7 d	Increased NK cell activity, which persisted up to 24 h after exposure. Increased TNF production in peritoneal macrophages and splenic T lymphocytes after exposures of 5 h – 3 d, and reduced TNF production in peritoneal macrophages after an exposure of 7 d.	Fesenko et al. (1999b)
Rats [strain not given]	2450 MHz PW; SAR, 0.15–0.4 W/kg; 25 mo	Transient increase in the number of B and T lymphocytes and their response to the mitogen PHA after exposure for 13 mo	Guy et al. (1985)
Sprague-Dawley rats	900 MHz (GSM); SAR, 0.075 and 0.27 W/kg; 2 h/d for 10 d	No alterations in the surface phenotype of splenic lymphocytes or in their concavalin A-stimulated mitogenic activity	Chagnaud & Veyret (1999)
Belgian White rabbits	2.1 GHz; 5 mW/cm ² ; 3 h/d, 6 d/wk for 3 mo	Suppression of T-lymphocyte numbers at 2 mo; stronger response of T-cell-mediated immunity (delayed-type hypersensitivity response)	Nageswari et al. (1991)

AM, amplitude modulation; CW, continuous wave; d, day; GSM, Global System for Mobile Communications; h, hour; LPS, lipopolysaccharides; min, minute; mo, month; MW, microwave; NK, natural killer; PHA, phytohaemagglutinin; PFC, plaque-forming cells; PW, pulsed-wave; TNF, tumour necrosis factor; wk, week.

and female BALB/c mice. The time-averaged power density was $100 \mu\text{W}/\text{cm}^2$, with a SAR of $0.14 \pm 0.02 \text{ W/kg}$. Exposure to RF radiation as CW or AM (3 hours per day for 6 days) induced a non-significant increase in the number of antibody-producing cells in the spleen of male mice. No effects were seen in female mice.

[Novoselova & Fesenko \(1998\)](#) and [Novoselova et al. \(1999\)](#) exposed male NMRI mice to RF radiation at 8150–18 000 MHz (power density, $1 \mu\text{W}/\text{cm}^2$) for 5 hours, and observed a significantly enhanced ($P < 0.05$) production of TNF in peritoneal macrophages and in T-cells in the spleen, and an increased mitogenic response in T lymphocytes.

Male NMRI mice received whole-body exposure to RF radiation at 10 GHz (average power density, $1 \mu\text{W}/\text{cm}^2$) for different time periods (1 hour to 7 days). A significant enhancement of the production of tumour necrosis factor (TNF) in peritoneal macrophages and in splenic T lymphocytes was seen after exposures of 5–72 hours. Prolonged irradiation after 72 hours resulted in a decrease in production of TNF. In mice exposed to RF radiation at 8.15–18 GHz (average power density, $1 \mu\text{W}/\text{cm}^2$) for 24 hours, TNF production in T-cells and macrophages was significantly increased ($P < 0.05$); in the latter cell type, this increase persisted for 3 days after termination of exposure ([Fesenko et al., 1999b](#)).

[Lushnikov et al. \(2001\)](#) exposed male NMRI mice to RF radiation at 42.0 GHz (energy-flux density, $150 \mu\text{W}/\text{cm}^2$) for 20 minutes per day, on five or twenty successive days before immunization with sheep erythrocytes, or for 20 minutes per day during five successive days after immunization. The response was estimated on day 5 after immunization by the number of antibody-forming splenic cells and by antibody titres. Humoral immunity and cellularity of the lymphoid organs did not change significantly after the single exposure, or after the series of five exposures before and after immunization. However, after daily exposure for 20 days before

immunization, statistically significant reductions ($P < 0.05$) of thymic and splenic cellularity were observed.

[Kolomytseva et al. \(2002\)](#) exposed mice to RF radiation at 4200 MHz (power density, $150 \mu\text{W}/\text{cm}^2$) for 20 minutes. The phagocytic activity of neutrophils was suppressed by about 50% in the 2–3 hours after a single exposure. The effect persisted for 1 day, and phagocytic activity then returned to normal within 3 days. A significant modification of the leukocyte profile in mice exposed for 5 days was observed after cessation of exposure: the number of leukocytes increased, mostly due to an increase in lymphocyte content.

[Gatta et al. \(2003\)](#) exposed C57BL/6 mice to GSM-modulated RF radiation at 900 MHz (SAR, 1 or 2 W/kg) for 2 hours per day for 1, 2 or 4 weeks. The number of spleen cells, the percentage of B and T-cells, and the distribution of T-cell subpopulations (CD4 and CD8) were not affected by the exposure. There was no difference in stimulation of T or B lymphocytes with specific monoclonal antibodies or lipopolysaccharides (LPS) between sham-exposed and exposed mice. After 1 week of exposure at a SAR of 1 or 2 W/kg, there was an increase in the production of interferon-gamma (IFN- γ), which was no longer observed when exposure was prolonged to 2 or 4 weeks.

[Nasta et al. \(2006\)](#) examined the effects of GSM-modulated RF radiation at 900 MHz (average SAR, 2 W/kg) on peripheral differentiation of B-cells and antibody production in female C57BL/6 mice exposed *in vivo*. Whole-body exposure for 2 hours per day, for 4 weeks, did not affect the frequencies of T1 and T2 B-cells, or of mature follicular B-cells and marginal zone B-cells in the spleen. Serum concentrations of IgM and IgG were not significantly affected. B-cells from mice exposed to RF radiation, which were then challenged *in vitro* with lipopolysaccharide (LPS) produced comparable amounts of IgM and IgG. Exposure to RF radiation did not alter the

ongoing antigen-specific immune response in immunized mice.

(b) *Rat*

In a study with rats receiving lifelong exposure to pulsed-wave RF radiation at 2450 MHz (SAR, 0.15–0.4 W/kg), [Guy et al. \(1985\)](#) found a significant increase in the number of splenic B and T lymphocytes at 13 months, but this effect had disappeared by the end of the study at 25 months. The exposed rats also showed a significant increase in their response to LPS and pokeweed mitogen after 13 months of exposure (no data available at 25 months).

[Chagnaud & Veyret \(1999\)](#) examined the effects of exposure to GSM-modulated RF radiation at 900 MHz (55 and 200 $\mu\text{W}/\text{cm}^2$; SAR, 0.075 and 0.279 W/kg; repetition rate, 217 Hz) for 2 hours per day for 10 days, on lymphocyte subpopulations in female Sprague-Dawley rats. The mitogenic response of the exposed rats was analysed by flow cytometry and a colorimetric method. No alterations were found in cell-surface markers (CD4, CD8 and IaAg) of splenic lymphocytes of exposed rats, or in their mitogenic activity when stimulated with concanavalin A.

(c) *Rabbit*

[Nageswari et al. \(1991\)](#) exposed male Belgian White rabbits to RF radiation at 2100 MHz (power density, 5 mW/cm^2 ; calculated average SAR, 0.83 W/kg) for 3 hours per day, 6 days per week, for 3 months, in specially designed miniature anechoic chambers. One group of rabbits was tested for T-lymphocyte-mediated cellular immune-response, being initially sensitized with bacille Calmette–Guérin (BCG) vaccine and challenged with tuberculin after termination of exposure. A second group was assessed for B-lymphocyte-mediated humoral immune-response. Samples of peripheral blood were collected each month during exposure or sham exposure and during follow-up at 5 and 14 days

after termination of exposure (second group only). Significant suppression of numbers of T lymphocytes was noted in the exposed rabbits at 2 months and during the follow-up period. Rabbits in the group initially sensitized with BCG showed an increase in foot-pad thickness, which is indicative of a good T-lymphocyte-mediated immune response (a delayed-type hypersensitivity response).

[The Working Group noted that the available evidence from the numerous experimental studies *in vivo* that have assessed the effects of short-term and prolonged low-level exposure to RF radiation on the function and status of the immune system, clearly indicates that various shifts in the number and/or activity of immunocompetent cells can be detected. However, results have been inconsistent between experiments, despite comparable exposure conditions at similar intensities and radiation parameters. Short-term exposure to weak RF fields may temporarily stimulate certain humoral or cellular immune functions, while prolonged irradiation inhibits the same functions. The relevance of these observations to carcinogenicity was unclear.]

4.2.3 *Immunotropic effects of exposure to RF radiation in experimental systems: studies in human cells in vitro*

See [Table 4.9](#)

[Cleary et al. \(1990\)](#) studied human peripheral blood cells that were sham-exposed or exposed *in vitro* to RF radiation at 27 MHz (SAR, 0–196 W/kg) or 2450 MHz (SAR, 0–50 W/kg) for 2 hours under isothermal conditions ($37 \pm 0.2^\circ\text{C}$). Immediately after exposure, peripheral blood mononuclear cells were isolated by Ficoll density-gradient centrifugation and cultured for 3 days at 37°C with or without mitogenic stimulation by PHA. Lymphocyte proliferation was assayed at the end of the culture period by a 6-hour pulse-labelling with [^3H]thymidine. Exposure to radiation at

Table 4.9 Immunotropic effects of exposure to radiofrequency radiation in experimental systems *in vitro*

Experimental system	Exposure conditions	Results	Reference
Mouse PBMC; assessment of IL-2-dependent cytolytic T-lymphocyte proliferation (CTLL-2)	2450 MHz, CW (SAR, 5–50 W/kg) or PW (SAR, 5 W/kg), for 2 h	Statistically significant reduction in CTLL-2 proliferation after CW-RF radiation at low IL-2 levels and at SAR ≥ 25 W/kg; increase after PW-RF radiation	Cleary et al. (1996)
Rat basophilic leukaemia RBL-2H3 cells (a mast cell line)	835 MHz; 81 W/m ² ; 3 \times 20 min/d for 7 d	From day 4 onwards, the rates of DNA synthesis and cell replication continued to increase in exposed cells, but decreased in controls; cell morphology was also altered	Donnellan et al. (1997)
Human PBMC, microculture with mitogen (PHA) stimulation	27 MHz (SAR, 0–196 W/kg) or 2450 MHz (SAR, 0–50 W/kg); isothermal conditions (37 \pm 0.2 °C); 2 h	Dose-dependent, statistically significant increase in [³ H] thymidine uptake in PHA-activated or unstimulated lymphocytes at SAR < 50 W/kg; uptake was suppressed at SAR ≥ 50 W/kg	Cleary et al. (1990)
Human lymphocytes; transformation of PBMC exposed to RF radiation or heated conventionally	2450 MHz CW or PW, at non-heating (37 °C) and various heating levels (temperature increases of 0.5, 1.0, 1.5, and 2 °C); SARs up to 12.3 W/kg	Both conventional and CW heating enhanced cell transformation to the same extent, which was correlated with the increase in incubation temperature. Exposure to PW RF radiation enhanced transformation at non-heating conditions.	Czerska et al. (1992)
Human mast cell line, HMC-1	864.3 MHz; average SAR, 7 W/kg; 3x20 min/d for 7 d	Effect on localization of protein kinase C (migration towards the cell membrane), upregulation of <i>c-kit</i> , down-regulation of <i>NDPK</i> -beta, and the apoptosis-associated gene <i>DAD-1</i> .	Harvey & French (1999)
Human PBMC, microculture with mitogens, assessment of interleukin release, T-cell suppression (SAT)	1300 MHz PW; SAR, 0.18 W/kg; 1 h	Decreased spontaneous incorporation of [³ H]thymidine; no change in response to PHA or concanavalin A; no change in SAT index and saturation of IL-2 receptors; production of IL-10 by lymphocytes increased. Pulse-modulated MWs have immunotropic effects.	Dąbrowski et al. (2003)
Human lymphocytes; analysis of CD25, CD95, CD28 antigens in unstimulated and stimulated CD4+ or CD8+ T-cells from PBMC	1800 MHz (10 min on, 20 min off); SAR, 2 W/kg; 44 h. Microculture with or without antibody anti-CD3 mitogenic stimulation	No significant difference in proportion of cell subsets between exposed and sham-exposed lymphocytes from young or elderly donors. Slight but significant downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly (average age, 88 yr) but not from younger (average age, 26 yr) donors.	Capri et al. (2006)

Table 4.9 (continued)

Experimental system	Exposure conditions	Results	Reference
Human PBMC, microculture with mitogens, assessment of interleukin (IL) release, T-cell suppression (SAT)	900 MHz (GSM); SAR, 0.024 W/kg; 15 min	Significantly increased response to mitogens and enhanced immunogenic activity of monocytes (LM index). The results suggest that immune activity of responding lymphocytes and monocytes can be enhanced by 900 MHz MW.	Stankiewicz et al. (2006)
Human PBMC, microculture with mitogens, assessment of several immune functions	1950 MHz (GSM; 5 min on, 10 min off); SAR, 1 W/kg; 8 h	No effects of RF radiation on immune functions: (i) the intracellular production of IL-2 and INF- γ in lymphocytes, and IL-1 and TNF- α in monocytes; (ii) the activity of immune-relevant genes (IL-1- α and β , IL-2, IL-2-receptor, IL-4, MCSF-receptor, TNF- α , TNF- α -receptor); or (iii) the cytotoxicity of lymphokine-activated killer cells (LAK cells) against a tumour cell line.	Tuschl et al. (2006)

d, day; h, hour; IL-2, interleukin 2; IL-10, interleukin 10; INF- γ , interferon γ ; LM, lymphocytes-monocytes; MCSF, macrophage colony-stimulating factor; MW, microwave; min, minute; mo, month; NDPK, nucleoside diphosphate kinase; PBMC, peripheral blood mononuclear cells; PHA, phytohaemagglutinin; PW, pulsed-wave; SAR, specific absorption rate; SAT index, a measure of the suppressive activity of T cells; TNF, tumour necrosis factor; yr, year

either frequency at SARs < 50 W/kg resulted in a dose-dependent, statistically significant increase in [³H]thymidine uptake in PHA-activated or non-stimulated lymphocytes. Exposure at SARs of ≥ 50 W/kg suppressed [³H]thymidine uptake. There were no detectable effects of RF radiation on lymphocyte morphology or viability.

[Czerska et al. \(1992\)](#) determined the effects of continuous- and pulsed-wave RF radiation at 2450 MHz (average SARs up to 12.3 W/kg) on spontaneous lymphoblastoid transformation of human lymphocytes *in vitro*. Peripheral blood mononuclear cells from healthy donors were exposed for 5 days to conventional heating, or to continuous- or pulsed-wave RF radiation at 2450 MHz under non-heating (37 °C) or various heating conditions (temperature increases of 0.5, 1.0, 1.5, or 2 °C). The pulsed exposures involved pulse-repetition frequencies from 100 to 1000 pulses per second at the same average SARs as the continuous exposures. At the end of the incubation period, spontaneous lymphoblastoid-cell transformation was detected by use of an image-analysis system. At non-heating levels, continuous-wave exposure did not affect transformation compared with sham-exposed cultures. Under heating conditions, both conventional heating and exposure to continuous-wave RF radiation enhanced transformation to the same extent, and correlated with the increases in incubation temperature. Exposure to pulsed-wave RF radiation enhanced transformation under non-heating conditions. At heating levels, it enhanced transformation to a greater extent than did conventional heating or continuous-wave exposure. The results indicate that pulsed-wave RF radiation at 2450 MHz had a different action on the process of lymphoblastoid cell transformation *in vitro* than continuous-wave radiation at 2450 MHz and at the same average SARs.

Human HMC-1 mast cells were exposed to RF radiation at 846.3 MHz (average SAR, 7.3 W/kg) for 20 minutes, three times per day

(at 4-hour intervals) for 7 days. During the 20 minutes of exposure, the cells were outside the incubator and the temperature in the cell-culture medium dropped to 26.5 °C. Effects were seen on the localization of protein kinase C (migration to the cell membrane), and on expression of three genes: the proto-oncogene *c-kit* (upregulated 36%), the gene encoding transcription factor nucleoside diphosphate kinase B (downregulated 38%), and the apoptosis-associated gene *DAD-1* (downregulated 47%) ([Harvey & French, 1999](#)).

[Dąbrowski et al. \(2003\)](#) exposed peripheral blood mononuclear cells from healthy donors (*n* = 16) to pulse-modulated RF radiation at 1300 MHz (power density, 1 mW/cm²; SAR, 0.18 W/kg) for 1 hour. This exposure decreased the spontaneous incorporation of [³H]thymidine, but the proliferative response of lymphocytes to PHA and concavalin A, the T-cell suppressive activity (SAT index), and the saturation of IL-2 receptors did not change. The IL-10 production by the lymphocytes increased (*P* < 0.001), and the concentration of interferon-gamma (IFN γ) remained unchanged or slightly decreased in the culture supernatants. Exposure to RF radiation modulated monokine production by monocytes. The production of IL-1 β increased significantly, the concentration of its antagonist (IL-1ra) dropped by half and the concentration of tumour necrosis factor α (TNF- α) remained unchanged. These changes in monokine proportion (IL-1 β versus IL-1ra) resulted in a significant increase in the immunogenic activity of the monocytes, *i.e.* the influence of monokines on the lymphocyte mitogenic response, which reflects the activation of monocyte immunogenic function. The results indicated that pulse-modulated microwaves have the potential to influence immune function, stimulating preferentially the immunogenic and pro-inflammatory activity of monocytes at relatively low levels of exposure.

[Capri et al. \(2006\)](#) analysed CD25, CD95, CD28 molecules in non-stimulated and stimulated CD4+ or CD8+ T-cells *in vitro*. Peripheral

blood mononuclear cells from 10 young (age, 26 ± 5 years) and 8 elderly (age, 88 ± 2 years) donors were sham-exposed or exposed to intermittent (10 minutes on, 20 minutes off) RF radiation at 1800 MHz (SAR, 2 W/kg) for 44 hours, with or without mitogenic stimulation. No significant changes in the percentage of these subsets of cells were found between exposed and sham-exposed non-stimulated lymphocytes in young or elderly donors. A small, but statistically significant downregulation of CD95 expression was noted in stimulated CD4⁺ T lymphocytes from elderly, but not from younger donors, after exposure to RF radiation.

[Stankiewicz et al. \(2006\)](#) investigated whether cultured human immune cells induced into the active phases of the cell cycle (G1, S) were sensitive to exposure to RF radiation at 900 MHz (GSM; 27 V/m; SAR, 0.024 W/kg) for 15 minutes. The exposed microcultures of peripheral blood mononuclear cells showed a significantly higher proliferative response to PHA or concanavalin A, a stronger response to mitogens, and a higher immunogenic activity of monocytes than sham-exposed control cultures.

[Tuschl et al. \(2006\)](#) exposed peripheral blood mononuclear cells to RF radiation at 1950 MHz, with a SAR of 1 W/kg, in an intermittent mode (5 minutes on, 10 minutes off) for 8 hours. Numerous immune parameters were evaluated, including: intracellular production of IL-2 and INF γ in lymphocytes, and IL-1 and TNF- α in monocytes; activity of immune-relevant cytokines (IL-1- α and β , IL-2, IL-2-receptor, IL-4, macrophage colony-stimulating factor (MCSF)-receptor, TNF- α , TNF- α -receptor); and cytotoxicity of lymphokine-activated killer cells (LAK cells) against a tumour cell line. For each parameter, blood samples from at least 15 donors were evaluated. No statistically significant effects of exposure were found.

[The Working Group concluded that exposure *in vitro* to non-thermal intensities of RF

radiation provided weak evidence for effects on immunocompetent cells.]

4.3 Effects of exposure to RF radiation on gene and protein expression

4.3.1 Gene expression

(a) Humans

There were no studies examining gene or protein expression after exposure to RF radiation in humans.

(b) Experimental animals

See [Table 4.10](#)

(i) *Caenorhabditis elegans*

No effect was found on the transgene expression of *hsp16* (encoding heat-shock protein hsp16, the equivalent of human hsp27) in the nematode *C. elegans* – transgenic for *hsp16* – exposed to continuous-wave or pulsed-wave RF radiation at 1.8 GHz (SAR, 1.8 W/kg) for 2.5 hours at 25 °C ([Dawe et al., 2008](#)). In a second study, *C. elegans* was exposed to continuous-wave RF radiation at 1 GHz (SAR, 0.9–3 mW/kg; power input, 0.5 W) for 2.5 hours at 26 °C. In this exposure set-up, with very low SAR, the difference in temperature between exposed and sham-exposed samples did not exceed 0.1 °C. In a gene-expression array, no statistically significant effects on the gene-expression pattern were found ([Dawe et al., 2009](#)). [The Working Group noted that experiments at these low SAR levels may favour a no-effect outcome.]

(ii) *Drosophila melanogaster*

Using a semiquantitative reverse-transcriptase polymerase chain reaction (RT-PCR), [Lee et al. \(2008\)](#) showed that exposure of fruit flies (*D. melanogaster*) to RF radiation at 835 MHz (SAR, 1.6 or 4.0 W/kg) for up to 36 hours (resulting in 90% or 10% survival, respectively, at low and high SAR) affected the

Table 4.10 Effects on gene expression in animal models after exposure to radiofrequency radiation *in vivo*

Biological model	Exposure conditions	Assessment of gene expression	Results	Comments	Reference
<i>Caenorhabditis elegans</i> (strain PC72)	1800 MHz (GSM); CW or DTX; SAR, 1.8 W/kg; 2.5 h at 25 °C	Stress-inducible reporter gene β -galactosidase under control of <i>hsp16</i> heat-shock promoter, measured as β -galactosidase activity	No effect on expression of <i>hsp16</i>		Dawe et al. (2008)
<i>Caenorhabditis elegans</i> wild-type (N2)	1000 MHz (CW); SAR, 0.9–3 mW/kg; 2.5 h	Affymetrix <i>C. elegans</i> Genome GeneChip array (> 22 000 probes)	21 upregulated and 6 downregulated genes; less than expected by chance		Dawe et al. (2009)
<i>Drosophila melanogaster</i> F, age 3 d	835 MHz; SAR, 1.6 and 4.0 W/kg; 12, 18, 24, 30, 36 h	Semi-quantitative RT-PCR; analysis of stress genes <i>rolled</i> (<i>Erk</i>), <i>Jra</i> (<i>Jun</i>), <i>Dfos</i> (<i>Fos</i>) and apoptosis-related genes: <i>Bcl2</i> , <i>Dmp53</i> (<i>Trp53</i>), <i>reaper</i> , <i>hid</i>	Increased expression of <i>rolled</i> (1.6 W/kg) and <i>Jra</i> and <i>Dfos</i> (4.0 W/kg); protein-expression changes confirmed gene-expression changes; increased expression of <i>Bcl2</i> (1.6 W/kg) and <i>Dmp53</i> , <i>reaper</i> , <i>hid</i> (4.0 W/kg)		Lee et al. (2008)
Mouse brain (BALB/c) age, 5–6 wk	800 MHz (GSM); SAR, 1.1 W/kg (whole-body); SAR, 0.2 W/kg (brain); 1 h	Affymetrix Mouse Expression Array 430A (22 600 probe sets)	Filtering microarray results for fold-changes > 1.5 and > 2.0 provided; respectively 301 and 30 differentially expressed probe sets	No consistent evidence of modulation of gene expression in whole brain	Paparini et al. (2008)
Rat brain (Wistar, M)	900 MHz (GSM); SAR, 0.3 or 1.5 W/kg; 900 MHz (CW), SAR, 7.5 W/kg; 4 h	Gene expression assessed immediately after exposure. Hybridization <i>in situ</i> ; <i>hsp70</i> , <i>c-fos</i> , <i>c-jun</i> , <i>GFAP</i> ; optical-density analysis	<i>hsp70</i> mRNA: increase at 7.5 W/kg (CW); <i>c-fos</i> mRNA: increase at all exposures; <i>c-jun</i> mRNA: decline at 1.5 W/kg (GSM) and 7.5 W/kg (CW). <i>GFAP</i> mRNA: no effect	Exposure by use of a mobile phone	Fritze et al. (1997a)
Rat brain (F344)	1600 MHz; SAR, 0.16, 1.6, 5 W/kg; 2 h	Northern blot for ornithine decarboxylase, <i>Fos</i> and <i>Jun</i> in total brain RNA; normalization to α -actin probe	No effect on mRNA expression		Stagg et al. (2001)
Rat brain (F344)	915 MHz GSM (DTX); average whole-body SAR, 0.4 W/kg; 2 h	Affymetrix U34A GeneChip (8800 genes)	11 upregulated genes; 1 downregulated gene		Belyaev et al. (2006)

Table 4.10 (continued)

Biological model	Exposure conditions	Assessment of gene expression	Results	Comments	Reference
Rat brain (F344)	1800 MHz (GSM); whole-body SAR, 0.013 W/kg (brain SAR, 0.03 W/kg); 6 h	Affymetrix rat 2302 chip (31 099 genes); categories: upregulated > 1.05-fold; downregulated < 0.95-fold; unaffected, 0.95–1.05-fold	Numerous upregulated and downregulated genes in nearly all 4956 gene ontologies analysed, especially regulatory genes of membrane integrity and cell signalling.	Less reliable due to small “fold-change” criteria; information on affected genes not given	Nittby et al. (2008)
Rat brain, facial nerves (Sprague-Dawley)	1.9 GHz (GSM); SAR, 0.9, 1.18, 1.8 W/kg; 6 h/d, for 126 d	RT-PCR analysis of mRNA for calcium ATPase, N-CAM, NGF-B, VEGF in brain and in facial nerves	Statistically significant upregulation of all mRNAs	Radiation source was a mobile phone; less reliable dosimetry	Yan et al. (2008, 2009)
Rat (newborn) kidney (pregnant Sprague-Dawley rats)	9.4 GHz (GSM); SAR, 0.5 mW/kg; continuously on days 1–3 or 4–7 after mating	RT-PCR analysis of mRNA expression of bone morphogenetic proteins (Bmp) and their receptors (Bmpr)	Increased mRNA expression of Bmp4 and Bmpr1a, and decreased expression of Bmpr2 in kidneys of newborns from rats exposed on days 1–3 or 4–7 of gestation. No effect on expression of Bmpr7.	These changes may reflect a delay in renal development	Pyrpasopoulou et al. (2004)

CW, continuous wave; d, day; DTX, discontinuous transmission mode; GSM, Global System for Mobile communication; h, hour; N-CAM, neural cell-adhesion molecule; NGF, neural growth factor; RT-PCR, reverse-transcriptase polymerase chain reaction; SAR, specific absorption rate; VEGF, vascular endothelial growth factor; wk, week

expression of genes encoding stress-response kinases and proteins involved in the regulation of apoptosis. Interestingly, some of these genes – involved in cell-survival signalling pathways – responded to the lower SAR, while others – involved in apoptotic pathways – were activated by the higher SAR. The changes in gene expression were followed by similar changes in expression of the corresponding proteins ([Table 4.11](#)), which strengthens the validity of the findings.

(iii) *Mouse*

[Paparini et al. \(2008\)](#) exposed BALB/c mice to RF radiation at 1800 MHz (whole-body SAR, 1.1 W/kg; brain-averaged SAR, 0.2 W/kg) for 1 hour, and analysed gene expression in total brain homogenate. The array analysis did not show any significant modulation of gene expression in the exposed mice compared with sham-exposed controls. Under less stringent conditions, 42 genes were found to be upregulated, while 33 were downregulated. However, these results could not be confirmed with RT-PCR. [The Working Group noted that analysing mRNA from a whole-brain homogenate might obscure the detection of any effect in specific brain regions.]

(iv) *Rat*

Groups of 30 male Wistar rats were exposed to RF radiation at 900 MHz (GSM; brain-averaged SAR, 0.3 or 1.5 W/kg) or to continuous-wave RF radiation at 900 MHz (brain-averaged SAR, 7.5 W/kg), for 4 hours. To mimic actual life exposure as closely as possible, the signal was generated with a commercial mobile GSM phone, and a telephone conversation was simulated by repeatedly playing the first half of H. von Kleist's comedy *Der zerbrochene Krug* ([Von Kleist, 1811](#)). Subgroups of 10 rats were processed immediately after exposure, or 24 hours or 7 days later. Enhanced expression of Hsp70 mRNA was observed in the brain at the higher SAR of 7.5 W/kg, and a small but significant increase

was seen in c-Fos expression in the brain at the two lower SAR values ([Fritze et al., 1997a](#)). [The Secretariat was pleased to learn that the spoken text to which the rats were exposed in this study mimicked actual life exposure of the authors, but was uncertain about confounding effects on the rat brain.]

Fischer 344 rats were exposed to RF radiation at 1600 MHz (brain-averaged SAR, 0.16, 1.6, and 5.0 W/kg) for 2 hours. No changes were seen in core body temperature and corticosterone or adrenocorticotrophic hormone levels in the brain that could be attributed to exposure to RF radiation. Also the levels of *Odc*, *Fos* and *Jun* mRNA in brain tissue showed no differences with sham-exposed controls that could be ascribed to RF radiation ([Stagg et al., 2001](#)).

Three groups of pregnant Wistar rats were sham-exposed, or exposed to pulsed-wave RF radiation at 9.4 GHz (SAR, 0.5 mW/kg) continuously during days 1–3 after mating, or during days 4–7 after mating, respectively. In 20–26 newborns collected from each of these groups, significantly altered expression and localization of proteins involved in bone morphogenesis were observed in the kidney. These changes may reflect a delay in renal development ([Pyrpasopoulou et al., 2004](#)).

Whole-body exposure of Fischer 344 rats to RF radiation at 915 MHz (GSM; SAR, 0.4 W/kg) for 2 hours led to significantly ($P < 0.0025$) increased expression (1.34–2.74-fold) of eleven genes and reduced expression (0.48-fold) of one gene in the cerebellum of the exposed rats. Only these genes showed significantly increased/decreased expression in all nine comparisons between three exposed and three sham-exposed rats ([Belyaev et al., 2006](#)).

[Nittby et al. \(2008\)](#) reported a strong response and changes in the expression of numerous genes after whole-body exposure of Fischer 344 rats to RF radiation at 1800 MHz (GSM; SAR, 13 mW/kg) for 6 hours. In this study, changes in gene expression were considered when expression

Table 4.11 Effects on protein expression in human and animal models after exposure to radiofrequency radiation in vivo

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Human skin, female volunteers	900 MHz (GSM); SAR, 1.3 W/kg; local exposure, 1 h; punch-biopsies collected immediately after exposure	Protein expression by 2DE-based proteomics	Expression was significantly increased for 7 proteins, reduced for 1; 2 proteins – one up, one down – were affected in all 10 volunteers	Proteins not identified	Kärinen et al. (2008)
<i>Drosophila melanogaster</i>	1900 MHz (GSM); SAR, 1.4 W/kg; 2 × 1 h per day for 10 d	Immunocytochemistry; serum response element (SRE)-binding, ELK1 phosphorylation, hsp70	Increase in expression of all measured proteins	Unreliable dosimetry: exposure by placing vials next to mobile-phone antenna; unreliable data analysis, single experiments; no statistical analysis	Weisbrot et al. (2003)
<i>Drosophila melanogaster</i>	835 MHz; SAR, 1.6 and 4.0 W/kg; 12, 18, 24, 30, 36 h	Immunocytochemistry; phospho-JNK, phospho-ERK, phospho-p38MAPK	Activation of ERK (at SAR 1.6 W/kg), activation of JNK (at SAR 4.0 W/kg); no effect on p38MAPK		Lee et al. (2008)
<i>Drosophila melanogaster</i>	900 MHz; SAR 0.64 W/kg; continuous/intermittent exposure	Immunofluorescence; phalloidin detection of actin stress fibres	Increase in disorganization of actin network	Unreliable dosimetry: exposure by placing vials next to mobile-phone antenna	Chavdoula et al. (2010)
Mouse brain (C57BL/6NTac) age, 8 wk	900 MHz (GSM); SAR, 4 W/kg. Mice were restrained for 1 h during exposure; brains perfusion-fixed immediately after exposure	Immunocytochemistry; c-fos	Non-significant decline (~50%) in c-fos expression in exposed cingulate cortex; no effects in other parts of the brain	Significant difference of exposed/sham-exposed with cage-controls; effects may be due to immobilization	Finnie (2005)
Fetal mouse brain (BALB/c)	900 MHz (GSM); SAR, 4 W/kg; 1 h daily, on days 1–19 of gestation. Mice were restrained during exposure	Immunocytochemistry; c-fos	Average expression of c-fos was non-significantly increased in basal ganglion and reduced in pyriform cortex		Finnie et al. (2006a)
Mouse brain (C57BL/6NTac)	900 MHz (GSM); SAR, 4 W/kg; 1 h/d, 5 d/wk, 104 wk. Mice were restrained during exposure	Immunocytochemistry; c-fos	No effects on c-fos expression, but no numerical analysis shown	No statistical details given. Significant difference of exposed/sham-exposed with cage-controls; effects may be due to immobilization	Finnie et al. (2007)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Fetal mouse brain (BALB/c)	900 MHz (GSM); SAR, 4 W/kg; 1 h daily on days 1–19 of gestation. Mice were restrained during exposure	Immunocytochemistry; Hsp25, Hsp32, Hsp70	No effect on expression of Hsp; no numerical analysis shown	No statistical details given; shown only examples of stained brain slices	Finnie et al. (2009a)
Mouse brain [strain NS]	900 MHz (GSM); SAR, 4.0 W/kg; 1 h single exposure or 1 h/d, 5 d/wk, 104 wk	Immunocytochemistry; aquaporin (AQP4, marker of blood–brain barrier function)	No effect on aquaporin expression; no numerical analysis shown	No statistical details given; shown only examples of stained brain slices	Finnie et al. (2009b)
Mouse brain [strain NS]	900 MHz (GSM); SAR, 4.0 W/kg; 1 h single exposure or 1 h/d, 5 d/wk, 104 wk	Immunocytochemistry; ionized calcium-binding adaptor molecule Iba1 (microglia activation marker)	No effect on Iba1 expression		Finnie et al. (2010)
Transgenic mouse (hsp70.1-deficient)	849 MHz or 1763 MHz; whole-body average SAR, 0.04 W/kg; 2 × 45 min/d with 15-min interval, 5 d/wk, for up to 10 wk; mice killed after 4, 8, 10 wk of exposure	Immunocytochemistry; PCNA Western blot: actin, HSP90, HSP70, HSP25, ERK and phospho-ERK, JNK and phospho JNK, p38MAPK and phospho-p38MAPK	No effect on HSP90, HSP70, HSP25 expression No effect on phosphorylation of ERK, JNK and p38MAPK		Lee et al. (2005)
Mouse brain (C57BL/6N)	849 MHz or 1763 MHz; brain average SAR, 7.8 W/kg; 1 h/d, 5 d/wk, for 6 or 12 mo	Immunocytochemistry: PCNA, GFAP, NeuN	No effect on expression of PCNA, GFAP, NeuN	No numerical data, no statistical details given Visual evaluation only	Kim et al. (2008b)
Mouse brain (ICR, M)	835 MHz; SAR, 1.6 and 4.0 W/kg; whole-body exposure; 5 h (single), 1 h/d for 5 d; daily [no time given] for 1 mo (1.6 W/kg only)	Immunocytochemistry: calbindin, calretinin	Changes in expression of calbindin and calretinin after 1 mo exposure, particularly in the inner molecular layer of the dentate gyrus of the brain	Alterations in calcium-binding proteins affect cellular Ca ²⁺ levels and hippocampal functions associated with neuronal connectivity and integration	Maskey et al. (2010)
Rat brain (Wistar, M)	900 MHz (GSM, SAR 0.3 and 1.5 W/kg; CW, SAR 7.5 W/kg CW); 4 h; protein expression examined 24 h after exposure	Immunocytochemistry; c-fos, fos B, c-jun, jun B, jun D, krox-20, krox-24, Hsp70, Gfap, MHCclass II;	No effect on expression of any of the proteins examined	Exposure by use of a mobile telephone; only visual inspection and evaluation of samples; no statistical details	Fritze et al. (1997a)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Rat brain (F344, M)	915 MHz (GSM, DTX); average whole-body SAR, 0.4 W/kg; 2 h	Western blot: Hsp70	No effect on expression of hsp70 protein		Belyaev et al. (2006)
Rat brain (Wistar albino)	900 MHz (GSM); SAR, 2.0 W/kg; 2 h/d, 7 d/wk, for 10 mo	Immunocytochemistry: caspase-3, Tp53	No effect on Tp53; caspase-3 re-localized to nucleus	Protein expression scored by visual inspection and evaluation	Dasdag et al. (2009)
Rat brain (Sprague-Dawley)	900 MHz (GSM); SAR, 6 and 1.5 W/kg; exposure 15 min/d for 7 d at high SAR, and 45 min/d for 7 d at low SAR	Cytochrome- <i>c</i> oxidase activity in brain slices by staining with di-amino-benzidine and horse-heart cytochrome- <i>c</i> as substrate	Decreased cytochrome- <i>c</i> oxidase activity in prefrontal, frontal and posterior cortex, septum, and hippocampus, at SAR 6 W/kg	Exposure may affect brain metabolism and neuronal activity	Ammari et al. (2008)
Rat brain (Sprague-Dawley)	900 MHz (GSM); SAR, 6 and 1.5 W/kg; exposure 15 min/d for 8 wk at high SAR, and 45 min/d for 8 wk at low SAR; samples taken 3 and 10 d after exposure	Immunocytochemistry: glial fibrillary acidic protein (Gfap)	Increase in Gfap expression	Gfap increase may be a sign of gliosis	Ammari et al. (2010)
Rat skin (hairless rat, F)	900 MHz or 1800 MHz (GSM); local skin SAR, 5 W/kg; 2 h; sampling immediately after exposure	Immunocytochemistry: Ki67, filaggrin, collagen, elastin	No effect on number of cells expressing Ki-67; no effect on density of filaggrin, collagen and elastin		Masuda et al. (2006)
Rat skin (hairless rat)	900 MHz or 1800 MHz (GSM); local skin SAR, 2.5 and 5 W/kg; 2 h/d, 5 d/wk, for 12 wk; samples taken 72 h after the last exposure	Immunocytochemistry: Ki67, filaggrin, collagen, elastin	No effect on number of cells expressing Ki-67, no effect on density of filaggrin, collagen and elastin		Sanchez et al. (2006a)
Rat skin (hairless rat)	900 MHz or 1800 MHz (GSM); local skin SAR, 5 W/kg; 2 h; sampling immediately after exposure. Multiple exposures to 900 MHz or 1800 MHz (GSM); local skin SAR, 2.5 or 5 W/kg; 2 h/d, 5 d/wk, for 12 wk; samples taken 72 h after the last exposure	Immunocytochemistry: Hsc70, Hsp70 and Hsp25	No effect on expression of stress proteins	Analysis of three areas on three photographs per stained skin slice, quantified by image-analysis software	Sanchez et al. (2008)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Rat kidney (Wistar; newborn)	9.4 GHz; 5 μ W/cm ² ; 0.5 mW/kg; continuously exposed on days 1–3 or 4–7 after mating	Kidneys from newborns of exposed rats were investigated by means of immunocytochemistry (Bmp4 and Bmp7) and <i>in situ</i> hybridization (receptors Bmpr2 and Bmpr1a)	Significant increase in expression and change in localization of Bmp4 Increase in Bmpr1a, decrease in Bmpr2 expression. Effects were stronger after exposure <i>in utero</i> on days 1–3 of gestation (embryogenesis) than on days 4–7 (organogenesis)	Effects dependent on timing of exposure <i>in utero</i>	Pyrrasopoulou et al. (2004)
Rat thyroid (Wistar)	900 MHz (GSM); SAR, 1.35 W/kg; 20 min/d, 3 wk	Immunocytochemistry, transmission electron microscopy; Casp3 and Casp9 (markers of apoptosis)	Significant increase in expression of Casp3 and Casp9; thyroid hypertrophy; reduced thyroid-hormone secretion; formation of apoptotic bodies	Histomorphometry of thyroid tissue	Esmekaya et al. (2010)
Rat testis (Sprague-Dawley)	848.5 MHz (CDMA signal); SAR, 2.0 W/kg; 2 \times 45 min/d with a 15-min interval; 12 wk	Western blot; p21, Tp53, Bcl2, Casp3, PARP	No effect for Tp53, Bcl2, Casp3; no result given for PARP or p21		Lee et al. (2010)

2DE, two-dimensional gel electrophoresis; CDMA, code division multiple access; d, day; DTX, discontinuous transmission mode; F, female; GSM, Global System for Mobile Communications; h, hour; M, male; min, minute; mo, month; NS, not specified; SAR, specific absorption rate; wk, week

had risen or declined by 5%, compared with controls. [The genes investigated in this study were not identified, and the changes in gene expression were not validated by RT-PCR.]

Sprague-Dawley rats were exposed to RF radiation at 1.9 GHz (with SARs of 0.9, 1.18, or 1.8 W/kg at a distance of 2.2 cm) from a mobile phone operating in three different modes, for 2×3 hours per day, for 18 weeks. A statistically significant upregulation of the mRNAs for calcium ATPase, neural cell-adhesion molecule, neural growth factor, and vascular endothelial growth factor was measured in the brain of these rats. In addition, these mRNAs were upregulated in the mandibular and buccal branches of the facial nerve. These results suggest that neurological damage may be associated with long-term mobile-phone use ([Yan et al., 2008, 2009](#)).

4.3.2 Protein expression

See [Table 4.11](#)

(a) Humans

In a pilot study, a small skin area of one forearm of 10 volunteers was exposed to RF radiation at 900 MHz (GSM; SAR, 1.3 W/kg) for 1 hour. Immediately after exposure, punch biopsies were taken from the exposed area and from the other non-exposed forearm of the same person. Proteins were extracted and analysed by means of 2D-gel electrophoresis. Changes in the expression of eight proteins were found; two of these proteins were observed in all 10 volunteers. Identity and function of these proteins were not given ([Karinén et al., 2008](#)).

(b) Experimental animals

(i) *Drosophila melanogaster*

Exposure of fruit flies (*D. melanogaster*) to RF radiation at 1900 MHz from a mobile phone (GSM; SAR, 1.4 W/kg) for 2×1 hour per day, for 10 days, resulted in an increase of 3.6–3.9-fold in the expression of heat-shock protein hsp70,

the phosphorylation of ELK1 kinase, and the DNA-binding activity of the serum-response element (SRE) ([Weisbrot et al., 2003](#)).

As indicated above, exposure of *D. melanogaster* to RF radiation at 835 MHz (GSM; SAR, 1.6 or 4.0 W/kg) for up to 36 hours affected the expression of genes encoding stress-response kinases and proteins involved in the regulation of apoptosis. The expression of the corresponding proteins was confirmed by Western blotting with protein-specific antibodies ([Lee et al., 2008](#)).

[Chavdoula et al. \(2010\)](#) exposed *D. melanogaster* to continuous or intermittent RF radiation at 900 MHz (GSM) from a digital mobile phone (SAR, 0.64 W/kg) for 6 minutes per day, for 6 days. The phone was fully charged and its antenna was in contact with the glass vials containing the flies, and parallel to the vial axis. Exposure to RF radiation caused an increased disorganization of the actin network of the egg chambers. This effect was due to DNA fragmentation, as measured with the TUNEL assay.

(ii) Mouse

Nine studies were performed in mice on changes in protein expression after exposure to RF radiation. The mice were of different age (fetus, or adults aged 6–8 weeks) and different strains (C57BL/6N, C57BL/6NTac, hsp70.1-deficient, BALB/c, ICR); mouse strain and age were not specified in two studies ([Finnie et al., 2009b, 2010](#)). Changes in protein expression were assessed by use of immunocytochemistry with monoclonal and polyclonal antibodies.

ICR mice were exposed to RF radiation at 835 MHz (SAR, 1.6 W/kg and 4.0 W/kg) for 5 hours, 1 hour per day for 5 days, or for 1 month. Changes in the expression of the calcium-binding proteins calbindin D28-k (CB) and calretinin (CR) were measured in the hippocampus by use of immunohistochemistry. Exposure for 1 month produced almost complete loss of pyramidal cells in the CA1 area of the brain. These alterations in calcium-binding proteins may cause

changes in cellular Ca^{2+} levels, which could affect hippocampal functions associated with neuronal connectivity and integration ([Maskey et al., 2010](#)).

Six of the published studies came from a single research group. Most of these studies were based on the same biological material that was separately stained to detect different proteins. Studies from this group have reported no effects on the expression of the following proteins after exposure to RF radiation: c-Fos in adult and fetal mouse brain, stress proteins Hsp25, Hsp32, and Hsp70 in fetal brain, aquaporin 4 in adult brain, and ionized calcium-binding adaptor molecule Iba1 in brain [age not given]. Others have reported similar findings (see [Table 4.11](#)). [The Working Group noted that these studies generally provided very few numerical and technical details.]

(iii) *Rat*

Eleven studies were performed with rats of different ages (newborn to adult) and different strains (Wistar, Fisher 344, hairless rat, Sprague-Dawley). In addition, different tissues were examined (brain, skin, kidney, testis, thyroid). Detection of changes in protein expression was mostly by immunocytochemistry with protein-specific monoclonal and polyclonal antibodies, and in some studies by Western blotting.

Five studies assessed the effects of exposure to RF radiation in rat brain ([Fritze et al., 1997a](#); [Belyaev et al., 2006](#); [Dasdag et al., 2009](#); [Ammari et al., 2008, 2010](#)). These studies considered a limited number of proteins, generally gave negative results for changes in expression, and provided limited statistical detail. Samples were often analysed visually and without calculating statistical significance. For this reason the results were considered less reliable (see comments in [Table 4.11](#)).

In three studies, the effects of mobile-phone radiation on the skin of hairless rats were investigated ([Masuda et al., 2006](#); [Sanchez et al., 2006a](#),

[2008](#)). No effects were observed on any of the proteins analysed.

[Pyrpasopoulou et al. \(2004\)](#) used immunocytochemistry and hybridization in situ to examine the effects of exposure to RF radiation on kidneys of newborn rats and found that exposure affected the expression of bone morphogenic protein (Bmp4) and bone morphogenic protein receptors (Bmpr2, Bmpr1a). Similar changes were observed in the expression of the corresponding genes, as noted above (Section 4.3.1).

[Eşmekaya et al. \(2010\)](#) observed increased expression and activity of the apoptosis-regulating proteins caspase 3 (Casp3) and caspase 9 (Casp9) by use of light microscopy, electron microscopy, and immunohistochemical methods in the thyroid of Wistar rats exposed to RF radiation at 900 MHz (SAR, 1.35 W/kg) for 20 minutes per day, for 3 weeks.

[Lee et al. \(2010\)](#) examined the effects on rat testis of exposure to RF radiation at 848.5 MHz (SAR, 2.0 W/kg) twice per day for 45 minutes, 5 days per week, for 12 weeks. No significant effects were found on any of the apoptosis-associated proteins tested (p21, Tp53, Bcl2, Casp3, PARP).

[The Working Group noted that only few studies in experimental animals have examined the effects of RF radiation on gene and protein expression. These studies used a variety of biological models, and had mixed and inconsistent results. Many proteins that are known to be important for the initiation and development of cancer in humans were not evaluated. The Working Group concluded that the available studies on gene and protein expression in humans and animals exposed to RF radiation did not provide evidence to support mechanisms of carcinogenesis in humans.]

(c) *In-vitro studies in human cells*

(i) *Heat-shock proteins*

See [Table 4.12](#)

Heat-shock proteins (HSPs) are a highly conserved family of chaperone proteins that are found in all cell types; they are expressed abundantly and have diverse functions. HSPs are expressed in response to cold, heat and other environmental stress factors, although some are expressed constitutively. HSPs increase heat tolerance and perform functions essential to cell survival under these conditions. Some HSPs serve to stabilize proteins in specific configurations, while others play a role in the folding and unfolding of proteins, acting as molecular chaperones. Stress-induced transcription of HSPs requires activation of heat-shock factors that bind to the heat-shock promoter element, thereby activating its transcription activity. Overexpression of HSPs has been linked to oncogenic development and poor prognostic outcome for multiple cancers, possibly through the roles of HSPs as mediators of signal transduction and inhibitors of oncogene-mediated senescence ([Evans et al., 2010](#)). Since markedly increased expression of HSPs is co-incident with exposure of cells to a variety of stress factors, expression of HSP genes and proteins in response to exposure to RF radiation has been extensively investigated in a variety of cell models.

Since the effects of RF radiation on HSP expression have been reviewed previously ([Cotgreave, 2005](#)), only recent publications on this issue are reviewed in detail in this Volume. Several studies have reported changes in HSP expression in human cell lines exposed to RF radiation.

[Tian et al. \(2002\)](#) exposed human glioma (MO54) cells to RF radiation at 2.45 MHz (SAR, 5–100 W/kg) for up to 16 hours. An increase in HSP70 protein levels at SARs of 25 and 78 W/kg was observed, but no effect was seen at SARs below 20 W/kg. [The Working Group noted that thermal confounding cannot be ruled out in this study due to the high relative SARs tested, the highly non-uniform SAR distribution within the exposure system, and the considerable reduction

in cell viability (~70%) in some samples during exposure.]

[Leszczynski et al. \(2002\)](#) exposed a human endothelial cell line (EA.hy926) to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 1 hour. The phosphorylation status of several proteins was altered. Specifically, HSP27 was found to undergo a transient increase in expression and phosphorylation immediately after exposure, but this effect had disappeared at 1 or 4 hours after exposure.

[Lim et al. \(2005\)](#) exposed human peripheral blood cells to RF radiation at 900 MHz (average SAR, 0.4, 2.0 or 3.6 W/kg) for 20 minutes, 1 hour, or 4 hours. No statistically significant differences were detected in the number of lymphocytes or monocytes expressing stress proteins HSP27 or HSP70 after exposure, compared with the numbers in sham-exposed samples.

[Miyakoshi et al. \(2005\)](#) exposed human malignant glioma MO54 cells to RF radiation at 1950 MHz (SAR, 1, 2, or 10 W/kg) for up to 2 hours. Exposed cells did not show increased expression of HSP27 or HSP70 protein, but levels of phosphorylated HSP27 had decreased significantly in cells exposed at a SAR of 10 W/kg for 1 or 2 hours.

The transcription of HSPs is regulated by the DNA-binding activity of heat-shock transcription factors (HSFs). These factors bind to specific regulatory elements in the promoter region of HSP genes. In a study by [Laszlo et al. \(2005\)](#), no DNA-binding activity of HSF protein was detected in hamster (HA-1), mouse (C3H 10T½) and human cells (HeLa S3) exposed to 835.62 MHz (SAR, ~0.6 W/kg) or 847.74 MHz (SAR, ~5 W/kg) RF radiation, for up to 24 hours.

[Lee et al. \(2006\)](#) observed no detectable alterations in the expression of HSP27, HSP70 or HSP90 transcripts after exposure of human T-lymphocyte Jurkat cells to RF radiation at 1763 MHz (SAR, 2 or 20 W/kg) for 30 minutes or 1 hour.

Table 4.12 Effects on heat-shock proteins in human cell lines exposed to radiofrequency radiation *in vitro*

Tissue/cell line	Exposure conditions	End-point and target	Results	Comments	Reference
MO54 glioma cells	2450 MHz, CW; SARs, 5, 20, 50, 100 W/kg; 2, 4, 8, 16 h	HSP70 protein expression	Increased expression of HSP70 only at SARs > 20 W/kg	SAR values very high; thermal confounding possible	Tian et al. (2002)
EA.hy926 endothelial cells	900 MHz (GSM); SAR, ~2 W/kg; 1 h	p-HSP27 protein level	Transient change in p-HSP27 and phosphorylation of other unidentified proteins; transient change in HSP27 protein level	Effect had disappeared at 1 or 4 hours after exposure	Leszczynski et al. (2002)
EA.hy926 endothelial cells	1800 MHz (GSM); SAR, 2.0 W/kg; 1 h	Protein HSP27 expression	No effect		Nylund et al. (2009)
Human lens epithelial cells (hLEC)	1800 MHz (GSM); SAR, 1, 2, 3 W/kg; 2 h	HSP70 mRNA and protein expression	Increased expression of HSP70 protein at SAR 2 and 3 W/kg; no change in mRNA levels		Lixia et al. (2006)
HeLa, S3 and EA.hy296 cell lines	837 MHz (TDMA); SAR, 5 W/kg; 1, 2, 24 h; or 900 MHz (GSM); SAR, 3.7 W/kg; for 1, 2, 5 h	p-HSP27 protein levels	No effect		Vanderwaal et al. (2006)
A172 cells and IMR-90 fibroblasts	2142.5 MHz (CW or W-CDMA); SAR, 0.08 and 0.8 W/kg; 2–48 h	HSP27, HSP40, HSP70, HSP105 mRNA and protein expression, p-HSP27 protein levels	No effect		Hirose et al. (2007)
Human blood	900 MHz (CW or GSM); SAR, 0.4, 2 or 3.6 W/kg; 20 min, 1 h, or 4 h	HSP27, HSP70 protein expression	No effect		Lim et al. (2005)
A172 cells	2450 MHz (CW); SAR, 5–200 W/kg; 1–3 h	HSP27, HSP70 protein expression; p-HSP27 protein levels	No effect	SAR values very high (thermal confounding possible)	Wang et al. (2006)
MO54 cells	1950 MHz (CW); SARs, 1, 2, 10 W/kg; 1 or 2 h	HSP27, HSP70 protein expression; p-HSP27 protein levels	Decrease in p-HSP27 at highest SAR		Miyakoshi et al. (2005)
Mono Mac 6 cells	1800 MHz (CW and GSM); SAR, 2 W/kg; 1 h	HSP70 protein expression	No effect		Simkó et al. (2006)
Mono Mac 6 and K562 cells	1800 MHz (CW and GSM); SARs, 0.5, 1, 1.5, or 2 W/kg; 45 min	HSP70 protein expression	No effect		Lantow et al. (2006a)
U-251MG cells	6000 MHz (CW); power density 5.4 $\mu\text{W}/\text{cm}^2$ or 0.54 mW/cm^2 ; 1–33 h	HSP70 mRNA and protein	No effect		Zhadoobov et al. (2007)

Table 4.12 (continued)

Tissue/cell line	Exposure conditions	End-point and target	Results	Comments	Reference
HTR-8/ neo; human trophoblast cell line	1817 MHz (GSM); SAR, 2.0 W/kg; 1 h	HSP70, HSC70 mRNA expression	No effect		Valbonesi et al. (2008)
Human keratinocytes, fibroblasts and reconstructed epidermis	900 MHz (GSM); SAR, 2 W/kg; 48 h	HSP27, HSC70, and HSP70 protein expression	Keratinocytes: no effect Epidermis: slight but significant increase in HSP70 Fibroblasts: significant decrease in HSC70		Sanchez et al. (2006b)
Human primary keratinocytes and fibroblasts	1800 MHz (GSM); SAR, 2 W/kg; 48 h	HSP27, HSP70 and HSC70 protein expression	No effect		Sanchez et al. (2007)
HeLa S3, HA-1, C3H 10T½	835 MHz (FDMA) and 847 MHz (CDMA); SAR, 0.6 W/kg (low dose) and 5 W/kg (high dose); 5–60 min, 24 h	HSF protein DNA- binding activity	No effect		Laszlo et al. (2005)
Jurkat cells	1763 MHz (CDMA), SAR, 2 or 20 W/kg; 30 min or 1 h	HSP27, HSP70, HSP90 protein expression	No effect		Lee et al. (2006)
MO54, A172 and T98 cell lines	1950 MHz (CW); SAR, 1 or 10 W/kg; 1 h	HSP27 mRNA and protein expression, p-HSP27 protein levels	No effect on HSP27 expression Slight decrease in p-HSP27 levels in MO54 cells		Ding et al. (2009)
TK6 cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 1 and 10 W/kg; 6 h	HSP27, HSP70 mRNA expression	No effect		Chauhan et al. (2006a)
HL60 and Mono Mac 6 cells	1900 MHz (pulse-wave; 5 min on, 10 min off); SAR, 1 and 10 W/kg; 6 h	HSP27, HSP70 mRNA expression	No effect		Chauhan et al. (2006b)
Mono Mac 6 and U87MG cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 0.1, 1 and 10 W/kg; 6–24 h	HSP27, HSP40, HSP70, HSP90, HSP105 mRNA expression	No effect		Chauhan et al. (2007a)
U87MG cells	1900 MHz; SAR, 0.1, 1, 10 W/kg; 4 h	HSP27, HSP40, HSP70, HSP86, HSP105 mRNA expression	No effect		Qutob et al. (2006)

CDMA, code-division multiple access; CW, continuous wave; FDMA, frequency-domain multiple access; GSM, Global System for Mobile Communications; h, hour; HSC, heat-shock cognate; HSF, heat-shock factor; HSP, heat-shock protein; p-HSP27, phosphorylated-HSP27; min, minute; RF, radiofrequency; SAR, specific absorption rate; SRE, serum-response element; TDMA, time-domain multiple access; WCDMA, wideband code-division multiple access

[Lixia et al. \(2006\)](#) exposed human lens epithelial cells to RF radiation at 1800 MHz (GSM; SAR, 1, 2, or 3 W/kg) for 2 hours. The authors noted increased expression of HSP70 protein at the higher SARs, but no corresponding change was observed in mRNA expression.

[Simkó et al. \(2006\)](#) exposed a human monocyte-derived cell line (Mono-Mac-6) to RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour, either alone or with ultra-fine particles. The authors observed no effect on the expression of HSP70 protein. In a follow-up study, [Lantow et al. \(2006a\)](#) investigated whether exposure to RF radiation at 1800 MHz (SAR, 0.5–2.0 W/kg) for 45 minutes had an effect on expression of HSP70 in Mono-Mac-6 and K562 cells. No significant effects of exposure to RF radiation were detected in the expression of HSP70 protein in either cell line under any of the conditions tested.

[Vanderwaal et al. \(2006\)](#) found no evidence of altered HSP27 phosphorylation in three human cell lines (HeLa, S3 and EA.hy296) after exposure to RF radiation at 837 MHz (SAR, 5.0 W/kg) for 1, 2, or 24 hours, or at 900 MHz (SAR, 3.7 W/kg) for 1, 2 or 5 hours.

[Wang et al. \(2006\)](#) did not detect any alterations in HSP27, HSP70 or expression of phosphorylated-HSP27 protein in human A172 cells – derived from a malignant glioblastoma – exposed to RF radiation at 2450 MHz (SARs of up to 50 W/kg) for 0–3 hours.

[Sanchez et al. \(2006b\)](#) evaluated possible stress-related effects in isolated human skin cells and in reconstructed human epidermis exposed to RF radiation at 900 MHz (SAR, 2 W/kg) for 48 hours. Immunohistochemical analysis did not reveal any detectable changes in expression of HSP27 or inducible HSP70 in exposed keratinocytes. However, levels of HSC70 (heat shock cognate) protein were significantly decreased in dermal fibroblasts isolated from human skin after exposure to RF radiation. Such results were not seen in reconstructed human epidermis. Human skin cells may thus react to exposure by

modulating the expression of some HSPs, but this response may depend on the cell model. In a follow-up study, the same investigators found that primary human skin cells (keratinocytes and fibroblasts) did not display any alterations in inducible HSP27, HSP70 or HSC70 protein levels after exposure at 1800 MHz (SAR, 2 W/kg) for 48 hours ([Sanchez et al., 2007](#)). [The authors did not discuss the different responses observed in these two studies.]

[Hirose et al. \(2007\)](#) examined HSP27 phosphorylation, gene and protein expression in human glioblastoma A172 cells and human IMR-90 fetal lung fibroblasts exposed to RF radiation at 2142.5 MHz (SARs up to 0.8 W/kg) for 2–48 hours. No evidence of altered HSP27 phosphorylation or increased mRNA expression of a variety of HSPs was found in either cell line.

[Zhadobov et al. \(2007\)](#) investigated the expression of stress-sensitive genes and proteins in a human glial cell line (U-251MG) exposed to RF radiation at 60 GHz (power density, 5.4 $\mu\text{W}/\text{cm}^2$ or 0.54 mW/cm^2) for 1–33 hours. No evidence was found for altered expression of stress-response genes, as determined by reporter assays and RT-PCR. Western-blot analysis indicated no effects of RF radiation on levels of clusterin or HSP70 protein.

[Valbonesi et al. \(2008\)](#) observed no change in expression of HSP70 in the human HTR-8/SVneo trophoblast cell-line exposed to RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour.

Exposure of the human endothelial cell line EA.hy926 to 1.8 GHz RF radiation (SAR, 2.0 W/kg) for 1 hour did not result in altered HSP protein expression; phosphorylation status was not assessed in this study ([Nylund et al., 2009](#)).

[Ding et al. \(2009\)](#) studied three human glioma cell-lines (MO54, A172, T98) and found no evidence of altered HSP expression or phosphorylation after exposure to RF radiation at 1950 MHz (SAR, 1 or 10 W/kg) for 1 hour. These findings were supported by results of a series of earlier studies by [Chauhan et al. \(2006a, b, 2007a\)](#)

and [Qutob et al. \(2006\)](#), in which exposure at 1900 MHz (SAR, 0.1–10 W/kg) for 4–24 hours did not alter the transcript expression of HSP27, HSP40, HSP70, HSP90 or HSP105, in several human cell lines (MM6, U87MG, HL60, TK6).

[The Working Group noted that a small number of studies reported altered expression of HSPs in certain cell lines ([Leszczynski et al., 2002](#); [Tian et al., 2002](#); [Miyakoshi et al., 2005](#); [Lixia et al., 2006](#); [Sanchez et al., 2006b](#)). However, it was not clear whether these responses were specific to the cell line, the frequency, the modulation or model used, or were false-positives, e.g. artefacts caused by irregularities in the exposure system. The majority of studies conducted in cultured human cells to date have found no evidence that exposure to RF radiation under non-thermal conditions elicits alterations in the expression of HSP genes or proteins.]

(ii) *Proto-oncogenes and signal-transduction pathways*

See [Table 4.13](#)

Several studies have investigated the ability of RF radiation to mediate the expression of proto-oncogenes and proteins involved in the regulation of signal-transduction pathways. Proto-oncogenes are genes with the capacity to induce cellular proliferation and/or transformation. While these genes are constitutively expressed at low levels, they are rapidly and transiently induced in response to external stress stimuli. Similarly, transcriptional activity in response to stress factors can be mediated by mitogen-activated protein kinase (MAPK) pathways, which include the extracellular signal-regulated kinase (ERK), p38 and the c-Jun N-terminal kinase (JNK) cascades. These pathways are complex and regulate a variety of cellular processes, including proliferation, differentiation, metabolism and the stress response. Upon phosphorylation of these kinases, a large number of regulatory proteins and transcription factors can become activated, thereby altering

cellular processes and allowing further gene transcription.

[Li et al. \(1999\)](#) exposed human fibroblasts to continuous-wave RF radiation at 837 MHz (SAR, 0.9–9.0 W/kg) for 2 hours. No evidence of altered expression of TP53 protein was found.

[Leszczynski et al. \(2002\)](#) exposed a human endothelial cell line (EA.hy926) to RF radiation at 900 MHz (SAR, 2 W/kg) for 1 hour. A transient increase was noted in p38-MAPK and in phosphorylation of HSP27. This effect could be inhibited by SB203580 (a specific inhibitor of p38-MAPK). Since accurate measurements indicated no alterations in cell-culture temperature during the exposure period, activation of the p38-MAPK stress-response pathway might be a potential mode of non-thermal molecular interaction of RF radiation with biological tissue.

[Caraglia et al. \(2005\)](#) exposed human epidermoid-cancer KB cells to RF radiation at 1950 MHz (SAR, 3.6 W/kg) for 1–3 hours. Decreased expression was noted for the proteins Ras, Raf-1 and Akt. The activity of Ras and ERK1/2 was determined by their phosphorylation status, and found to be reduced. This exposure to RF radiation increased JNK1/2 activity and expression of HSP27 and HSP70, but caused a reduction in p38-MAPK activity and HSP90 expression. [The Working Group noted that details on the exposure system were incompletely described, and that these observations may have been due to thermal effects.]

[Miyakoshi et al. \(2005\)](#) exposed human glioma cells (MO54) to RF radiation at 1950 MHz (SAR, 10 W/kg) for 2 hours. A decrease was noted in the phosphorylation of HSP27 at serine-78, indicating repression of the p38-MAPK cascade or activation of an HSP27 phosphatase.

[Lee et al. \(2006\)](#) exposed Jurkat cells to RF radiation at 1763 MHz (SAR, 2 or 20 W/kg) for 30 minutes to 1 hour in the presence or absence of the phorbol-ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). There was no evidence of an altered phosphorylation status of ERK1/2,

Table 4.13 Studies on the effect of radiofrequency radiation on the expression of proto-oncogenes in human cells *in vitro*

Tissue/cell line	Exposure	End-point and target	Results	Comments	Reference
Human endothelial EA.hy926 cells	900 MHz (GSM); ~2 W/kg; 1 h	p38MAPK protein expression	Transient change		Leszczynski et al. (2002)
Rat1, HeLa cells	800/875/950 MHz; power density 0.07–0.31 mW/cm ² ; 5–30 min	ERK1/2, JNK1/2, p38MAPK, EGFR, Hb-EGF protein expression, phosphorylation status	Transient increase of ERK1/2 phosphorylation at 0.10 mW/cm ² . Phosphorylation of p38MAPK and JNK1/2 (stress-activated cascades) is not changed. Phosphorylation is ROS-dependent	Stress-activated cascades are not affected, which may indicate that effects are non-thermal. Temperature remained constant within 0.05 °C.	Friedman et al. (2007)
Human epidermoid KB cell line	1950 MHz; SAR, 3.6 W/kg; 1, 2, 3 h	Ras, Raf-1, Akt, ERK1/2, JNK1/2, HSP27, HSP70, HSP90 protein expression, phosphorylation status	Expression of ras, Raf-1, Akt, and HSP90 was reduced; expression of HSP27 and HSP70 was increased. Phosphorylation of ERK1/2, ras, p38MAPK was reduced, while that of JNK1/2 was increased	Incomplete details on RF exposure; no temperature control; possible thermal confounding	Caraglia et al. (2005)
Human neuroblastoma (SH-SY5Y) cells	900 MHz (GSM); SAR, 1 W/kg; 5, 15, 30 min, 6 h, 24 h	EGRI, ERK1/2, SAPK/JNK, p38MAPK, ELK1, BCL2, survivin mRNA and protein expression, phosphorylation status	Transient increase in EGRI and ELK1 transcript levels; transient increase in ERK1/2, SAPK/JNK phosphorylation. Evidence of apoptosis after 24 h exposure	Confounding due to environmental factors unclear	Buttiglione et al. (2007)
Jurkat cells	1763 MHz (CDMA); SAR, 2 or 20 W/kg; 30 min or 1 h	p38MAPK, ERK1/2, JNK1/2 protein expression, phosphorylation status	No effect on protein expression for HSP90, HSP70, HSP27; no effect on phosphorylation without TPA	Exposure conditions and temperature properly controlled	Lee et al. (2006)
Human glioma MO54 cells	1950 MHz (CW); SAR, 10 W/kg; 1h and 2h	Phosphorylated HSP27 protein levels	Decrease in phosphorylation of HSP27		Miyakoshi et al. (2005)
TK6, MM6, HL-60 cells	1900 MHz (PW); 5 min on, 5 min off; SAR, 1 or 10 W/kg; 6 h	c-fos, c-myc, c-jun mRNA expression	No effect		Chauhan et al. (2006a, b)
WSIneo human foreskin fibroblasts	837 MHz (CW); SAR, 0.9 or 9 W/kg; 2 h	TP53 protein expression	No effect		Li et al. (1999)
Human glioblastoma A172, human lung IMR-90 fibroblasts	2142.5 MHz (CW, W-CDMA); SAR, 80, 250, 800 mW/kg; 24, 28, 48 h	APAF1, TP53, TP53BP2 and CASP9 protein levels, phosphorylation status	No effect	Temperature control unclear	Hirose et al. (2006)

CDMA, code-division multiple access; CW, continuous-wave; FDMA, frequency-division multiple access; FMCW, frequency-modulated continuous wave; GSM, Global System for Mobile communications; h, hour; min, minute; RF, radiofrequency; SAR, specific absorption rate; TDMA, time-division multiple access; TPA, 12-O-tetradecanoylphorbol-13-acetate; W-CDMA, wideband code-division multiple access

JNK1/2 or p38-MAPK after exposure to RF radiation, with or without TPA.

[Chauhan *et al.* \(2006a, b\)](#) exposed three human-derived cell lines (TK6, MM6, HL-60) to intermittent (5 minutes on/10 minutes off) RF radiation at 1900 MHz (SAR, 1 or 10 W/kg) for 6–24 hours. No significant differences were observed in relative expression levels of the proto-oncogenes *c-JUN*, *c-FOS* and *c-MYC* in any of the cell lines examined.

[Hirose *et al.* \(2006\)](#) examined gene-transcript levels in human A172 and IMR-90 cells following exposure to RF radiation. A series of genes known to be involved in TP53-mediated apoptosis (including *APAF1*, *TP53*, *TP53BP2* and *CASP9*) were assessed after the cells had been exposed at 2142.5 MHz (SAR, 0.08–0.8 mW/kg) for up to 48 hours. No significant differences were observed in the expression of these TP53-related apoptosis genes, relative to the sham-exposed control groups, under any of the conditions tested.

[Buttiglione *et al.* \(2007\)](#) assessed the expression levels of several transcription factors (*EGR1*, *BCL2*, *ELK1*) downstream of the MAPK pathways. *EGR1* transcript expression and phosphorylation of ERK1/2 and JNK in human SH-SY5Y neuroblastoma cells were evaluated after exposure to 900 MHz RF radiation (SAR, 1 W/kg) for 5 minutes up to 24 hours. There was a transient increase in *EGR1* levels at 5–30 minutes after exposure; this effect was no longer evident at 6–24 hours after exposure. Phosphorylation of ERK1/2, JNK1/2 and *ELK1* was also transiently increased after various exposure times (5 minutes to 6 hours), while a significant decrease in the transcript levels of *BCL2* and survivin was observed after 24 hours of exposure. However, a significant decrease in cell viability (as determined by the MTT assay) was noted, as well as the appearance of subG₁ nuclei and a G₂–M block (as determined by flow cytometry) after 24 hours of exposure. [The Working Group noted that the appearance of subG₁ nuclei is indicative of possible induction of apoptosis in the cell

culture. It was unclear whether this effect was thermal or non-thermal in nature.]

[Friedman *et al.* \(2007\)](#) reported that low-level exposure of serum-starved HeLa cells to RF radiation at 875–950 MHz (power densities, 0.07–0.31 mW/cm²) for 5–30 minutes, significantly activated the ERK1/2 signal-transduction pathway via generation of ROS through NADPH-oxidase activation. Neither the p38-MAPK nor the JNK1/2 stress-response pathways were activated by RF radiation. [The Working Group noted that the description of the exposure conditions in this study was poor.]

[The Working Group noted that there was weak evidence from studies with human cell lines that non-thermal RF exposure could result in alterations in the expression or phosphorylation of proto-oncogenes or proteins involved in signal-transduction pathways. Most studies that report altered expression of genes or proteins, or phosphorylation of proteins involved in cell homeostasis, proliferation and signal-transduction pathways, appeared to have been conducted under unique exposure conditions, with results that show no clear dose- and time-response.]

(d) *High-throughput studies of gene and protein expression*

See [Table 4.14](#)

In recent years, many studies have employed high-throughput techniques to analyse differential gene/protein expression in human cells in response to exposure to RF (reviewed by [Vanderstraeten & Verschaeve, 2008](#); [McNamee & Chauhan, 2009](#)). While such technology offers ample opportunity for understanding potential biological interactions of RF radiation in a hypothesis-free testing approach, it is also subject to generating a large number of “false-positive” results. For this reason, it is fundamentally important that such high-throughput studies employ rigorous statistical-inference analysis, include an appropriate number of biological replicates, and validate the differential expression of gene

Table 4.14 High-throughput studies on the effects of radiofrequency radiation on gene and protein expression

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
C3H 10T½ mouse cells	847.7 MHz (CDMA) or 835.6 MHz (FDMA); SAR, 5 W/kg; 24 h	Affymetrix GeneChip U74Av2	Differential expression of ~200 genes	Not confirmed by RT-PCR	Whitehead et al. (2006)
Mouse embryo primary cultured neurons/astrocytes	1900 MHz (GSM); SAR not reported; 2 h	GEArray Q Series Mouse Apoptosis gene array, RT-PCR	Neurons: upregulation of <i>Casp2</i> , <i>Casp6</i> , <i>Pycard</i> ; <i>Casp9</i> and <i>Bax</i> mRNA levels unchanged Astrocytes: upregulation of <i>Casp2</i> , <i>Casp6</i> , <i>Pycard</i> , <i>Bax</i>	Uncontrolled experimental conditions (exposure from mobile phone). Confirmed by RT-PCR	Zhao et al. (2007a)
Rat neurons	1800 MHz (GSM) PW; 5 min on, 10 min off; SAR, 2 W/kg; 24 h	Affymetrix GeneChip Rat Neurobiology U34 Array	Of 1200 screened genes, 24 were upregulated and 10 were downregulated	Confirmed by RT-PCR; fair agreement with micro-array data	Zhao et al. (2007b)
EA.hy926 human endothelial cells	900 MHz (GSM); SAR, 2.4 W/kg; 1 h	2DE protein analysis (silver staining), MALDI-MS	Found 38 altered spots; 4 spots identified by MALDI-MS; 2 spots (increased expression) were identified as vimentin isoforms (confirmed by Western blot) 2 spots (downregulated expression) were identified as IDH3A and HNRNP1	Nylund & Leszczynski (2004)	
EA.hy926, EA.hy926v1,	900 MHz (GSM); SAR, 2.8 W/kg; 1 h	Atlas Human vl.2 cDNA arrays (1167 genes screened); 2DE protein analysis (silver staining)	EA.hy926 cells: 1 gene downregulated, 38 altered protein spots in EA.hy926 EA.hy926v1 cells: 13 genes upregulated, 45 altered protein spots	No confirmation of gene-expression results with RT-PCR, or of proteome results with Western blotting; minimum number of biological replicates	Nylund & Leszczynski (2006)
MCF7 cells	849 MHz (CDMA); SAR, 2 or 10 W/kg; 1 h/d for 3 d	2DE protein analysis (silver staining), electrospray ionization MS-MS, Western blotting, RT-PCR	No reproducible changes in protein expression; GRP78 protein/RNA not differentially expressed	Exposure conditions and temperature properly controlled. Minimum number of biological replicates	Kim et al. (2010)
Human lens epithelial cells (hLEC)	1800 MHz (GSM); SAR, 1, 2, 3.5 W/kg; 2 h	2-DE protein analysis (silver staining), electrospray ionization MS-MS	More than 1600 protein spots were differentially expressed in each condition vs sham-exposed control. Of four upregulated proteins (at SAR 2 and 3.5 W/kg), two were identified by MS (hnRNP K, HSP70)	Number of independent experiments unclear; no confirmation by Western blotting	Li et al. (2007)

Table 4.14 (continued)

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
Jurkat cells, fibroblasts, leukocytes	1800 MHz (GSM PW, 5 min on, 10 min off); SAR, 2 W/kg; 8 h	2DE protein analysis (fluorescence), ion-trap MS-MS	No differentially expressed protein spots by fluorescence 2DE. Increased rate (> 2-fold) of <i>de novo</i> protein synthesis in exposed cells	Not corrected for multiple comparisons; no confirmation by Western blotting; minimum number of biological replicates	Gerner et al. (2010)
NB69, U937 EA.hy926, CHME5, HL60, lymphocytes, used pooled RNA	900 or 1800 MHz (GSM); SAR, 0.77 or 1.8–2.5 W/kg; 1, 24, and 44 h	Human Unigene RZPD-2 cDNA array (~75 000 probes screened)	Differential gene expression in three cell lines (EA.hy926, U937, HL60)	No confirmation of results with RT-PCR; insufficient number of biological replicates. Exposure conditions and temperature properly controlled	Remondini et al. (2006)
Jurkat cells	1763 MHz (CDMA); SAR, 10 W/kg; 1 h/d for 3 d	Applied Biosystems 1700 full genome array (30000 probes)	No gene-expression changes > 2-fold; 10 genes changed > 1.3-fold ($P < 0.1$)	No confirmation of results with RT-PCR	Huang et al. (2008a)
A172, H4 and IMR90 cell lines	2142.5 MHz (CW and W-CDMA); SAR, 0.08, 0.25, 0.80 W/kg; 96 h	Affymetrix Human Genome HG-U133A and B arrays	Differential expression (>2-fold) of 8 genes (H4 cells), 5 genes (A172 cells) and 1 gene (IMR90 cells)	Genes not all identified; insufficient number of independent experiments; no confirmation by RT-PCR	Sekijima et al. (2010)
MCF7 cells	1800 MHz (GSM PW; 5 min on, 10 min off); SAR, 2 or 3.5 W/kg; 24 h	Affymetrix GeneChip Test3 arrays (~22 000 probes screened)	No effect at 2 W/kg; five genes upregulated at 3.5 W/kg	RT-PCR analysis did not confirm differential expression of the five candidate genes identified by microarray analysis. Insufficient number of biological replicates	Zeng et al. (2006)
A172 and IMR90 cells	2142.5 MHz (CW and W-CDMA); SAR, 0.08, 0.25, 0.8 W/kg; 24, 28, 48 h	Affymetrix Human Genome U133 Plus 2.0 GeneChip (38 000 probes screened)	No consistent changes in gene expression in two experiments. Lack of response for TP53-related gene expression (TP53, TP53BP2, APAF1 and CASP9) confirmed by microarray hybridization and RT-PCR	Insufficient number of biological experiments	Hirose et al. (2006)
A172 cells and IMR90 fibroblasts	2142.5 MHz (CW and W-CDMA); SAR, 0.08 or 0.8 W/kg; 2–48 h	Affymetrix Human Genome U133 Plus 2.0 GeneChip (38 000 probes screened)	No effect	No parallel experiments with RT-PCR; insufficient number of biological replicates	Hirose et al. (2007)

Table 4.14 (continued)

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
U87MG glioblastoma cells	1900 MHz (PW); SAR 0.1, 1, 10 W/kg; 4 h	Agilent Human 1A arrays (~22 000 probes screened)	No effect	Lack of effect on several HSPs confirmed by RT-PCR; multiple doses of RF radiation tested; concurrent positive, negative and sham controls; exposure conditions and temperature properly controlled	Qutob et al. (2006)
TK6, HL60, Mono Mac 6 cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 0.1, 1, 10 W/kg; 6 or 24 h	Agilent Human 1Av2 arrays (~22 000 probes screened)	No effect	No parallel experiments with RT-PCR; multiple doses of RF radiation tested; concurrent positive, negative and sham controls; exposure conditions and temperature properly controlled	Chauhan et al. (2007a)
Glial cell line (SVGp12)	2450 MHz (CW); SAR, 1, 5, 10 W/kg; 1, 2, 24 h	AceGene Premium Human DNA Array, RT-PCR	Microarray analysis identified 23 differentially expressed genes and showed 5 unassigned gene spots; 17 genes were upregulated, 11 were downregulated	RT-PCR analysis with 22 of the 23 genes did not confirm microarray data. Minimum number of biological replicates	Sakurai et al. (2011)
EA.hy926 cells	1800 MHz (GSM); SAR, 2 W/kg; 1 h	2DE protein analysis, MALDI-TOF MS analysis, Western blotting	Eight differentially expressed protein spots; three identified as SRM, GRP78 and PSA1	Western blot found no response in GRP78, or changes in HSP27 and vimentin expression	Nylund et al. (2009)
HUVEC, HBMEC cells	1800 MHz (GSM); SAR, 2 W/kg; 1 h	2DE-DIGE	No differentially expressed spots in either cell line when corrected for multiple comparisons (correction for false-discovery rate)	Exposure conditions and temperature properly controlled	Nylund et al. (2010)

2DE, two-dimensional gel electrophoresis; CDMA, code-domain multiple access; CW, continuous wave; d, day; DIGE, difference gel electrophoresis; FDMA, frequency domain multiple access; GSM, Global System for Mobile Communications; h, hour; HSC, heat-shock cognate; HSF, heat-shock factor; HSP, heat-shock protein; min, minute; MALDI-MS, matrix-assisted laser desorption/ionization mass spectrometry; MALDI-TOF MS, matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MS-MS, tandem mass spectrometry; p-HSP27, phosphorylated-HSP27; PW, pulsed wave; RT-PCR, reverse-transcriptase polymerase chain reaction; SAR, specific absorption rate; SRE, serum response element; W-CDMA, wideband-code division multiple access

and proteins by use of alternative techniques (e.g. RT-PCR or Western blotting).

(i) *Proteomics studies in human cells*

[Nylund & Leszczynski \(2004\)](#) reported altered expression of 38 protein spots – observed in a two-dimensional (2D) electrophoresis gel – and identified 4 proteins by matrix-assisted laser desorption/ionization–mass spectrometry (MALDI-MS) in the human endothelial cell line EA.hy926, exposed to RF radiation at 900 MHz (SAR, 2.4 W/kg) for 1 hour. Of particular interest was that two of the spots identified were isoforms of the cytoskeletal protein, vimentin. In a subsequent genomics/proteomics study, [Nylund & Leszczynski \(2006\)](#) observed that 1 gene was downregulated in the EA.hy926 cell line and 13 genes were upregulated in a related EA.hy926v1 cell line exposed to RF radiation at 900 MHz (SAR, 2.8 W/kg) for 1 hour. Proteome analysis indicated 38 differentially expressed proteins in the EA.hy926 cell line and 45 altered proteins in the EA.hy926v1 cell line. The identity of the differentially expressed proteins was not determined. More recent studies by these authors, with exposure of the cells at 1800 MHz (SAR, 2.0 W/kg) did not show the altered expression of, e.g. vimentin ([Nylund et al., 2009, 2010](#)). [The Working Group noted that the observations reported in these studies were either not confirmed by Western blotting, or were identified as artefacts upon further investigation. The discrepancy in the results with RF radiation at 900 and 1800 MHz may be attributable to the different exposure frequencies; the different distribution of SAR within the cell cultures, *i.e.* less uniform SAR distribution at 900 MHz; and the occurrence of false positives when using the silver-stain-based 2D gel-electrophoresis technique.]

[Li et al. \(2007\)](#) exposed human lens epithelial cells to RF radiation at 1800 MHz (SAR, 1, 2, and 3.5 W/Kg) for 2 hours. In the 2D-electrophoresis pattern, enhanced expression was noted of two stress-related proteins, namely HSP70 and

ribonucleoprotein K. [The Working Group noted that failure to confirm the identity of the spots by Western blotting made the results of this study difficult to interpret.]

[Kim et al. \(2010\)](#) employed 2D gel-electrophoresis to examine the proteome of human MCF7 breast-cancer cells exposed to RF radiation at 849 MHz (SAR, 2 or 10 W/kg) for 1 hour per day, on three consecutive days. At 24 hours after exposure, no significant differences in protein expression were identified between exposed and sham-exposed cells.

[Gerner et al. \(2010\)](#) assessed relative protein expression in Jurkat cells, human fibroblasts and primary mononuclear cells (leukocytes) exposed to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 2 W/kg during the “on” phase) for 8 hours, in growth medium containing [³⁵S]methionine/cysteine. No significant differences were observed between sham-exposed and RF-exposed samples in the expression of any particular proteins by use of 2D gel-electrophoresis with fluorescence detection. However, cells exposed to RF radiation for 8 hours displayed a significant increase in protein synthesis, measured as enhanced incorporation of ³⁵S in autoradiographs of the 2D gel: in Jurkat cells, 14 proteins showed a doubling of the spot intensity in the autoradiograph. All these proteins were identified by ion-trap mass spectrometry. Of these 14 proteins, 13 were also enhanced in 2D autoradiographs prepared with samples from exposed fibroblasts. Several stress-responsive proteins were particularly affected, including Hsp70 and Hsp90. The enhancement of the signals in the leukocytes (stimulated/non-stimulated) were much weaker, with only heat-shock protein Hsp60 showing a more than twofold increase. These results suggest increased synthesis de novo of these proteins in cells exposed to RF radiation. None of these observations were validated with other techniques.

[The Working Group noted that the studies assessing proteomic changes in human cells

were limited in number, and shortcomings were evident in some.]

(ii) *Transcriptomics studies in human cells*

[Remondini et al. \(2006\)](#) isolated RNA from six human-derived cell lines (NB69, EA.hy926, T lymphocytes, U937, CHME5, and HL-60) after exposure to RF radiation at 900 MHz or 1800 MHz (SAR, 1.0, 1.3, 1.4, 1.8–2.5, and 2.0) for 1, 2, or 44 hours. In some cases, the exposure at 1800 MHz was intermittent with 5/5, 5/10, or 10/20 minutes on/off. Total RNA was isolated and processed for transcriptome analysis, i.e. to detect changes in gene expression. There was no evidence of differential gene expression in three of the cell lines tested (NB69, T lymphocytes, CHME5), but alterations in gene expression (12–34 differentially expressed genes) were observed in EA.hy926, U937, and HL-60 cells under various exposure conditions. [The Working Group noted that the conclusions that could be drawn from this study were limited since the data analysis was carried out using a single RNA pool for each condition, making it impossible to estimate the true biological variance for statistical inference testing. Furthermore, no validation of results by RT-PCR was performed.]

[Zeng et al. \(2006\)](#) exposed human MCF7 breast-cancer cells to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 2.0 or 3.5 W/kg) for 24 hours. No statistically significant differences were observed at the lower SAR, but five differentially expressed genes were detected in cells exposed at the SAR of 3.5 W/kg. [These findings were not validated with RT-PCR.]

[Hirose et al. \(2006\)](#) observed no noticeable changes in *TP53*-related gene expression in human A172 or IMR-90 cells exposed to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg) for 24–48 hours. In this study the authors confirmed the absence of a response in the microarray analysis for four genes (*APAF1*, *TP53*, *TP53BP2* and *CASP9*) involved in *TP53*-mediated apoptosis

by use of RT-PCR. In a similar study, [Hirose et al. \(2007\)](#) exposed the same two cell lines to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg) for 2–28 hours. Despite assessing a variety of exposure conditions, including exposure duration, signal modulation and SAR levels, the authors reported no differential expression in hsp-related genes under any of the conditions tested in either cell line.

[Qutob et al. \(2006\)](#) exposed human glioblastoma-derived (U87MG) cells to pulsed-wave RF radiation at 1900 MHz (SAR, 0.1, 1 or 10 W/kg) for 4 hours. There was no evidence for differential gene expression in any of the exposed samples relative to the sham-exposed cells. As a positive control, exposure to heat-shock (43 °C, 1 hour) did induce several stress-responsive genes. In an extension of this study, the same research group exposed U87MG cells to RF radiation at 1900 MHz (SAR, 0.1, 1 or 10 W/kg) for 24 hours, and harvested RNA at 6 hours after exposure. In addition, the human-derived monocyte cell line (Mono-Mac-6) was exposed under similar conditions for 6 hours, and RNA was harvested either immediately or 18 hours after exposure. No evidence for differential gene expression was observed in either cell line, at any SAR or time-point tested ([Chauhan et al., 2007a](#)).

[Huang et al. \(2008a\)](#) exposed human-derived Jurkat cells to RF radiation at 1763 MHz (SAR, 10 W/kg) for 1 hour per day, for 3 days. Genome-wide analysis did not identify any genes that were differentially expressed at a significant level ($P < 0.05$) with a greater than twofold change, but 10 genes were identified with a 1.3-fold change, with $P < 0.1$.

[Sekijima et al. \(2010\)](#) exposed three human cell lines (A172, glioblastoma; H4, neuroglioma; IMR-90 fibroblasts) to continuous-wave or W-CDMA-modulated RF radiation at 2142.5 MHz (SAR, 0.08, 0.25 or 0.8 W/kg) for up to 96 hours. Differential expression of a small number of genes was observed in each cell line. Ribosomal protein S2, growth arrest-specific

transcript 5, and integrin beta 5 were differentially expressed in H4 cells at the two higher SARs tested. [These findings were not validated with RT-PCR.]

[Sakurai et al. \(2011\)](#) assessed differential gene expression in a normal human astroglia cell-line (SVGp12) exposed to continuous-wave RF radiation 2450 MHz at (SAR, 1, 5 or 10 W/kg) for 1, 4, or 24 hours. With the high-throughput microarray, this study identified 17 genes that were upregulated and 11 that were downregulated in response to exposure to RF radiation. However, RT-PCR analysis found that the expression of these genes was not statistically different from that in the sham-exposed control group. [The Working Group noted that these results highlight the importance of proper validation of results generated by means of high-throughput screening.]

(iii) *Transcriptomics studies in cultured mammalian cells*

[Whitehead et al. \(2006\)](#) exposed C3H 10T½ mouse cells to RF radiation at 847.74 MHz (CDMA) or at 835.2 MHz (FDMA) (SAR, 5 W/kg) for 24 hours. Three independent experiments were conducted for each of the signal modulations, and matching samples were exposed to X-radiation (0.68 Gy) as positive controls. By intercomparison of the six sham-exposed samples an empirical estimate was made of the false-discovery rate. From the results of this analysis, the authors concluded that all of the gene-expression changes found after exposure to RF radiation were false positives, and that exposure to RF radiation had no effect on gene expression. No validation with RT-PCR was conducted. [The Working Group noted that genes responding to RF radiation were disregarded on the basis of the calculated false-discovery rate, rather than validated by means of RT-PCR. This was not scientifically justified as genes that were not false-positives may have been accidentally

disregarded. Therefore, this study provided little useful information.]

[Zhao et al. \(2007a\)](#) investigated the expression of genes related to apoptosis in primary cultured neurons and astrocytes isolated from ICR mouse embryos aged 15 days. The cells were exposed to GSM-modulated RF radiation at 1900 MHz (SAR not given) from a mobile phone placed over the culture dish for 2 hours. Upregulation of several genes involved in the apoptotic pathway was observed, including *Casp2*, *Casp6* and *Pycard*. For the astrocytes, these effects were exposure-dependent, and not observed after sham-exposure (with the mobile phone on “stand-by”). These results were confirmed by RT-PCR analysis. [The Working Group noted that this study had some methodological deficiencies. The cells were exposed to RF radiation from a mobile phone under poorly defined experimental conditions with regards to control for electromagnetic-field components, such as SAR levels within the cell cultures during exposure.]

In a second study, [Zhao et al. \(2007b\)](#) observed significant changes in gene expression in primary rat neurons exposed to intermittent (5 minutes on, 10 minutes off) GSM-modulated RF radiation at 1800 MHz (SAR, 2 W/kg) for 24 hours. Ten downregulated and 24 upregulated genes were identified among the 1200 genes that were screened, with “fold-change” as the analysis criterion. These findings were confirmed by RT-PCR analysis of 17 of the upregulated and 8 of the downregulated genes, showing fair agreement with the microassay data.

[Nylund et al. \(2009\)](#) examined the proteome of human endothelial cells (EA.hy926) exposed to GSM-modulated RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour. In 2D gel-electrophoresis, eight proteins were found to be differentially expressed in exposed cells, three of which were identified as SRM, GRP78, and PSA1. Western blotting did not confirm the response of GRP78 [SRM and PSA1 not tested due to lack of specific antibodies]. No effect was seen on the

expression of vimentin or HSP27 protein, which were found to respond to radiation at 900 MHz in earlier studies (see above). In a subsequent study, [Nylund et al. \(2010\)](#) exposed umbilical vein endothelial cells (HUVEC) and human brain microvascular endothelial cells (HBMEC) to the same type of RF radiation. No effects on protein expression were reported.

[Of the numerous studies that investigated the potential for RF radiation to modify gene-transcription and protein-expression levels in a variety of animal models *in vivo* and human models *in vitro*, some reported effects under conditions where the possibility of thermal confounding could not be excluded. Other studies reported alterations in gene/protein expression under non-thermal exposure conditions, but typically in single, usually unreplicated experiments, or under experimental conditions with methodological shortcomings. There were no studies in human populations. Overall, there was weak evidence that exposure to RF radiation affects gene and protein expression.]

4.4 Other relevant effects

4.4.1 Humans

(a) Neuroendocrine system

The majority of studies on the effects of exposure to RF radiation on the endocrine system in volunteers have focused on hormones released into the blood stream by the pineal and pituitary neuroendocrine glands. Both are situated in the brain and are intimately connected with and controlled by the nervous system. Some studies have investigated urinary excretion of the major melatonin metabolite: 6-sulfatoxymelatonin (aMT6s). Fewer studies have been carried out on circulating concentrations of pituitary hormones or hormones released from other endocrine glands, such as the adrenal cortex. The pituitary hormones exert a profound influence on body metabolism and physiology, particularly during

development and reproduction, partly via their influence on the release of hormones from other endocrine glands situated elsewhere in the body. The main pituitary hormones investigated in studies on electromagnetic fields are thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), which regulates the function of the adrenal cortex and particularly the release of cortisol, and growth hormone (GH). Pituitary hormones with important sexual and reproductive functions have also been studied, particularly follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL). ACTH, cortisol and prolactin are also involved in the response to stress, and were often used as a marker for the effects of exposure to RF radiation.

No cumulative effects on serum melatonin or pituitary hormones were observed after repeated exposure to RF radiation for 1 month. Most studies did not report an effect after a single exposure, but the statistical power of these studies was often insufficient because of the small number of volunteers involved ([Mann et al., 1998](#); [de Seze et al., 1999](#); [Radon et al., 2001](#); [Bortkiewicz et al., 2002](#); [Braune et al., 2002](#); [Jarupat et al., 2003](#); [Wood et al., 2006](#)).

(b) Neurobehavioural effects

(i) Electrical activity of the brain

The electroencephalogram (EEG) reflects synchronous activity in relatively large populations of cortical neurons. The “spontaneous” EEG of subjects who are awake is generally divided into several frequency bands, in which the relative amount of activity depends on the psychological state of the subject and the nature of the cognitive function in which she or he is engaged. The designation of the frequency bands is not always strictly applied, which results in specific frequencies sometimes being assigned to different bands in different studies. Generally, the following division is used: delta (δ) < 4 Hz; theta (θ) 4–8 Hz; alpha (α) 8–12 Hz; beta (β) 12–30 Hz;

and gamma (γ) > 30 Hz. Slightly different band designations are used by some authors, which are also cited in this Volume. The functional significance of these different components of the normal “waking” EEG is poorly understood. Thus, while a demonstration that mobile-phone signals influence these components would be indicative of a biological effect of such signals, interpretation of the effect would be uncertain. In addition, intra-individual variability is very high. In contrast, EEG patterns associated with sleep are well characterized and routinely used as indices of the different sleep stages that a typical healthy individual will experience during the night. Only studies on EEG during sleep are discussed here.

A review of studies on EEG during sleep and RF radiation was compiled by [Hamblin & Wood \(2002\)](#) and more recently, with a broader scope, by [Kwon & Hämäläinen \(2011\)](#). They cited studies by [Mann & Röschke \(1996\)](#), [Mann et al. \(1998\)](#), [Wagner et al. \(1998, 2000\)](#), [Borbély et al. \(1999\)](#), [Huber et al. \(2000, 2002, 2003\)](#), [Loughran et al. \(2005\)](#), [Fritzer et al. \(2007\)](#), [Hung et al. \(2007\)](#), [Regel et al. \(2007b\)](#), and [Lowden et al. \(2011\)](#). Some but not all studies on exposure to RF radiation during sleep have indicated increased EEG power in α or β bands. A reported shortening of sleep latency could not be reproduced. Other studies that looked at exposure to RF radiation for 30 minutes before going to sleep also showed variable results, sometimes reporting increases in α and β band power. In one study this was observed only after exposure to a modulated but not a continuous RF radiation signal, while in another study a dose-dependent increase in α and β power was seen. Two studies reported an increase in time taken to fall asleep. A recent study by [Lowden et al. \(2011\)](#) indicated that self-reported differences in sensitivity to emissions from mobile-phone use were not reflected in sleep parameters.

[The Working Group concluded that exposure to a GSM-type signal may result in minor effects on brain activity during sleep.]

(ii) *Auditory and vestibular systems*

As mobile phones are held close to the ear, various studies have checked for possible effects of exposure to mobile-phone type (GSM) RF radiation on the vestibular (balance) and cochlear (auditory) organs that comprise the inner ear. The hair-cell receptors present in each organ respond to head movement or to audible sound. This topic was recently reviewed by [Kwon & Hämäläinen \(2011\)](#), who concluded that neurophysiological studies showed no significant effects on cochlear and brainstem auditory processing, or on the vestibular system. [The Working Group noted that the results on spontaneous and evoked electrical activity in the brain were inconsistent.]

(iii) *Cognitive performance*

Studies on cognitive performance in relation to exposure to RF radiation have been carried out in healthy adult volunteers, in adults who self-reported a variety of symptoms such as headaches in the vicinity of RF sources, and in children and adolescents, following the recommendations of [IEGMP \(2000\)](#).

Dynamic changes in brain anatomy occur throughout childhood and adolescence. The amount of white matter, which corresponds to myelination of nerve axons and is related to the speed of neuronal processing, increases linearly throughout adolescence. Changes in the amount of grey matter are thought to reflect changes in size and complexity in neurons, such as the number of synaptic connections, rather than changes in number of neurons themselves. These changes are considered to be related to maturation of behaviour; they are more complex and continue into the early 20s ([Giedd, 2004](#)).

Reviews of studies on neurobehavioural effects of exposure to RF radiation have been compiled by [Barth et al. \(2008\)](#) and more recently

by [Kwon & Härmäläinen \(2011\)](#). The latter authors indicated that improvement of cognitive performance after exposure to RF radiation, as reported in earlier studies, had not been confirmed in more recent behavioural studies with improved analyses.

(iv) Subjective symptoms

Some people self-report having a variety of subjective complaints, including headaches and migraines, fatigue, skin itches, and sensations of heat, after exposure to RF radiation ([Frey, 1998](#); [Hocking, 1998](#); [Chia et al., 2000](#); [Hocking & Westerman, 2000](#); [Sandström et al., 2001](#); [Santini et al., 2002a, b](#)). These symptoms are attributed to exposures at home or at work to RF radiation emitted by mobile phones, nearby base stations, digital enhanced cordless telecommunications (DECT) cordless phones and, more recently, wireless local area network (LAN) systems. Less commonly reported symptoms include dizziness, blurred vision, memory loss, confusion and vagueness, toothaches, and nausea. An increasing number of these people consider themselves to be electrosensitive. Provocation studies provide the most direct way of studying a possible effect of exposure to RF radiation on the occurrence of such symptoms. A weakness of these studies is that they focus on direct, short-term interactions, while symptoms may only occur after a longer exposure. In their review, [Kwon & Härmäläinen \(2011\)](#) conclude that provocation studies provided no evidence that the subjective symptoms could be attributed to mobile-phone use, which suggests that there are other explanations for the induction of such symptoms in hypersensitive people.

(c) Thermal effects and thermoregulation

There is an established literature on cardiovascular responses to heating associated with exposure to RF radiation, such as those involved in thermoregulation. Several studies addressed these end-points in connection with

thermoregulation and heat-stress disorders, to place the possible health consequences of such heating into a broader occupational and environmental context ([ICNIRP, 2009](#)).

RF energy is absorbed by the body, resulting in the production of heat due to an increase in molecular rotational and translational kinetic energy. The absorbed heat energy is distributed throughout the body in the circulation and is partially lost to the external environment. Significant whole-body heating has a major impact on cardiovascular physiology. In addition, the ability to carry out cognitive tasks is compromised before physiological limits of tolerance are reached ([Hancock & Vasmatazidis, 2003](#)). [ICNIRP \(2009\)](#) has indicated that adequately hydrated, inactive, healthy volunteers exposed to RF radiation under laboratory conditions will accommodate whole-body heat loads of approximately 1 W/kg for 45 minutes at environmental temperatures of up to 31 °C, to 6 W/kg for at least 15 minutes at ambient temperatures, with increased skin blood-flow and profuse local sweating, but with minimal changes in core temperature. With regard to local heating of the skin, skin blood-flow and local sweating increase with increasing skin temperature by up to 4 °C in response to a local peak SAR of about 15 W/kg at the irradiated site, but it is not known how less superficial and less vascular tissues may respond.

A full assessment of whole-body heat stress can only be properly derived from a consideration of all sources of heat and from the ease with which heat can be lost from the body, as given by the heat-balance equation. Heat gain through solar radiation or other sources of radiant heat may also have to be taken into account. The main adverse health effects expected to result from excessive heat loads are heat-related disorders such as heat exhaustion and, in elderly people, an increase in the risk of heat-related mortality ([Lakatta, 2002](#)). These effects are well documented in people exposed to hot environments and in elderly people during prolonged periods

of hot weather, but have not been associated with exposure to RF radiation. In addition, adverse effects on cognitive function may be expected to result from increased body temperature, with the potential to increase accident rates, but this has proven to be difficult to quantify in studies with volunteers. Several studies of acute exposure have been carried out to assess the adverse effects of increased tissue temperature in experimental animals, often in the context of providing guidance on the use of ultrasound or hyperthermia treatments in clinical practice ([Ryan et al., 1997](#)). Lesions, including those that result from cell death, generally occur when temperatures exceed 42 °C for more than about 1 hour. The central nervous system and testes appear to be particularly susceptible to heat-induced damage and show significant changes in cell numbers after exposures to 40–41 °C and higher.

Studies on mobile-phone use by volunteers have investigated the effects of RF radiation from mobile phones at levels generally assumed to be too low to induce significant heating. In principle, such “athermal” effects on the cardiovascular centres of the brainstem, which regulate the heart and circulation via outflow in the sympathetic and parasympathetic systems, are possible ([Benham et al., 2003](#); [Patapoutian et al., 2003](#); [Moran et al., 2004](#); [Glaser, 2005](#); [Bandell et al., 2007](#); [Foster & Glaser, 2007](#)). Several studies focused on possible effects on heart rate, heart-rate variability, blood pressure and cerebral blood flow. There is no clear evidence of an effect of such exposure on resting heart rate or blood pressure. However, small but inconsistent variations in heart-rate variability have been reported.

(d) Cerebral blood flow and neural biochemical activity

Changes in regional cerebral blood flow could reflect (or cause) local changes in neural activity. There are some indications of changes in regional cerebral blood flow during and after exposure to RF radiation. In their review, [Kwon](#)

[& Hämäläinen \(2011\)](#) concluded that approaches such as measurement of the haemodynamic response in the brain were promising, but the findings were few and not conclusive. The studies reviewed were [Braune et al. \(1998, 2002\)](#), [Reid & Gettinby \(1998\)](#), [Borbély et al. \(1999\)](#), [Huber et al. \(2000, 2002, 2003, 2005\)](#), [Haarala et al. \(2003a\)](#), [Sandström et al. \(2003\)](#), [Tahvanainen et al. \(2004\)](#), [Aalto et al. \(2006\)](#), [Nam et al. \(2006\)](#), [Barker et al. \(2007\)](#), and [Parazzini et al. \(2007\)](#). Also linked to cerebral blood flow, a more recent study by [Volkow et al. \(2011\)](#) using glucose-uptake positron-emission tomography (PET) showed an increase in local cerebral metabolism after exposure to a mobile phone in reception mode.

[The small changes seen in electrical activity in the brain and possibly in regional cerebral blood flow may not have functional significance. No consistent effects on cognitive performance have been found, although the use of a large variety of techniques to assess cognitive performance makes it difficult to directly compare the results of different studies. No research data were available that would link these findings to cancer.]

4.4.2 Experimental systems: in vivo

(a) Oxidative stress

Numerous experiments have been conducted to explore the possibility that exposure to RF radiation may trigger oxidative stress in tissues of exposed animals (most frequently rats). Markers of oxidative stress include increased levels of malondialdehyde (indicative of lipid peroxidation), nitric oxide (NO), and reduced glutathione (GSH), and the activities of antioxidant enzymes such as SOD, catalase, or GSH-Px, or of pro-oxidant enzymes such as xanthine oxidase (XO).

(i) *Brain*

[Many of the studies in this section used a mobile phone as the source of exposure to RF radiation, which limits the value of these studies in hazard identification.]

[Irmak et al. \(2002\)](#) exposed male rabbits to radiation from a commercially available GSM mobile phone (900 MHz; peak power, 2 W; average power density, 0.02 mW/cm²) for 30 minutes per day, for 7 days. The telephones were positioned “in close contact with the rabbits.” The concentrations of malondialdehyde and NO, and activities of several relevant enzymes were measured in brain and serum of exposed and sham-exposed rabbits. No significant changes were noted in any parameter in the brain; a significant increase in SOD activity ($P = 0.042$) and a significant decrease in concentrations of NO ($P = 0.004$) were observed in the serum of exposed rabbits.

[Ilhan et al. \(2004\)](#) exposed female rats to a GSM signal from a mobile phone (900 MHz; continuous wave; analogue phone), 1 hour per day, for 7 days, at SARs of 2 W/kg (brain) or 0.25 W/kg (whole body), with or without administration of a *Ginkgo biloba* extract. Treatment with this extract by daily oral gavage started 2 days before and was continued throughout the 7 days of exposure to RF radiation. Immediately after exposure, histopathological changes and biochemical markers of oxidative stress were evaluated in the brain. “Dark” neurons (degenerative neurons that can be visualized by staining with cresyl violet) were detected in all locations, particularly in the cortex, hippocampus and basal ganglia. The concentrations of NO and malondialdehyde, and the activities of the enzymes XO and adenosine deaminase were increased in brain tissues, while the activities of SOD and glutathione peroxidase were decreased. Co-exposure with the *Ginkgo biloba* extract prevented these effects. [The Working Group noted that the experimental protocol in this study

was imprecise. The SAR was given without any information on how it was derived; the mention of analogue with GSM was contradictory.]

[Elhag et al. \(2007\)](#) exposed rats of unspecified strain and sex to RF radiation from a GSM mobile phone (900 MHz) for either 1 hour, or for 15 minutes per day, for 4 days, at a SAR of 0.25 W/kg, and reported a reduction in concentrations of vitamins C and A in serum, a decreased level of vitamin E in erythrocytes, and a reduction in the activities of catalase and SOD and concentrations of reduced glutathione in erythrocytes. [The Working Group noted the imprecise experimental protocol of this study, and did not take the results into further consideration.]

[Meral et al. \(2007\)](#) exposed guinea-pigs to RF radiation at 890–915 MHz (SAR, 0.95 W/kg) from a mobile phone for 12 hours per day (11 hours 45 minutes “stand-by” and 15 minutes “on”) for 30 days. At the end of the exposure period, lipid peroxidation, enzymatic activities and vitamins in blood and brain tissue were measured biochemically, and compared between exposed and non-treated controls. Increased concentrations of malondialdehyde, and reduced glutathione concentrations and catalase enzyme activity were observed in brain tissue, but there was no change in levels of vitamins A, E and D3 in the brain. In the blood of the exposed animals, increased concentrations of malondialdehyde, vitamins A, D3 and E, and catalase enzyme activity were seen, as well as decreased levels of glutathione. [The Working Group noted the lack of sham-exposed controls.]

[Ammari et al. \(2008\)](#) studied the activity of cytochrome oxidase in the brain of rats exposed to RF radiation at 900 MHz (GSM) from an RF generator, for 15 minutes per day for 7 days at a SAR (brain) of 6 W/kg, or for 45 minutes per day for 7 days at a SAR of 1.5 W/kg. While exposure at the lower SAR had no effect, exposure at a SAR of 6 W/kg induced a decrease in the activity of cytochrome oxidase in some areas of the rat brain (frontal cortex, posterior

cortex, hippocampus and septum). [This result showed that GSM signals at high SAR may affect the activity of cytochrome oxidase in the brain, which is a metabolic marker of neuronal activity.]

[Sokolovic et al. \(2008\)](#) exposed male rats to continuous-wave RF radiation at 900 MHz (GSM) from a mobile phone placed in the cage, for 4 hours per day during the light period (06:00–18:00) for 20, 40 or 60 days, at an estimated whole-body SAR of 0.043–0.135 W/kg, with or without daily intraperitoneal injections of melatonin (2 mg/kg bw) or saline. A false phone was placed in the cages of the control groups and the groups receiving melatonin only. A significant 20–50% increase in brain concentrations of malondialdehyde and carbonyl groups was observed during exposure. Catalase activity was decreased (–20%) during exposure, while the activity of XO was increased (15–25%) after 40 and 60 days of exposure. Treatment with melatonin prevented increases in malondialdehyde content and XO activity in brain tissue after 40 and 60 days of exposure.

[Dasdag et al. \(2009\)](#) exposed male Wistar rats to RF radiation at 900 MHz (GSM) delivered to the head for 2 hours per day, 7 days per week, for 10 months. No difference was found in oxidative-stress indexes between the groups, while total oxidant capacities and catalase in the brain were significantly higher ($P < 0.05$) in the exposed group than in the sham-exposed group.

[Imge et al. \(2010\)](#) exposed female rats to RF radiation at 900 MHz (GSM) from a mobile phone (SAR, 0.95 W/kg) placed 10 cm above the cages, for 4×10 minutes per day, for 4 weeks, with or without daily oral administration of vitamin C (250 mg/kg bw). The activities in brain tissue of 5'-nucleotidase and catalase were significantly reduced compared with those of the non-treated control group, and there was a non-significant reduction in the activity of glutathione peroxidase and in concentrations of malondialdehyde in the brain. Vitamin C had a protective effect

in some of these analyses. [The Working Group noted the lack of sham-exposed controls.]

(iii) *Kidney*

The justification for studying oxidative stress in the kidney following exposure to electromagnetic fields stems from the fact that the kidney would be the organ with the greatest exposure when a mobile phone is worn at the belt.

[Oktem et al. \(2005\)](#) exposed groups of eight Wistar albino rats to RF radiation at 900 MHz (GSM; average power density, 1.04 mW/cm²) for 30 minutes per day for 10 days, with or without treatment with melatonin (100 µg/kg bw; subcutaneous injection) before the daily exposure to RF radiation. SAR values were not reported. Increases in tissue concentrations of malondialdehyde and urinary *N*-acetyl-β-D-glucosaminidase (NAG), a marker of renal tubular damage, were observed. The activities of SOD, catalase, and GSH-Px were reduced. Administration of melatonin reversed or prevented these effects.

The same group ([Ozguner et al., 2005b](#)) compared the protective effects of melatonin (100 µg/kg bw; subcutaneous injection) and of caffeic acid phenethyl ester (CAPE; dose unclear), a component of honey-bee propolis used in traditional medicine, in Sprague-Dawley rats exposed to RF radiation. The experimental protocol was similar to that of [Oktem et al. \(2005\)](#), with antioxidants being injected daily for 10 days before exposure to RF radiation at 900 MHz (GSM; average power density, 1.04 mW/cm²). Urinary NAG and renal MDA were increased, while renal SOD and GSH-Px were decreased. Melatonin and CAPE reversed or prevented many of these effects, with melatonin being the more potent antioxidant. The results were similar to those reported previously, with the exception of catalase, the activity of which was not modified.

(iii) *Myocardium*

[Ozguner et al. \(2005a\)](#) assessed the protective effects of CAPE in myocardium of Sprague-Dawley rats exposed to RF radiation at 900 MHz, using an experimental protocol similar to that used for studies in the kidney (see above) and found comparable results.

(iv) *Eye*

[Ozguner et al. \(2006\)](#) compared the protective effects of melatonin and CAPE (a component of honey-bee propolis used in traditional medicine) on oxidative stress induced in rat retina by exposure to RF radiation at 900 MHz (whole-body SAR, 0.016 W/kg; local SAR at the head, 4 W/kg). The experimental protocol was similar to that in [Ozguner et al. \(2005b\)](#): antioxidants were injected daily for 60 days (rather than 10 days) before exposure to RF radiation for 30 minutes per day for 60 days (rather than 10 days). Significantly increased ($P < 0.0001$) retinal concentrations of NO and MDA were found in exposed rats, which remained at control values after pre-treatment with melatonin and CAPE. Likewise, the activities of SOD, GSH-Px and CAT were significantly reduced in the retina of exposed rats. Again, prior treatment with melatonin and CAPE prevented this reduction in the activities of these antioxidant enzymes. These data indicated that antioxidants reduce oxidative stress in the rat retina caused by long-term exposure to RF radiation. [The Working Group was uncertain about the dosimetry in this study, and noted the lack of a cage-control group to assess the effect on the rats of being restrained in a tube during the exposures.]

[Balci et al. \(2007\)](#) exposed female rats to RF radiation at 900 MHz from a mobile phone (GSM; SAR, 1.2 W/kg), placed 10 cm above the cages, for 4×10 minutes per day, for 4 weeks, with or without daily oral administration of vitamin C (250 mg/kg bw). In the cornea, a significant increase was found in the concentration of malondialdehyde and in the activity of

catalase compared with the control group and with the exposed group receiving vitamin C, while the activity of SOD was decreased. In the lens tissues, the malondialdehyde concentration was significantly increased, but no significant differences in the activities of SOD, GSH-Px or catalase were observed. The presence of vitamin C generally diminished the effects of exposure to RF radiation. [The Working Group noted several design flaws in this study (e.g. the exposure system, the absence of dosimetry, absence of sham-exposed controls) and did not further consider these results.]

(v) *Liver*

[Ozgun et al. \(2010\)](#) investigated oxidative damage and antioxidant-enzyme status in the liver of guinea-pigs exposed to RF radiation at 1800 MHz (GSM; SAR, 0.38 W/kg) for 10 or 20 minutes per day, for 7 days. In this study the potential protective effects of *N*-acetylcysteine (NAC) and epigallocatechin-gallate (EGCG) were also investigated. A significant increase in the concentrations of malondialdehyde and nitrogen oxides (NO_x) and a reduction in the activities of SOD, myeloperoxidase and GSH-Px were observed in the liver of exposed guinea-pigs. Some of these changes appeared to be proportional to the duration of exposure). In addition, treatment with NAC induced an increase in hepatic GSH-Px activities, whereas treatment with EGCG attenuated concentrations of malondialdehyde.

[Tomruk et al. \(2010\)](#) evaluated the effects of whole-body exposure to RF radiation at 1800 MHz (GSM) for 15 minutes per day, for 1 week, on oxidative DNA damage and lipid peroxidation in the liver of nonpregnant or pregnant New Zealand White rabbits, and in their newborns. Concentrations of malondialdehyde increased significantly in exposed nonpregnant and pregnant animals compared with nonpregnant controls, but there was no difference between exposed and sham-exposed pregnant rabbits. The same results were observed with lipid

peroxidation, measured by means of the ferrous oxidation-xylenol orange [FOX] assay. Exposure to RF radiation had no effect on the amount of oxidative DNA damage (8-OHdG adducts) in the liver of RF-exposed and sham-exposed nonpregnant and pregnant rabbits. No differences in concentrations of malondialdehyde and 8-OHdG were found in the liver of newborns exposed to RF radiation *in utero* compared with newborns of sham-exposed mothers. However, a significant reduction in lipid peroxidation, *i.e.* reduced FOX levels, in the liver of RF-exposed newborns was observed. [The Working Group noted that SAR values were not stated.]

(vi) *Miscellaneous*

[Mailankot et al. \(2009\)](#) exposed adult male Wistar albino rats to RF radiation at 900/1800 MHz (SAR not given) from a GSM mobile phone “in active mode” for 1 hour per day for 28 days, while control rats were exposed to a mobile phone “without battery.” There was no difference in sperm counts in the epididymis between exposed and control rats, but a 40% reduction in the proportion of motile sperm was observed after exposure. In addition, the concentration of malondialdehyde was significantly increased and intracellular GSH was significantly reduced in the testis and epididymis of exposed rats, compared with sham-exposed controls, together with a significant decrease in intracellular GSH in both testis and the epididymis of RF-exposed rats.

[Kumar et al. \(2010\)](#) exposed male Wistar rats to continuous RF radiation at 10 or 50 GHz (SAR, 0.014 and 0.0008 W/kg, respectively) for 2 hours per day, for 45 days. Total levels of ROS and catalase activity were higher and the proliferative index, and the activities of SOD and reduced GSH-Px in the serum were lower in exposed rats than in sham-exposed controls.

(b) *Differentiation and apoptosis*

[Dasdag et al. \(2003\)](#) exposed male Sprague-Dawley rats to RF radiation at 900 MHz from commercially available mobile phones (average calculated whole-body SAR, 0.52 W/kg; peak SAR, 3.13 W/kg) for 20 minutes per day, 7 days per week, for 1 month. The mobile phones were placed 0.5 cm under the cages. There were no differences between exposed and sham-exposed groups in terms of structure of testes, sperm counts, phospholipid composition or Tp53 immunoreactivity. [The Working Group noted the ill-defined exposure set-up and the approximative SAR calculations.]

In a study mentioned before, [Dasdag et al. \(2009\)](#) exposed male Wistar rats to RF radiation at 900 MHz (GSM; SAR, 0.19–0.58 W/kg) delivered to the head for 2 hours per day, 7 days per week, for 10 months. The apoptosis score – based on immunostaining of active caspase-3 – in the brain of the exposed rats was significantly lower than in sham-exposed or cage-control rats.

Apoptosis induced in the endometrium was studied by [Oral et al. \(2006\)](#) by exposing female Wistar albino rats in a plastic tube to RF radiation at 900 MHz (GSM) (SAR, 0.016–4 W/kg) for 30 minutes per day, for 30 days. Different group of rats received vitamin E (50 mg/kg bw) or vitamin C (20 mg/kg bw) by intramuscular or intraperitoneal injection, respectively, just before the daily exposure to RF radiation. Increased concentrations of malondialdehyde (indicative of lipid peroxidation) and enhanced apoptosis were observed in endometrial tissue (stromal cells) of exposed rats. These effects were partly reverted by vitamin treatment. Using the same experimental protocol, [Guney et al. \(2007\)](#) observed an increase in oxidation products (NO, malondialdehyde), a decrease in activities of antioxidant enzymes (SOD, catalase, GSH-Px), and diffuse and severe apoptosis in the endometrial surface epithelial and glandular cells and in

stromal cells. [Both studies lacked details on SAR measurement.]

[Odaci et al. \(2008\)](#) examined paraffin-embedded sections of the brain of rats aged 4 weeks born from females exposed to RF radiation at 900 MHz (GSM; calculated whole-body SAR, 2 W/kg), for 60 minutes per day during the entire gestation period. A slight but statistically significant reduction in the number of granule cells in the dentate gyrus of pups of exposed dams was observed; this reduction may affect postnatal behavioural and cognitive functions. [The Working Group noted the apparent lack of a sham-exposed control group.]

More recently, [Sonmez et al. \(2010\)](#) examined paraffin-embedded sections of the cerebellum of female rats aged 16 weeks exposed to RF radiation at 900 MHz (calculated average SAR, 0.016 and 2 W/kg, respectively, for whole-body or head-only) for 1 hour per day, for 28 days. A significant reduction in the number of Purkinje cells was observed in the cerebellum of exposed rats compared with sham-exposed controls and cage controls.

[The Working Group concluded that there was weak evidence that exposure to RF radiation at 900 MHz induces differentiation or apoptosis in the brain or endometrium of exposed rats.]

(c) Blood–brain barrier

The blood–brain barrier regulates exchange between blood and the brain. An increase in the normally low permeability of this barrier for hydrophilic and charged molecules after exposure to RF radiation could potentially be detrimental by enabling the extravasation of substances that could potentially act as brain carcinogens.

In vivo, several methods have been used to evaluate the integrity of the blood–brain barrier. These methods are based either on assessment of the permeability of the barrier to endogenous molecules such as albumin, which can be visualized by immunohistochemistry on brain sections, or on the injection of dyes (Evans

blue) or labelled molecules that do not cross the blood–brain barrier under normal physiological conditions and hence may serve as permeability markers. Models of brain injury (e.g. cold injury or chemical injury) are informative positive controls in these experiments. Another method comprises the evaluation of alterations in nervous tissue by detecting degenerating neurons (“dark neurons”) through staining with cresyl violet, or with the fluorescent molecule Fluoro-Jade B, which is more specific for neurons.

Dozens of experiments in rodents have assessed the functioning of the blood–brain barrier in animals exposed to various intensities of RF radiation at frequencies \geq 900 MHz (for reviews, see [Stam, 2010](#) and [Nittby et al., 2011](#)). Here are described only experimental studies of exposure at frequencies \geq 900 MHz and at exposure levels that did not – or were unlikely to – produce a thermal effect: in the rat brain, hyperthermia of > 1 °C induces alterations in the blood–brain barrier. It should be noted also that anaesthesia itself may modify the permeability of the blood–brain barrier.

One research group has reported effects on the permeability of the blood–brain barrier and alterations in nervous tissue (dark neurons) after exposure of Fisher 344 rats (males and females) to continuous or GSM-modulated RF radiation at 900 and 915 MHz, with SARs of 2–5 W/kg. Among recently published studies from this group, three ([Eberhardt et al., 2008](#); [Nittby et al., 2009, 2011](#)) reported an increase in permeability to albumin at 1 or 2 weeks after 2 hours of exposure to a 900 MHz GSM signal (SAR, 0.0001–0.13 W/kg). Another study from this group ([Grafström et al., 2008](#)) assessed permeability of the blood–brain barrier 5–7 weeks after exposure to a GSM signal (SAR, 0.0006–0.6 W/kg) for 2 hours per week for 55 weeks, and found no increase in permeability using several markers, and no appearance of dark neurons.

[Masuda et al. \(2009\)](#) did not observe albumin extravasation or appearance of dark neurons

in experiments in two-compartment transverse electromagnetic (TEM) transmission line cells. Male Fischer F344 rats were exposed to a 915 MHz GSM signal (whole-body SAR, 0.02, 0.2 or 2 W/kg) for 2 hours. Positive controls (cold and chemical injury) were included. Analyses were performed 14 and 50 days after exposure.

[McQuade et al. \(2009\)](#) did not observe any leakage of albumin across the blood–brain barrier in male Fischer 344 rats sham-exposed or exposed to 915 MHz RF radiation (SAR, 0.0018–20 W/kg) for 30 minutes in TEM cells. Both continuous-wave and pulsed modes of 16 and 217 Hz were used, with pulse parameters based on those in studies from the research group mentioned above ([Persson et al., 1997](#)). Positive controls (hyperthermia at 43 °C, and urea 10 M) were included. Albumin extravasation was investigated by immunohistochemical staining of brain sections. A subset of the microscopic slides was sent to Sweden and analysed by scientists associated with the original studies. No alterations in the blood–brain barrier were observed at any exposure level.

[De Gannes et al. \(2009\)](#) found no changes in the integrity of the blood–brain barrier or neuronal degeneration in Fischer 344 rats exposed head-only to a 900 MHz GSM signal (brain-averaged SAR, 0.14 or 2 W/kg) for 2 hours. Complete numerical and experimental dosimetry was included in this study. Albumin leakage, dark neurons, or changes in neuronal apoptosis were not observed. [It is worthy of note that in these three studies, homogeneous samples of male rats of the same age and weight were used. The SAR values tested were higher or of a wider power range than in experiments of the Swedish group.]

[The Working Group concluded that despite consistent results from one laboratory, the experimental evidence did not support the notion that non-thermal RF radiation affects the permeability of the blood–brain barrier.]

4.4.3 Experimental systems: in vitro

(a) Human cells

(i) Free radicals and ROS

Free radicals are highly reactive molecules that carry unpaired electrons in the outer orbit. Free radicals that are derived from oxygen metabolism are known as reactive oxygen species (ROS). These radicals are continuously neutralized by antioxidants present in body tissues. When production of these species exceeds the scavenging capacity of antioxidants, oxidative stress results. Production of radicals is a known pathway involved in the development of cancer.

[Lantow et al. \(2006a, c\)](#) measured production of ROS and expression of HSPs (described in section 4.3.2.c (i)) in human Mono Mac 6 and K562 cells exposed to RF radiation at 1800 MHz (SAR, 0.5, 1.0, 1.5 or 2.0 W/kg) as three different GSM modulation signals, for 45 minutes. Heat and phorbol 12-myristate-13-acetate (PMA) induced a significant increase in superoxide radical anions and in the production of ROS. In general, no effects were observed from exposure to RF radiation alone or in combination with PMA or lipopolysaccharide. [Lantow et al. \(2006b\)](#) used human umbilical cord blood-derived monocytes and lymphocytes to examine release of ROS after continuous or intermittent (5 minutes on, 5 minutes off) exposure at 1800 MHz (SAR, 2 W/kg) for 30 or 45 minutes. Exposure to RF radiation did not enhance the effects of PMA. In another study from the same group, [Simkó et al. \(2006\)](#) exposed human Mono Mac 6 cells to RF radiation under similar conditions, but combined exposures were carried out with ultrafine particles. Exposure to RF radiation alone had no effect on radical production. In addition, RF radiation did not enhance the production of superoxide anion radicals induced by ultrafine particles.

[Luukkonen et al. \(2009\)](#) investigated intracellular production of ROS and DNA-damage induction in human SH SY5Y neuroblastoma

cells exposed to continuous-wave or pulsed-wave RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour. The experiments also involved combined exposure to RF radiation and menadione. The production of ROS was measured by use of the fluorescent probe dichlorofluorescein. No effects were seen from exposure to RF radiation alone. Consistent with the increase in DNA damage (described in Section 4.1.3.b.ii), the level of ROS measured after treatment with menadione was higher in cells exposed to a continuous-wave RF field. However, no effects of the pulsed-wave RF radiation were seen at identical SARs. In a second study using identical exposure conditions and the same cell line, [Luukkonen et al. \(2010\)](#) found no effects on ROS production induced by ferrous choride from continuous-wave or pulsed-wave RF radiation. This finding was consistent with lack of effect on DNA-damage induction in the same study, as described earlier.

[Höytö et al. \(2008a\)](#) exposed human SH-SY5Y neuroblastoma cells and mouse L929 fibroblasts to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour or 24 hours, under isothermal conditions. To investigate possible combined effects with other agents, menadione was used to induce ROS, and *tert*-butylhydroperoxide (*t*-BOOH) was used to induce lipid peroxidation. After the 1-hour exposure, there was a statistically significant enhancement by RF radiation of *t*-BOOH-induced lipid peroxidation in SH-SY5Y cells exposed to the GSM-modulated signal. After the 24-hour exposure, there was a statistically significant increase by RF radiation of menadione-induced caspase-3-like protease activity in mouse L929 fibroblasts exposed to the GSM-modulated signal. No effects were seen in any of the other experimental conditions, or from exposure to RF radiation alone.

Purified human spermatozoa were exposed to RF radiation at 1800 MHz (SAR, 0.4 W/kg to 27.5 W/kg) ([De Iuliis et al., 2009](#)). With increasing SAR, motility and vitality of the sperm cells were significantly reduced after exposure,

while the mitochondrial generation of ROS and DNA fragmentation were significantly elevated. Furthermore, highly statistically significant relationships between SAR, the oxidative DNA damage biomarker 8-OHdG, and DNA fragmentation were observed in exposed cells. The temperature during these experiments was kept at 21 °C; the highest observed exposure-induced temperature increase was +0.4 °C, at SAR 27.5 W/kg; control experiments in which spermatozoa were incubated at 21 °C–50 °C – without RF radiation – indicated that the end-points measured were only significant above 40 °C.

Human sperm was exposed *in vitro* for 1 hour to RF radiation at 850 MHz (SAR, 1.46 W/kg) from a mobile phone in talk mode, and markers of oxidative stress were evaluated ([Agarwal et al., 2009](#)). The results showed a significant increase in production of ROS in exposed samples and a decrease in sperm motility, viability, and in the ROS-total antioxidative capacity (ROS-TAC) score in exposed samples.

[The Working Group concluded that there was weak evidence that RF radiation activates a stress response or production of ROS in human cells under non-thermal conditions.]

(ii) Cell proliferation

[Kwee & Raskmark \(1998\)](#) exposed human AMA epithelial amnion cells to RF radiation at 960 MHz (GSM; SAR, 0.021, 0.21 or 2.1 mW/kg) for 20, 30, and 40 minutes at 37 °C. Cellular proliferation was assessed by means of the formazan test, and found to decrease linearly with exposure time at the lowest and highest SAR level. In a follow-up study, [Velizarov et al. \(1999\)](#) exposed human AMA cells to RF radiation at 960 MHz (GSM; SAR, 2.1 mW/kg) for 30 minutes at two different temperatures (39 °C and 35 °C), to evaluate whether the earlier results (see above) were temperature-dependent. There was a marginally significant reduction in cellular proliferation rate – measured with the formazan test – after the 30-minute exposure at both

temperatures ($P = 0.086$ and 0.072 , respectively, based on 11 independent experiments); the change in proliferation rate of the sham-exposed cells was not different at the two temperatures tested. The authors considered it unlikely that the effect of exposure to RF radiation on cell proliferation was a thermal effect.

[Pacini et al. \(2002\)](#) exposed human Detroit 550 skin fibroblasts to RF radiation at 960 MHz (GSM; estimated SAR, 0.6 W/kg) for 60 minutes. The radiation source was a mobile phone placed underneath the culture dish. No changes in the rate of cell replication were seen, as tested by [^3H] thymidine incorporation. [The use of a mobile phone as a radiation source made this study difficult to interpret; with only three replicates, the sample size was small.]

[Capri et al. \(2004a\)](#) exposed peripheral blood mononucleated cells from healthy volunteers to RF radiation at 900 MHz (GSM or continuous-wave; average SAR, 70–76 mW/kg) for 1 hour per day, for 2 or 3 days. Cells were treated with the mitogens PHA or alphaCD3 to stimulate replication. A statistically significant ($P = 0.04$) decrease in cell replication – as judged by [^3H] thymidine incorporation – was seen only for the cells exposed to the GSM RF-radiation and stimulated with the lowest dose of PHA; all other differences were non-significant. There was no effect at all after exposure to the continuous-wave RF radiation.

[Marinelli et al. \(2004\)](#) exposed human CCRF-CEM T-lymphoblastic leukaemia cells to continuous-wave RF radiation at 900 MHz (SAR, 3.5 mW/kg) for 2, 4, 12, 24, or 48 hours. There was a significant decrease in total viable cell number after 24 and 48 hours of exposure, and a significant increase in the percentage of apoptotic cells – measured by fluorescence-activated cell sorting (FACS) analysis – after 2 hours, which gradually diminished but remained significant after 24 and 48 hours of exposure. In addition, after 48 hours the number of cells that had started S-phase had increased, while the percentage of

cells in growth-arrest diminished. These data support the notion that RF radiation may lead cancer cells to acquire an advantage to survive and proliferate. [The Working Group had some difficulty in understanding the description of the exposure conditions in this study.]

[Sanchez et al. \(2006b\)](#) exposed reconstructed human primary keratinocytes to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 48 hours. No apoptosis was induced in these cells, and there was no alteration of cell proliferation. A small increase in expression of heat-shock protein (Hsp) 70 was noted after 3 and 5 weeks of culture. [Merola et al. \(2006\)](#) exposed human LAN-5 neuroblastoma cells to RF radiation at 900 MHz (GSM; SAR, 1 W/kg) for 24, 48 or 72 hours, and found no effects on cellular replication. [Gurisik et al. \(2006\)](#) exposed human SK-N-SH neuroblastoma cells and monocytic U937 cells to 900 MHz (GSM-modulated) RF radiation (SAR of 0.2 W/kg) for 2 hours. There were no effects on cell-cycle distribution, apoptosis, or HSP levels. [Lantow et al. \(2006c\)](#) exposed human macrophagic Mono Mac 6 cells to pulse-modulated RF radiation at 1800 MHz (GSM-DTX; SAR, 2 W/kg) for 12 hours. No changes in cell-cycle distribution or cell proliferation were reported. [Takashima et al. \(2006\)](#) exposed human MO54 glioma cells to 2450 MHz continuous-wave RF radiation (SAR, 0.05, 0.5, 5, 50, 100, 200 W/kg) for 2 hours, or to intermittent RF radiation at 2450 MHz (mean SAR, 50 or 100 W/kg) for 2 hours. Exposure to continuous-wave RF radiation at 200 W/kg caused a decrease in cell replication and cell survival. Other exposures had no effect. [It should be noted that the temperature of the medium increased to 44.1 °C at exposures with SAR of 200 W/kg.] [Sun et al. \(2006\)](#) exposed human lens epithelial cells to GSM-modulated RF radiation at 1800 MHz (SAR, 1, 2, 3, 4 W/kg) for 2 hours. No effects of RF exposure were observed on cell proliferation (incorporation of bromodeoxyuridine) up to 4 days after exposure. [Chauhan et al. \(2007b\)](#) exposed human lymphoblastoid TK6,

lymphoblastic HL60 and myeloid Mono Mac 6 cells to intermittent (5 minutes on, 10 minutes off) pulse-modulated RF radiation at 1900 MHz (SAR, 1 and 10 W/kg) for 6 hours. There were no effects on cell-cycle progression.

[The Working Group concluded that there was weak evidence that exposure to RF radiation affects cell proliferation.]

(iii) Apoptosis

Defects in apoptosis-signalling pathways are common in cancer cells; apoptosis is an important mechanism by which damaged cells are removed, thus preventing the proliferation of potential cancer cells.

[Marinelli et al. \(2004\)](#) reported increased apoptosis, determined by flow cytometry and DNA-ladder analysis, in human CCRF-CEM T-lymphoblastoid leukaemia cells exposed to continuous-wave RF radiation at 900 MHz (SAR, 0.0035 W/kg) for 2–48 hours. Measurement of gene expression indicated activation of both TP53-dependent and -independent apoptotic pathways after shorter exposures (2–12 hours), while decreased pro-apoptotic signals were seen at longer exposure times (24–48 hours). As indicated above, these data support the notion that RF radiation may lead cancer cells to acquire an advantage to survive and proliferate. [The Working Group noted that the statistical comparisons with respect to FACS analysis were with unexposed, not sham-exposed cells.]

[Port et al. \(2003\)](#) exposed human myeloid leukaemia cells (HL-60) to pulsed-wave RF radiation at 400 MHz (SAR not given) for 6 minutes. The electric-field strength was 50 kV/m. No effects on the number of apoptotic cells or micronuclei were found. [The Working Group noted that interpretation of these findings was difficult due to the lack of SAR values and very short exposure times.]

[Capri et al. \(2004a\)](#) exposed human peripheral blood mononuclear cells to continuous-wave or GSM-modulated RF radiation at 900 MHz

(average SAR, 70–76 mW/kg) for 1 hour per day, for 2 or 3 days. In general, no differences were detected in apoptosis – measured by means of annexin V-FITC staining – between exposed and sham-exposed cells, irrespective of whether or not the cells were treated with 2-deoxy-D-ribose, an inducer of apoptosis. In a similar study ([Capri et al., 2004b](#)), the cells were exposed intermittently (10 minutes on, 20 minutes off) to RF radiation at 1800 MHz with three different GSM-modulation schemes (SAR, 1.4 or 2 W/kg) for 44 hours. No effects on apoptosis were observed from RF radiation alone or from RF radiation combined with the apoptosis-inducing agent, 2-deoxy-D-ribose.

[Hook et al. \(2004a\)](#) reported no effects on apoptosis, detected by use of the annexin V affinity assay, in human Molt-4 lymphoblastoid leukaemia cells exposed to RF radiation at 847.74 MHz as CDMA, 835.62 MHz as FDMA, 813.56 MHz as iDEN, or 836.55 MHz as TDMA signals, for up to 24 hours. The SARs were 3.2 W/kg for CDMA and FDMA, 0.0024 or 0.024 W/kg for iDEN, and 0.0026 or 0.026 W/kg for TDMA.

[Gurisik et al. \(2006\)](#) exposed human neuroblastoma SK-N-SH cells to RF radiation at 900 MHz (GSM; SAR, 0.2 W/kg) for 2 hours. Apoptosis was measured by means of propidium iodide/YO-PRO-1 staining. No differences were detected between sham-exposed and exposed samples.

[Hirose et al. \(2006\)](#) reported no effects on apoptosis, measured by the annexin V-FITC affinity assay, or on apoptosis-related gene expression, in human glioblastoma A172 or human IMR-90 fibroblasts exposed to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg), with or without W-CDMA modulation, for 24–48 hours.

[Joubert et al. \(2006\)](#) studied apoptosis in human neuroblastoma SH-SY5Y cells exposed to GSM-modulated RF radiation at 900 MHz (SAR, 0.25 W/kg) or continuous-wave RF radiation at 900 MHz (SAR of 2 W/kg) for 24 hours.

No effects on apoptosis were detected, either immediately or 24 hours after exposure, with three different techniques, *viz.* 4',6-diamino-2-phenylindole (DAPI) staining of nuclei, flow cytometry with double staining (TUNEL and propidium iodide), or measurement of caspase-3 activity by fluorometry.

[Lantow et al. \(2006c\)](#) reported no effects on apoptosis – measured with the annexin V-FITC assay – in human Mono Mac 6 cells exposed to 1800 MHz GSM-modulated RF radiation (SAR, 2.0 W/kg) for 12 hours, either alone or in combination with the apoptosis-inducing agents PMA or gliotoxin.

[Merola et al. \(2006\)](#) exposed human neuroblastoma LAN-5 cells to RF radiation at 900 MHz (GSM; SAR of 1 W/kg) for 24 or 48 hours. This exposure did not affect apoptosis, measured by an assay for caspase activation. In addition, RF-radiation did not enhance camptothecin-induced apoptosis.

[Sanchez et al. \(2006b\)](#) exposed human epidermal keratinocytes and fibroblasts to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 48 hours. No alteration in apoptosis was detected in the annexin V/FITC affinity assay, while a very clear response was seen for UVB radiation, which was used as a positive control. In a subsequent study, [Sanchez et al. \(2007\)](#) exposed the same types of cell to RF radiation at 1800 MHz (GSM; SAR, 2 W/kg) for 2 hours. No effects on apoptosis were observed in the annexin V-FITC affinity assay.

[Chauhan et al. \(2007b\)](#) reported that apoptosis assessed by the neutral comet assay to detect DNA double-strand breaks was not affected in human TK6, HL-60, or Mono Mac 6 cells exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1900 MHz (SAR, 1, 10 W/kg) for 6 hours.

[Höytö et al. \(2008a\)](#) exposed human SH-SY5Y neuroblastoma cells to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 or 24 hours under isothermal

conditions, with or without the apoptosis-inducing agent menadione. No direct effects of RF radiation on apoptosis, or on menadione-induced apoptosis were observed in assays for caspase-3 activity and DNA fragmentation.

Human KB oropharyngeal epidermoid carcinoma cells were exposed to RF radiation at 1.95 GHz (SAR, 3.6 mW/kg) for 1, 2, or 3 hours. The exposure caused a time-dependent increase in apoptosis (45% after 3 hours), along with a 2.5-times decrease in the expression of the genes *RAS* and *RAF1* and in the activity of the proteins *RAS* and *ERK-1/2*. The overall results showed that RF radiation can induce apoptosis via inactivation of the *ras*–*Erk* survival-signalling pathway ([Caraglia et al., 2005](#)) [the Working Group noted the lack of specific control of the temperature of the cells during the exposure periods in this study].

[The Working Group concluded that there was weak evidence that RF radiation induces apoptosis in human cells *in vitro*.]

(b) Other mammalian cells

See [Table 4.15](#)

(i) Stress response and ROS formation

Exposure of J774.16 mouse macrophages stimulated with γ -interferon and bacterial lipopolysaccharide to RF radiation at 835.62 MHz as FMCW, or to at 847.74 MHz as a CDMA signal (SAR, 0.8 W/kg) for 20–22 hours at 37 ± 0.3 °C did not alter the concentrations of intracellular oxidants (NO, glutathione disulfide), or activities of the enzymes CuZnSOD, MnSOD, catalase, or GSH-Px ([Hook et al., 2004b](#)).

[Zmysłony et al. \(2004\)](#) reported an increase in cellular ROS production in rat lymphocytes coexposed to RF radiation and iron ions. The cells were exposed to continuous-wave RF radiation at 930 MHz (SAR, 1.5 W/kg) for 5 or 15 minutes in the presence of FeCl_2 (10 $\mu\text{g}/\text{ml}$). Intracellular ROS production, measured with the fluorescent probe 2',7'-dichlorofluoresceindiacetate

Table 4.15 Effects of exposure to radiofrequency radiation in cultured mammalian cells *in vitro*

Cell type	Exposure conditions	End-points	Results	Comments	Reference
<i>Stress response and formation of reactive oxygen species</i>					
Mouse, J774.16 macrophages	835.62 MHz (FMCW) or 847.74 MHz (CDMA); SAR, 0.8 W/kg; 20–22 h; 37.0 ± 0.3 °C; stimulation with IFN and bacterial LPS	Oxidative stress evaluated by oxidant and antioxidant levels, oxidative damage and NO production. Oxidation of thiols measured by accumulation of GSSG. Cellular antioxidant defenses evaluated by SOD activity (CuZnSOD and MnSOD), CAT and GSH-Px activities.	No effect on parameters indicative of oxidative stress, levels of intracellular oxidants, accumulation of GSSG, or induction of antioxidant defences in IFN/LPS-stimulated cells. No toxicity was observed.		Hook et al. (2004b)
Hamster ovary HA-1 fibroblasts, Mouse C3H10T½, Human HeLa S3 cells	835.62 MHz (FMCW), 847.74 MHz (CDMA); SAR, 0.6 or 5 W/kg; 50–60 min, or 24 h; at 37.0 ± 0.28 °C, 36.9 ± 0.18 °C and 37.1 ± 0.28 °C for FDMA-, sham-, and CDMA-exposure, respectively.	DNA-binding activity of HSF – a necessary condition for induction of a heat-shock response – monitored with a gel-shift assay.	No increase in the DNA-binding ability of HSF after any exposure tested in any of the cell lines	A 10% increase was detectable after a 1 °C temperature increase	Laszlo et al. (2005)
Mouse L929 fibroblasts, Human SH-SY5Y neuro-blastoma cells	872 MHz (CW or GSM); SAR, 5 W/kg; 1 h or 24 h.	Co-exposure (1 hour) with menadione (to induce ROS) or t-BOOH (to induce lipid peroxidation). Assessment of apoptosis (caspase3-like protease activity and DNA-fragmentation analysis) after 24 h exposure to RF	No effects of RF radiation alone. Menadione induced caspase-3 activity in L929 (not in SH-SY5Y) cells; lipid peroxidation was induced by t-BOOH in SH-SY5Y (not in L929) cells. Effects significant only for GSM-RF. Other end points not affected.	The positive findings may reflect effects that occur in cells sensitized by chemical stress.	Höyrtö et al. (2008a)
Mouse L929 fibrosarcoma cells	900 MHz (CW or GSM); SAR, 0.3 or 1 W/kg; 10 or 30 min; with/without co-exposure to 500 µM of MX.	ROS formation measured by a fluorimetric method just after the exposure and at different times until 1 h after exposure	No effect of RF radiation (with or without MX) on formation of ROS		Zeni et al. (2007b)
Wistar rat; primary cortical astrocytes	900 MHz (CW or amplitude-modulated); electric field 10V/m; 5, 10, 20 min. Electric field at the sample position: 10 V/m.	Evaluation of intracellular ROS production, and of DNA damage (comet assay).	Increased ROS levels and DNA fragmentation after a 20-min exposure to AM-RF radiation. No effects of CW	Few details of experimental procedures; no temperature control	Campisi et al. (2010)
Rat lymphocytes	930 MHz (CW); SAR 1.5 W/kg; 5 or 15 min	Intracellular ROS measured with the fluorescent probe dichlorofluorescein diacetate (DCF-DA).	No effect on ROS formation		Zmysłony et al. (2004)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Rat, age 1–2 d, primary cortical astrocytes	1763 MHz (CDMA); average SAR, 2 or 20 W/kg; 30 min or 1 h.	Assessment of expression of HSPs and activation of MAPKs	No detectable effect on expression of HSP90, HSP70, HSP27; no change in MAPK phosphorylation, ERK1/2, JNK1/2, p38; no effect on TPA-induced MAPK phosphorylation	Temperature-control at $37 \pm 0.2^\circ\text{C}$	Lee et al. (2006)
Newborn rat, primary cortical neurons	1800 MHz; average SAR 2 W/kg; (5 min on, 10 min off); 24 h	Melatonin was given 4 h before exposure to RF radiation. Immunostaining and HPLC analysis of 8-OHdG in mitochondria; number of copies of mtDNA; levels of mtDNA transcripts.	RF radiation induced a significant 2-fold increase in 8-OHdG in the mitochondria of neurons, and a reduction in the copy number of mtDNA and the amount of mtRNA transcripts. The effects could be partly reversed by pre-treatment with melatonin.		Xu et al. (2010)
<i>Cell proliferation and cell cycle</i>					
Mouse C3H 10T½ cells	835.62 MHz (CW or CDMA); average SAR, 0.6 W/kg; 13 h (short exposure), up to 100 h (long-term exposure)	Cell-cycle parameters (transit of cells through G1, G2, S phase; probability of cell division) evaluated immediately after cells were exposed for 3 h, or after 100 h exposure	No changes in cell-cycle parameters after exposure to either CW or CDMA	Controlled exposure and temperature	Higashikubo et al. (2001)
Mouse pre-neoplastic CLS1 mammary epithelial cells	Nanopulse electric-field strength of 18 kV/m; repetition rate 1–1000 kHz; up to 6 h. Cells cultured in the presence EGF (10 ng/ml) and insulin (10 µg/ml) as comitogens. After exposure, cells in all treatment groups were returned to the incubator for 72 h	After exposure, cells in all treatment groups were returned to the incubator for 72 h; cell growth and viability were assessed	No effect on CLS1 cell growth or viability during the subsequent culture period of 72 h after 0.25–3 h exposure to nanopulse radiation. Prolonged exposure (4–6 h) caused a significant increase in cell proliferation.	Radar-type signal. Increase in cell proliferation associated with MAPK activation in EGF-supplemented medium.	Sylvester et al. (2005)
Mouse embryonic stem cells	1720 MHz; SAR, 1.5 W/kg (5 min on, 30 min off); 6 or 48 h	Transcript levels of cell-cycle regulatory, apoptosis-related, and neural-specific genes and proteins; changes in proliferation, apoptosis, and cytogenetic effects (quantitative RT-PCR and comet assay).	No difference in rates of cell proliferation between exposed and sham-exposed cells		Nikolova et al. (2005)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Mouse HEI-OC1 immortalized auditory hair cells	1763 MHz (CDMA); SAR, 20 W/kg; 24 or 48 h	Cell cycle (flow cytometry), DNA damage (comet assay: tail length, tail moment) were evaluated. Stress response (HSP) and gene activation were analysed with Western blotting and DNA microarray (Affymetrix full mouse genome chips, 32 000 genes)	No cell-cycle change or DNA damage. No change in expression of HSP or in phosphorylation of MAPK; minimal changes in gene expression: only 29 genes down- or upregulated; no consistent group of functional categories.		Huang et al. (2008b)
Mouse CTLL-2 cytolytic T lymphocytes	2450 MHz (CW, PW); SAR, 25 or 50 W/kg (CW) and 5 W/kg (PW); 2 h	Effects of exposure on IL-2- dependent proliferation.	Consistent and statistically significant reduction in cell proliferation at low concentrations of IL-2.	Large sample size: 24 replicates per exposure group	Cleary et al. (1996)
Chinese hamster ovary (CHO) cells	27 MHz; SAR, 5 or 25 W/kg; 2 h	Cell-cycle alterations determined by flow-cytofluorometric DNA determinations	Significant SAR-dependent changes in cell-cycle progression, with maximum change occurring 3 d after the initial exposure		Cao et al. (1995)
Chinese hamster lung fibroblasts (V79 cells)	935 MHz (CW); SAR, 0.12 W/kg; 1, 2, 3 h	Microtubule protein morphology determined by immunocytochemistry immediately after exposure; cell proliferation examined by cell counts up to 5 d after exposure	No changes after 1 or 2 h exposure. After 3 h exposure, microtubules appeared morphologically grainy, comparable to those in colchicine-treated positive controls; no consistent change in proliferation.	Only one proliferation value decreased 3 d after exposure (but not at 4 and 5 d) in cells exposed for 3 h	Pavicic & Trosic (2008)
Chinese hamster ovary (CHO) cells	2450 MHz PW; SAR, 33.8 W/kg; 2 h; simultaneous exposure to adriamycin	Evaluation of percentage of first- and second-division mitotic cells after treatment with BrdU.	Exposure did not affect changes in cell progression caused by adriamycin.		Ciaravino et al. (1991)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Chinese hamster ovary CHO-K1 cell line	2450 MHz, continuous or intermittent; SAR, 0.05–200 W/kg; 2 h	Cell survival, growth and cell cycle (flow cytometry at 0–24 h) were determined	Exposure to CW RF radiation (SAR ≤ 100 W/kg) did not affect cell growth, survival, or cell-cycle distribution. At 200 W/kg, cell growth was suppressed and cell survival decreased. Exposure to intermittent RF radiation caused no significant effects. Exposures ≤ 200 W/kg (continuous) or ≤ 900 W/kg (intermittent) did not affect cell-cycle distribution.	Effects on proliferation due to temperature rise at SAR 50–200 W/kg	Takashima et al. (2006)
Chinese hamster V79 cells	7700 MHz, CW; power density, 30 mW/cm ² ; 15, 30, 60 min	Incorporation of [³ H]thymidine and autoradiography	Decreased [³ H]thymidine incorporation immediately after exposure. Between 4 and 24 h after exposure, incorporation returns to control values; labelling index decreased after exposure, returned to normal after 24 h.	Normal incorporation rate is recovered within one cell generation; no information on temperature control	Garaj-Vrhovac et al. (1990)
Chinese hamster V79 cells	7700 MHz, CW; power density, 0.5, 10, 30 mW/cm ² ; 10, 20, 30, 60 min	Cell survival assessed by colony-forming ability	Surviving fraction reduced in a time- and energy-dependent manner.	Exposure system kept under controlled temperature conditions at 22°C.	Garaj-Vrhovac et al. (1991)
Rat RBL-2H3 mast cells	835 MHz; estimated power density, 81 W/m ² ; for 3 × 20 min/day for 7 days	Effects on cell proliferation, morphology and secretion	Increased [³ H]thymidine uptake and increased cell counts at days 6 and 7. Increased release of calcium	Exposure was variable across the chamber, based on temperature variation	Donnellan et al. (1997)
Transformed C6 rat glioma and normal primary glial cells (from d 17 rat embryos)	836.55 MHz (TDMA); power density 0.09, 0.9, 9 mW/cm ² ; SAR, 0.15–59 mW/kg; 24 h	Monitoring of cell growth, DNA synthesis assay ([³ H]thymidine).	No difference in growth curves and doubling times between sham-exposed and exposed cells		Stagg et al. (1997)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Rabbit lens epithelial cells	2450 MHz (CW); intensity, 0.5–20 W/m ² ; 2–8 h	Cell cycle (flow cytometry), cell viability (MTT assay); cell-cycle regulatory RNA and proteins (RT-PCR and Western blot).	Decreased number of cells in S-phase (decreased cellular replication) at exposures > 0.5 W/m ² after 8 h	Inadequate description of the exposure conditions	Yao et al. (2004)
<i>Apoptosis</i>					
Mouse-embryo primary neurons and astrocytes	1900 MHz (GSM) from a mobile phone; SAR not given; 2 h, mode “on” (exposure) or “stand-by” (sham).	Expression of apoptosis-related genes studied by array analysis. Genes showing ≥ 35% decrease or increase further studied by real time RT-PCR.	Up-regulation of <i>Pycard</i> , <i>Casp2</i> , and <i>Casp6</i> genes, both in “on” and “stand-by” modes, in neurons. <i>Pycard</i> , <i>Casp2</i> , <i>Casp6</i> , and <i>Bax</i> were upregulated in astrocytes, when cell phone in the “on” mode, but not in the “stand by” mode.	Cell phone placed over the culture dish; no dosimetry; no temperature control	Zhao et al. (2007a)
Mouse neuroblastoma N2a cells	935 MHz (GSM basic, GAM “talk”, CW); SAR, 2 W/kg; 24 h. Cells were in proliferative and differentiated states.	Apoptosis assessed – up to 48 h after exposure – by fluorescence microscopy: annexin V, caspase activation, and <i>in situ</i> end-labelling.	No differences in apoptosis levels between exposed and sham-exposed proliferating or differentiated cells		Moquet et al. (2008)
Rat-embryo primary neurons	900 MHz (CW); SAR 2 W/kg; 24 h	Apoptosis assessed by condensation of DAPI-labelled nuclei, and TUNEL assay. Caspase-3 activity assessed by fluorimetry, and apoptosis-inducing factor (AIF) by immunofluorescence.	A highly significant increase in the percentage of apoptotic cells was seen at 24 h after exposure, compared with sham-exposed cells and cells incubated at 39 °C; no increase in caspase-3 activity, but increase in AIF labelling.	Results suggest caspase-independent mitochondrial apoptosis. Increase in temperature was 2 °C during exposure. Control experiments (no RF) with neurons at 39 °C did not show an increase in apoptosis	Joubert et al. (2008)

8-OHdG, 8-hydroxy-2'-deoxyguanosine; Asc, apoptosis associated speck-like protein containing a CARD; BrdU, bromodeoxyuridine; CDMA, code-division multiple access; CAT, catalase; CW, continuous wave; d, day; ERK1/2, extracellular signal-regulated kinases; FDMA, frequency-division multiple access; FM, frequency-modulated; GSH-Px, glutathione peroxidase; GSM, Global Systems Mobile communications; GSSG, glutathione disulfide; h, hour; HSF, heat-shock transcription factor; HSP, heat-shock protein; IFN, γ-interferon; JNK1/2, c-Jun N-terminal protein kinases; LPS, lipopolysaccharide; NO, nitric oxide; RF, radiofrequency; ROS, reactive oxygen species; RT-PCR, reverse-transcriptase polymerase chain reaction; SOD, superoxide dismutase; t-BOOH, *tert*-butylhydroperoxide

(DCF-DA), was elevated by 16.6% and 14.6%, respectively, at these time-points. Exposure to RF radiation alone did not affect ROS production.

Exposure of mouse C3H 10T½ cells and hamster ovary HA-1 fibroblasts to RF radiation at 835.62 MHz as FMCW signal, or at 847.74 MHz as CDMA signal (SAR, 0.6 or 5 W/kg) for 1 or 24 hours did not increase the DNA-binding activity of heat-shock transcription factor ([Laszlo et al., 2005](#)).

Exposure of mouse L929 fibrosarcoma cells to continuous-wave or GSM-modulated RF radiation at 900 MHz (SAR, 0.3 or 1 W/kg) for 10 or 30 minutes, did not induce ROS formation by itself, or in combination with subtoxic concentrations of MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, a by-product of water chlorination). In this study, MX strongly induced ROS formation ([Zeni et al., 2007b](#)).

[Höytö et al. \(2008b\)](#) exposed mouse L929 cells to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg), for 1 hour or 24 hours, under isothermal conditions. To investigate possible effects of co-exposure with other agents, menadione was used to induce ROS, and *tert*-butylhydroperoxide (*t*-BOOH) was used to induce lipid peroxidation. No effects were observed after exposure to RF radiation only. Menadione-induced caspase-3 activity was significantly increased (but not in human neuroblastoma cells used in the same experiments) only by exposure to the GSM-modulated signal; *t*-BOOH-induced lipid peroxidation was not modified by RF radiation.

[Lee et al. \(2006\)](#) exposed cultures of primary astrocytes from newborn rats (aged, 1–2 days) to RF radiation at 1763 MHz as CDMA signal (average SAR, 2 or 20 W/kg) for 30 minutes or 1 hour, under temperature-controlled conditions at 37 ± 0.2 °C. RF radiation alone did not elicit a stress response and had no effect on TPA-induced MAPK phosphorylation.

[Campisi et al. \(2010\)](#) exposed cultures of primary astrocytes from newborn rats (age,

1–2 days) to continuous-wave or amplitude-modulated (50 Hz) RF radiation at 900 MHz (no SAR given; power density, 0.26 W/m^2), for 5, 10 or 20 minutes. There was an increase in ROS levels and DNA fragmentation (measured with the comet assay) after an exposure of 20 minutes to the amplitude-modulated RF radiation. With regards to the temperature of the cells during the exposure, the authors note that low-intensity RF radiation caused a minimal increase (0.03 °C) in temperature. [The publication gave few details about the experimental procedures.]

[Xu et al. \(2010\)](#) exposed primary cortical neurons from newborn rats to intermittent (5 minutes on, 10 minutes off) GSM-modulated RF radiation at 1800 MHz (average SAR, 2 W/kg) for 24 hours, and found significant increases ($P < 0.01$) in ROS production and in mitochondrial concentrations of 8-OHdG, and a reduction in copy numbers of mitochondrial DNA and mitochondrial RNA transcripts. These effects were partly reversed by treatment with melatonin 4 hours before exposure to RF radiation.

[The Working Group concluded that there was weak evidence that exposure to RF radiation activates stress response or ROS production in a variety of rodent cells *in vitro* under conditions not confounded by thermal effects.]

(ii) Cell proliferation and cell cycle

Exposure of Chinese hamster ovary (CHO) cells to pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg) for 2 hours, did not affect cell-cycle progression, measured by analysis of first- and second-division mitotic cells after incorporation of bromodeoxyuridine. In the presence of adriamycin (given immediately before the exposure) RF radiation did not affect the cell-cycle progression induced by this drug ([Ciaravino et al., 1991](#)).

[Huang et al. \(2008b\)](#) did not find evidence for the induction of cellular responses, including cell-cycle distribution, DNA-damage induction,

stress response and altered gene expression, in immortalized HEI-OC1 mouse auditory hair cells exposed to RF radiation 1763 MHz (CDMA; SAR, 20 W/kg) for 24 or 48 hours. [The Working Group noted that the choice of auditory hair cells was justified by the fact that auditory cells may be exposed to radiation from mobile phones.]

In V79 Chinese hamster lung fibroblasts, microtubule morphology – analysed by use of immunocytochemical methods – appeared modified following a 3-hour exposure to continuous-wave RF radiation at 935 MHz (SAR, 0.12 W/kg). No changes were noted after exposure for 1 or 2 hours ([Pavicic & Trosic, 2008](#)).

In V79 Chinese hamster cells exposed to continuous RF radiation at 7.7 GHz (SAR not given; power density, 30 mW/cm²) for 15, 30, or 60 minutes, the incorporation of [³H]thymidine decreased immediately after exposure. At longer time intervals after exposure, the incorporation of [³H]thymidine increased and it returned to control values by 24 hours ([Garaj-Vrhovac et al., 1990b](#)). In the same cells exposed to RF radiation under the same conditions with power densities of 0.5, 10, 30 mW/cm², the surviving fraction – assessed by colony-forming ability – was reduced in a time- and energy dependent manner ([Garaj-Vrhovac et al., 1991](#)).

[Cao et al. \(1995\)](#) exposed CHO cells in different phases of the cell cycle to continuous-wave RF radiation at 27 MHz (SAR, 5 or 25 W/kg), for 2 hours. The cells were followed at sampling time-points up to 96 hours after exposure. Significant SAR-dependent changes in cell-cycle progression were observed, with the maximum change occurring at 3 days after exposure.

[Cleary et al. \(1996\)](#) exposed CTLL-2 mouse cytolytic cells to continuous-wave RF radiation at 2450 MHz (SAR, 5–50 W/kg), or to pulsed-wave RF radiation at 2450 MHz (SAR, 5 W/kg) for 2 hours. There was a decrease in cell proliferation (assessed by means of [³H]thymidine incorporation) with continuous-wave, and an increase with pulsed-wave radiation. The effects

were dependent upon the IL2 concentrations in the culture and the stage of the cell cycle.

[Donnellan et al. \(1997\)](#) exposed rat RBL-2H3 mast cells to RF radiation at 835 MHz (estimated power density, 81 W/m²) for 20 minutes, three times per day for 7 days. Increased uptake of [³H]thymidine and increased cell counts were observed at days 6 and 7, and an increase in the release of calcium was detected in the exposed group. [The exposure was variable across the exposure chamber based on temperature variations; eight samples were used for each group for analysis.]

[Stagg et al. \(1997\)](#) exposed rat primary glial cells and C6 glioma cells to RF radiation at 836.55 MHz as TDMA signal (SAR, 0.59, 5.9, 59 mW/kg) for 4 or 24 hours. A small but significant increase ($P = 0.026$) in the uptake of [³H]thymidine was detected in C6 glioma cells at 5.9 mW/kg. In the other exposure groups no effects from exposure to RF radiation were observed ([³H]thymidine uptake, cell growth).

[Higashikubo et al. \(2001\)](#) exposed mouse fibroblast (C3H 10T $\frac{1}{2}$) and human glioblastoma (U87MG) cells to RF radiation at 847.74 MHz as CDMA signal or at 835.62 MHz as TDMA signal (SAR, 0.6 W/kg) for up to 100 hours. No significant effects were found on cellular replication, as measured with the bromodeoxyuridine pulse-chase flow-cytometry method.

[Takashima et al. \(2006\)](#) exposed Chinese hamster ovary CHO-K1 cells to continuous-wave RF radiation at 2450 MHz (SAR, 0.05–200 W/kg) for 2 hours, or to intermittent RF radiation at 2450 MHz (average SAR, 50 or 100 W/kg) for 2 hours. Continuous-wave RF radiation at 200 W/kg decreased cell replication and cell survival. None of the other exposures showed an effect. [The temperature of the medium increased to 44.1 °C during exposure at a SAR of 200 W/kg.]

[Yao et al. \(2004\)](#) exposed replicates of rabbit-lens epithelial cells to continuous-wave RF radiation at 2450 MHz (no SAR given; power density,

0.1–2 mW/cm², for 8 hours at 25 °C. Cell viability was significantly reduced at power densities of 0.5 mW/cm² and higher. The numbers of cells in S-phase decreased and that of cells in G₀/G₁ phase increased – both significantly – at power densities ≥ 0.5 W/m². [The Working Group had some difficulty in understanding the description of the exposure conditions in this study.]

[Nikolova et al. \(2005\)](#) exposed mouse embryonic stem cells to intermittent (5 minutes on, 30 minutes off) RF radiation at 1720 MHz (time-averaged SAR, 1.5 W/kg; during actual exposure, 12 W/kg) for 6 or 48 hours. No effects on the incorporation of bromodeoxyuridine were observed.

[Sylvester et al. \(2005\)](#) exposed mouse pre-neoplastic CL-S1 mammary epithelial cells to RF radiation as ultra-wide band pulses with an electric-field strength of 18 kV/m and a repetition rate in the range of 1–1000 kHz for up to 6 hours. No effect on CL-S1 cell growth or viability was observed after exposures of 0.25–3 hours. Exposure for 4 hours resulted in a significant increase in cell proliferation compared with untreated controls. There was no further increase at 5 or 6 hours.

[The Working Group concluded that the evidence that RF radiation has an effect on cell proliferation and cell cycle was weak.]

(iii) *Ornithine decarboxylase activity (rodent and human cells)*

Ornithine decarboxylase (ODC) is the first and rate-limiting enzyme in the polyamine biosynthesis pathway. Because polyamines are involved in the control of cell replication and differentiation, a change in cellular ODC activity is relevant to carcinogenesis. Tumour promoters such as TPA induce ODC activity, and a high level of ODC activity has been found in several premalignant conditions.

[Byus et al. \(1988\)](#) exposed Reuber H35 hepatoma, Chinese hamster ovary (CHO), and human 294 T melanoma cells to

amplitude-modulated RF radiation at 450 MHz (SAR not given; power density, 1.0 mW/cm²) for 1 hour. A 50% increase in ODC activity was observed after exposure to RF radiation alone. In addition, ODC activity induced by TPA was further enhanced by exposure to RF radiation in H35 and CHO cells.

[Litovitz et al. \(1993\)](#) reported a 90% increase in ODC activity in murine L929 fibroblasts exposed to RF radiation at 915 MHz (SAR, 2.5 W/kg; amplitude-modulated at 55, 60, or 65 Hz) for 8 hours. A continuous-wave signal did not affect cellular ODC activity. Subsequent findings from the same laboratory ([Litovitz et al., 1997](#); [Penafiel et al., 1997](#)) showed increased ODC activity in L929 cells exposed at 840 MHz (SAR, 2.5 W/kg) as a TDMA mobile-phone signal (burst-modulated at 50 Hz, with 33% duty cycle) for 2–24 hours. Also, signals with amplitude modulation at 60 Hz or 50 Hz induced ODC activity, whereas a signal modulated with speech, the signal of an analogue mobile phone, or a signal frequency modulated at 60 Hz, did not affect ODC activity. Various exposure times between 2 hours and 24 hours were used and the effect was most pronounced after exposure for 8 hours.

[Desta et al. \(2003\)](#), in an attempt to replicate the study of [Penafiel et al. \(1997\)](#), did not find any increase in ODC activity in murine L929 cells exposed to RF radiation at 835 MHz (SAR, < 1 W/kg; TDMA modulated) for 8 hours. In contrast, a decrease in ODC activity was observed at SARs of 1–5 W/kg. This decrease became statistically significant at SAR values > 6 W/kg, associated with a temperature increase of > 1 °C in the cell-culture medium.

In another replication study, [Höytö et al. \(2007\)](#) found no increase in ODC activity in L929 cells from two different sources using the same exposure system as [Penafiel et al. \(1997\)](#): a decrease in ODC activity was observed at the highest SAR used (6 W/kg). With a different exposure system and better temperature control

was used, a small increase in ODC activity was observed after 8 hours of exposure at 6 W/kg. This increase could be related to the temperature-control system, creating a temperature gradient in the cell cultures (lower temperature at the bottom of the cell culture). [Höytö et al. \(2006\)](#) reported no effects on ODC activity in L929 cells exposed to continuous-wave or GSM-modulated RF radiation at 900 MHz (SAR, 0.2 or 0.4 W/kg) for 2, 8, or 24 hours. ODC activity decreased after conventional heating (without exposure to RF radiation), consistent with the findings of [Desta et al. \(2003\)](#). Apparently, temperature differences of < 1 °C are sufficient to influence ODC activity.

[Höytö et al. \(2007b\)](#) also exposed L929 murine fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes to continuous-wave and GSM-modulated RF radiation at 815 MHz (SAR, 1.5, 2.5 or 6 W/kg) for 2, 8 or 24 hours. A significant decrease in ODC activity was consistently observed in all experiments with rat primary astrocytes exposed to GSM-modulated or continuous-wave RF radiation at SARs of 1.5 or 6.0 W/kg. No effects were seen in the other cell lines.

[Billaudel et al. \(2009a\)](#) found no effects on ODC activity in L929 mouse fibroblasts exposed to RF radiation at 835 MHz, 900 MHz, or 1800 MHz as GSM or DAMPS-modulated signals (SAR, 0.5–2.5 W/kg) for 2–24 hours. The same authors reported that – consistent with the findings in murine cells – ODC activity was unaffected in human SH-SY5Y neuroblastoma cells exposed to GSM-modulated RF radiation at 1800 MHz, or DAMPS-modulated RF radiation at 835 MHz (SAR for both, 1 or 2.5 W/kg) for 8 or 24 hours ([Billaudel et al., 2009b](#)).

[The Working Group concluded that there was moderate evidence that RF radiation alters ODC activity.]

(iv) Apoptosis

Rat embryo primary neurons were exposed to continuous-wave RF radiation at 900 MHz (SAR, 2 W/Kg) for 24 hours. Because the temperature increased by 2 °C during the exposure, a control experiment at 39 °C was included (without RF radiation). Apoptosis was measured with two different methods (staining of nuclei with 4',6-diamino-2-phenylindole (DAPI) and analysis of DNA fragmentation with TUNEL-flow cytometry). With both techniques, a highly significant increase in the percentage of apoptotic cells was seen at 24 hours after exposure, compared with the sham-exposed cells and the cells incubated at 39 °C ([Joubert et al. \(2008\)](#)).

[Nikolova et al. \(2005\)](#) exposed mouse embryonic stem cell-derived neural progenitor cells to intermittent (5 minutes on, 30 minutes off) GSM-modulated RF radiation at 1710 MHz (time-averaged SAR, 1.5 W/kg; during actual exposure, 12 W/kg) for 6 or 48 hours. No effects on apoptosis or on mitochondrial membrane potential were found.

[Höytö et al. \(2008a\)](#) exposed mouse L929 cells to 872 MHz continuous-wave or GSM-modulated RF radiation (SAR of 5 W/kg) for 1 or 24 hours under isothermal conditions. Menadione-induced apoptosis (tested by measuring caspase-3 activity) was increased in cells exposed to the GSM-modulated signal, but not in cells exposed to the continuous-wave signal. No effects were seen from RF radiation in the absence of menadione. As described earlier, no effects or RF radiation on apoptosis were observed in human cells in this same study.

[Höytö et al. \(2008b\)](#) exposed mouse L929 fibroblasts that had been stimulated with fresh medium, stressed by serum deprivation, or not subjected to stimulation or stress, to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour under isothermal conditions. Increased apoptosis (tested by measuring caspase-3 activity) was

seen as a response to serum deprivation, but no consistent effects of exposure to RF radiation were found.

[Joubert et al. \(2007\)](#) studied apoptosis in rat primary cortical neurons exposed to GSM-modulated RF radiation at 900 MHz (SAR, 0.25 W/kg), or continuous-wave at 900 MHz (SAR, 2 W/kg) for 24 hours. No effects on apoptosis were detected, either just after the exposure or 24 hours later, with three different techniques, *viz.* 4',6-diamino-2-phenylindole (DAPI) staining, flow cytometry with double staining (TUNEL and propidium iodide), or measurement of caspase-3 activity by fluorometry.

[Zhao et al. \(2007a\)](#) exposed cultured primary mouse embryonal neurons and astrocytes to 1900 MHz RF radiation from a working mobile phone (SAR not given) for 2 hours. The phone was placed with its antenna over the centre of the culture dish. During sham-exposures the phone was on “stand-by.” Three apoptosis-associated genes (*Pycard*, encoding the Asc protein – apoptosis-associated speck-like protein containing a caspase-recruitment domain – *Casp2*, and *Casp6*) were upregulated in neurons, both after exposure and sham-exposure. In astrocytes the upregulation was observed in exposed cells only. In addition, the astrocytes – not the neurons – showed RF radiation-dependent upregulation of the *Bax* gene. [The Working Group noted the ill-defined exposure conditions in this study; see above.]

[Moquet et al. \(2008\)](#) exposed mouse neuroblastoma N2a cells to RF radiation at 935 MHz (SAR, 2 W/kg) for 24 hours, as GSM basic (amplitude-modulated), GSM “talk,” and continuous-wave signal. No significant differences in levels of apoptosis were observed between exposed and sham-exposed cells.

[The Working Group concluded that there is weak evidence that RF radiation affects apoptosis in mammalian cells.]

4.5 Physical factors that affect interpretation of study results

4.5.1 Effects of critical RF-field parameters

(a) Modulation

There is evidence that modulation of the carrier waves of RF radiation can cause changes in biological processes that do not occur when the waves are not modulated. Examples of biological reactions to modulated RF radiation were clearly shown by [Bawin et al. \(1975\)](#), replicated by [Blackman et al. \(1979\)](#). For more examples and details, see the reviews by [Blackman \(2009\)](#) and [Juutilainen et al. \(2011\)](#).

(b) Power-intensity “windows”

Studies by [Bawin et al. \(1975, 1978\)](#) and [Blackman et al. \(1980\)](#) have characterized the power-density response in detail for the RF radiation-induced release of calcium ions from the chick brain ex vivo. Both groups observed regions of power density, termed “windows,” in which the release of calcium ions was exposure-dependent, separated by regions that did not respond as a function of the power density of incident radiation. Subsequent reports by [Dutta et al. \(1984, 1989\)](#) revealed similar power-density windows of induced response in nervous system-derived cultures of human and animal cells, and [Schwartz et al. \(1990\)](#) observed windows of calcium-ion release from the frog heart ex vivo. This phenomenon appeared to be caused by the response characteristics of the particular biological preparations. The extensive characterization of exposure-response at 50, 147 and 450 MHz (amplitude-modulated, 16 Hz) in the chick brain showed that the windows could be aligned across carrier frequencies if one used the calculated electric-field strength at the tissue surface, rather than the incident power density ([Joines & Blackman, 1980, 1981](#); [Joines et al., 1981](#); [Blackman et al., 1981, 1989](#)). See reviews by [Blackman \(2009\)](#) and [Belyaev \(2010\)](#).

4.5.2 Frequency dependence and frequency windows

Effects of RF radiation are dependent on the frequency of the carrier wave. Differences in the response of human cells to GSM-type RF radiation were observed at frequency channels of 905 and 915 MHz, where the other conditions of exposure were the same ([Belyaev et al., 2009](#); [Marková et al., 2010](#)). Thus, it is important to know which difference in carrier frequency is acceptable to compare results from different studies.

The frequency-dependence of the effects of microwave radiation in different model systems and with different end-points measured has been reviewed ([Grundler, 1992](#); [Grundler et al., 1992](#); [Belyaev et al., 2000](#); [Belyaev, 2005, 2010](#)). The effects of resonance-type microwave radiation were observed within multiple frequency-windows at intensity values well below those at which any thermal effects had been observed. The half-width of resonances and distance between them varied in dependence on the intensity of the RF radiation. Sharper and narrower resonances, and half-widths reaching at least 2 MHz were observed at the lower intensities.

4.5.3 Polarization

Different kinds of polarization were applied in the experimental studies discussed above: linear, left-handed circular, and right-handed circular polarization. It has been shown in many studies that biological effects are dependent upon polarization ([Belyaev et al., 1992a, c, d, 1993a, b](#); [Shcheglov et al., 1997](#); [Ushakov et al., 1999, 2006a](#); [Belyaev & Kravchenko, 1994](#); [Belyaev, 2010](#)). For example, polarization should be taken into account when attempting to replicate the results of previous studies. For example, [Lai & Singh \(1996\)](#) used circular polarization, whereas linear polarization was applied in subsequent studies aimed at replicating their results, thus reducing sensitivity.

4.5.4 Dose and duration of exposure

While accumulated absorbed energy is measured as “dose” (dose rate multiplied by exposure time) in radiobiology, guidelines for exposures to RF radiation usually state power density or SAR (dose rate analogue) to define exposure. Several studies have analysed the relationship between dose and duration of exposure, with results suggesting that duration of exposure and dose may be important for cancer-relevant effects. In particular, prolonging the duration of exposure could compensate for the effects of a reduction in intensity.

[Kwee & Raskmark \(1998\)](#) analysed proliferation of human epithelial amnion cells exposed to RF radiation at 960 MHz, with SARs of 0.021, 0.21, or 2.1 mW/kg. These authors reported linear correlations between duration of exposure at 0.021 and 2.1 mW/kg and changes in cell proliferation, although no clear correlation was seen at 0.21 mW/kg.

Exposure of *E. coli* and rat thymocytes to RF radiation at power densities 0.01–1 mW/cm² resulted in significant changes in chromatin conformational state, if exposure was performed at resonance frequencies for 5–10 minutes ([Belyaev et al., 1992a, b](#); [Belyaev & Kravchenko, 1994](#)). Decreases in these effects caused by lowering the power density by an order of magnitude could be compensated for by a several-fold increase in the duration of exposure. At exposures longer than 1 hour, the same effect could be observed even at the lowest power density ([Belyaev et al., 1994](#)).

4.5.5 Background fields of extremely low frequency (ELF)

Background ELF (1–300 Hz) fields vary between laboratories. Even within the same laboratory or the same RF exposure system, variations of up to 5 µT are not uncommon. Four studies investigated the influence of background

ELF fields on the effects of exposure to RF radiation: ODC activity in L929 cells (Litovitz *et al.*, 1997), hypoxia sensitization caused by long-term repeated exposures of chick embryos (Di Carlo *et al.*, 2002), spatial learning deficits in rats induced by microwave radiation (Lai, 2004), and DNA-damage induction in rat brain cells (Lai & Singh, 2005). In these studies, the effects caused by RF radiation were significantly reduced by imposing an ELF field of up to 5 μ T.

4.5.6 Net static geomagnetic field

The static geomagnetic field (30–70 μ T, depending on the location) may alter the cellular response to RF radiation (Belyaev *et al.*, 1994; Ushakov *et al.*, 2006b). Net static magnetic fields vary by location, even within the same laboratory and with the same exposure system, due to the ferromagnetic properties of laboratory equipment. For example, the resonance effects of microwave radiation on DNA repair and chromatin conformation in *E. coli* depend on the magnitude of the net static geomagnetic field at the site of exposure (Belyaev *et al.*, 1994; Ushakov *et al.*, 2006b).

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

This Monograph is concerned with non-ionizing radiation in the radiofrequency (RF) range of the electromagnetic spectrum, i.e. between 30 kHz and 300 GHz. The corresponding wavelengths – the distance between successive peaks of the RF waves – range from 10 km to 1 mm, respectively. Human exposure to RF radiation can occur from many different sources and under a wide variety of circumstances, including the use of personal devices (mobile phones, cordless phones, Wi-Fi, Bluetooth, amateur radios, etc.), occupational sources (high-frequency dielectric and induction heaters, broadcast antennas, high-power pulsed radars, and medical applications), and environmental sources (mobile-phone base stations, broadcast antennae). These multiple sources contribute to an individual's total exposure, with contributions varying by different characteristics, e.g. place of residence. The dominant sources of human exposure to RF radiation are near-field sources for workers, and transmitters operating on or in close vicinity to the body, such as hand-held devices, for the general population.

Electromagnetic fields generated by RF sources couple with the human body, which results in induced electric and magnetic fields and associated currents inside body tissues. The most important factor that determines exposure is the distance of the transmitter from the human body, within the main radiation beam. In a first approximation, the induced field strength

is proportional to the time-averaged radiated power and inversely proportional to the distance from the source. In addition to distance, the efficiency of coupling and the resulting field distribution inside the body strongly depend on properties of the fields, such as frequency, polarization, distance from the antenna and direction of incidence, and on anatomical features of the exposed person, including height, posture, body mass index, shape of the head and associated structures such as the pinna (the outer ear), and dielectric properties of tissues. Induced fields within the body are highly non-uniform, with local hotspots and variations of several orders of magnitude. An important theme in studies on RF dosimetry is the focus on demonstrating compliance with exposure limits defined in terms of the localized and whole-body specific absorption rate (SAR) of energy. In recent years, measurement and simulation tools have been refined to allow exposure estimates in specific tissues or organs to be made for particular exposure scenarios, including those involving devices such as mobile phones.

While the number of mobile-phone subscriptions has been increasing rapidly around the world (4.6 billion subscribers in 2009), changes in mobile-phone technology have led to lower time-averaged RF power emitted from mobile phones used at present than those of previous generations. Of major interest to this *Monograph* is the exposure scenario in which mobile phones are held against the ear during a voice call. The

magnitude and spatial distribution of the ensuing SAR inside the brain depend on the design of a phone and its antenna, its position relative to the head, the anatomy of the head, how the hand holds the phone, as well as on the quality of the connection between the base station and the phone. GSM900/1800/PCS phones (Global System for Mobile communications/Personal Communications Service, operating at 900 or 1800 MHz) held next to the ear induce high spatial-averaged SAR values in the brain. This is because adaptive power control on average only reduces the output power to about 50% of its maximum during calls, but this would vary depending on the network software. The use of discontinuous transmission during voice calls would give a further 30% reduction in power. Analogue phones, which ceased to be used around the year 2000, produced still higher absorption of energy in the brain for two reasons: the handsets had higher output powers than modern phones, and the larger size of the handsets and antennae led to a more diffuse pattern of energy absorption in the head. Adaptive power control is much more effective with third-generation (3G) phone technologies, and this has led to a reduction of SAR in the brain by almost two orders of magnitude compared with that from GSM phones. The DECT (Digital Enhanced Cordless Telecommunications) phone is another widely used device that is held against the ear to make and receive voice calls. The average SAR in the brain from use of DECT phones is around five times lower than that measured for GSM phones.

The maximum spatial peak exposure to RF fields from mobile phones is very similar between different technologies. However, it may vary by up to a factor of 10 dependent on specific phone design. The spatial maximum exposure from cordless DECT phones is an order of a magnitude lower than that from mobile phones. Modulation and access schemes have also evolved to give a complicated output-power variation with time,

while analogue technologies had a more constant pattern of output power.

Mobile-phone use is widespread in industrialized countries and rapidly growing elsewhere. Certain phone functions, such as text messaging, which involves considerably less exposure than voice calls, have become very popular among teenagers. Due to the closer proximity of the phone to the brain of children compared with adults, the average exposure from use of the same mobile phone is higher by a factor of 2 in a child's brain and higher by a factor of 10 in the bone marrow of the skull. In addition, dielectric properties of certain tissues, notably the bone marrow, change with age. The marrow progressively incorporates more fat, and the bone itself increases in thickness, hardens, and loses water over time. Both these tissues, therefore, have a higher conductivity in children than in adults and they receive a higher energy deposition from RF sources.

The use of hands-free kits lowers exposures from mobile phones to less than 10% of the value resulting from use at the ear, but it may increase exposure to other parts of the body. The rise in temperature inside the brain from use of a typical 3G mobile phone is small, approximately 0.1 °C or less.

Measures of mobile-phone use for epidemiological studies have historically relied on self-reporting, but recent validation studies among adults and children have demonstrated that there can be considerable random and systematic errors in the reported number of calls, the duration of calls, and the side of head where the phone is held during use. This is particularly problematic for epidemiological studies of cancer in humans, where information is needed on phone use many years in the past.

Assessments of household exposures to RF radiation often rely on spot measurements with a focus on burst activity, rather than on average values over time, which are better measures of RF exposure. Environmental sources are dominated

by possible RF exposures from being in close proximity to mobile-phone base stations, but actual measurements have shown that distance to a base station is not a good proxy for exposure, due to the considerable variability in characteristics of the antennae, and shielding and reflection of the waves. Typical exposures from rooftop- or tower-mounted mobile-phone base stations are lower by more than five orders of magnitude than those from GSM handsets. Exposures to the brain from television and radio stations are typically lower than those from base stations. Epidemiological studies of environmental RF sources need to include rigorous assessments of exposures to RF radiation, documented by direct measurements or through validated models.

Many occupations involve the use of sources of RF radiation at much higher power levels than those from mobile phones. For people exposed to high-power RF sources at work, cumulative energy deposition in the whole body may be much greater than from mobile-phone use, but the spatial peak SAR in the head will be less.

Tissue heating is the most firmly established mechanism for effects of RF radiation in biological systems. Although it has been argued that RF radiation cannot induce physiological effects at exposure intensities that do not cause a detectable increase in tissue temperature, except for reactions mediated by free radical pairs, it is likely that not all mechanisms of interaction between weak RF fields, with the various signal modulations used in wireless communications, and biological structures have yet been discovered or fully characterized.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Institute of Electrical and Electronics Engineers (IEEE) have developed guidelines for maximum human exposures to RF fields. These guidelines are designed to protect against adverse effects due to whole-body or partial body heating as a result of energy absorption above 100 kHz,

and against nervous system effects at frequencies up to 10 MHz.

5.2 Human carcinogenicity data

The epidemiological evidence on possible associations of exposure to RF radiation with cancer comes from studies of diverse design that have assessed a range of sources of exposure: the populations included people exposed in occupational settings, people exposed through sources in the general environment, e.g. transmission towers, and people exposed through use of wireless (mobile and cordless) telephones. The most robust evidence is for mobile phones, the most extensively investigated exposure source. The general methodological concerns related to this evidence are covered in the introduction to Section 2 and are not reviewed again here.

As for any compilation of findings of epidemiological studies, interpretation of this evidence needs to give consideration to the possibility that observed associations reflect chance, bias, or confounding, rather than an underlying causal effect. The investigation of risk of cancer of the brain associated with mobile-phone use poses complex methodological challenges in the conduct of the research and in the analysis and interpretation of the findings.

5.2.1 Personal use of wireless telephones

(a) *Tumours of the central nervous system: gliomas of the brain*

One cohort study from Denmark and five case-control studies (from the USA, Finland, Greece, Sweden, and a multicentre international study) were judged by the Working Group to offer useful epidemiological information regarding associations between use of wireless phones and glioma. There are also several studies of time trends in occurrence of cancer of the brain in relation to the great temporal increase in mobile-phone use.

(i) Time-trend studies

It has been suggested that time trends in the incidence of cancer might reflect the impact of increasing use of mobile phones on cancer risk. In that regard, there have been some reports from various countries describing rates of brain cancer over time. In general, there has not been a documented and stable increase in rates since the advent of the mobile-phone era. However, the general absence of any documented increase in rates of tumours of the brain must be interpreted in light of the fact that most time trends were examined only before the early 2000s. However, any large risk associated with relatively recent exposure should have been detected in the studies conducted to date. Time trends in cancer of the brain have not shown evidence of a trend that would indicate a promptly acting and powerful carcinogenic effect of mobile-phone use.

(ii) Cohort study and early case-control studies

A large cohort study in the entire population of Denmark included mobile-phone subscribers with a median of 8 years of subscription. The study showed no excess risk of glioma, based on 257 exposed cases. Because of the reliance on subscription to a mobile-phone provider as a surrogate for mobile-phone use, this study involved considerable misclassification in exposure assessment.

Several case-control studies were carried out in a time window that was relatively early in the period of rising use. Three of these studies used self-reported histories of mobile-phone use, while a Finnish study made a link to mobile-phone subscription records. Effect estimates from these studies were generally too imprecise to make them informative.

(iii) The INTERPHONE study

The INTERPHONE study, a multicentre case-control study, comprised the largest investigation so far of mobile-phone use and brain tumours, including component studies of

glioma, acoustic neuroma, and meningioma. The Working Group primarily considered the pooled analyses published in 2010 and 2011, rather than the findings as reported by site investigators or groups of investigators.

The pooled analysis of the INTERPHONE study on the risk of glioma in relation to use of mobile phones included 2708 cases of glioma and 2972 controls. Participation rates were 64% among cases of glioma and 53% among controls, with a wide variation in control participation rates among centres. For regular users, an overall reduced odds ratio (OR) was seen for glioma (OR, 0.81; 95% confidence interval [CI], 0.70–0.94); this was also observed in most study centres. Odds ratios of below unity were also found for all categories of time since start of use and of cumulative number of calls. The reason for these low odds ratios has not been established, but they probably reflect selection bias, at least in part. In terms of cumulative call time, all odds ratios were uniformly below unity for all deciles of exposure except for the highest decile (≥ 1640 hours of cumulative call time). For this exposure group, the odds ratio for glioma was 1.40 (95% CI, 1.03–1.89). Some other analyses of the same data also pointed to a possible association of mobile-phone use with risk of glioma, including the findings related to location of tumour (a higher odds ratio for tumours in the temporal lobe) and laterality of mobile-phone use (an apparently higher odds ratio in those who used a mobile phone on the same side of the head as the tumour). In an attempt to obviate the distortions that might have been generated by differential non-participation, an analysis was conducted with the lowest exposure decile as the reference; this showed a high odds ratio in the highest exposure decile. Recent reports presented findings based on methodological enhancements that derived dose indicators based on models applied to magnetic resonance imaging or computed tomography scans of the cases; these analyses in subsets of the INTERPHONE studies provide

additional insights into the patterns of risk of glioma associated with mobile-phone use.

The Working Group recognized several strengths of the INTERPHONE study, including its large sample size, the common core protocol, rapid case ascertainment, comprehensive data collection, and in-depth data analyses that included a wide variety of sensitivity and validation studies. However, the rather low participation rates may well have led to complicated and important patterns of selection bias.

In summary, in the INTERPHONE study there was no increased risk of glioma associated with having ever been a regular user of mobile phones. However, there were indications of an increased risk of glioma at the highest levels of cumulative call time, for ipsilateral exposures, and for tumours in the temporal lobe, but chance or bias may explain this increased risk.

(iv) *Studies from Sweden*

In 2011, Swedish investigators reported the findings of a pooled analysis of associations of mobile-phone and cordless-phone use and risk of glioma. Cases were ascertained from 1997 through 2003 in two waves. The Working Group considered the latest combined analysis of the study data. Both cases and controls were selected by use of population registries. A sequential approach by self-administered questionnaire and interview was used to collect information on the exposures and covariates of interest, including the use of mobile and cordless phones.

The analysis included 1148 cases with a diagnosis of glioma, and 2438 controls. When mobile-phone users were compared with people who reported no use of mobile or cordless phones, or exposure > 1 year before the reference date, an increased odds ratio was estimated (OR, 1.3; 95% CI, 1.1–1.6). The odds ratios increased progressively with increasing time since first mobile-phone use, and with increasing cumulative call time for the ordered categories of exposure duration (1–1000, 1001–2000, and > 2000 hours)

as follows: 1.2 (95% CI, 0.98–1.4), 1.5 (95% CI, 1.1–2.1), and 2.5 (95% CI, 1.8–3.5), respectively. Ipsilateral use of the mobile phone was associated with higher risk. Further, there were similar findings in relation to the use of cordless phones.

The Working Group noted several strengths of the study. It was the only study to assess exposure to cordless phones. By using registries for case ascertainment and population-based controls, and by achieving high response rates, the investigators minimized the potential for selection bias. However, the possibility of information bias cannot be excluded, and specific validation studies were not carried out in this population.

(v) *Comparison of the findings of INTERPHONE and the Swedish studies*

Because these two studies represent the most robust evidence on risk of tumours of the brain associated with wireless-phone use, the Working Group compared the methods and findings of the two studies, drawing on comparisons made by the Swedish investigators – Hardell and colleagues – published in 2008 and 2010. The data were collected in overlapping calendar periods (1997–2003 for Hardell *et al.*, with separate analyses available for 2000–2003, and 2000–2004 for INTERPHONE) and had some shared design features, e.g. collection of exposure information via a comprehensive set of questions. The studies differ in their general design, a single population-based study in the case of Hardell *et al.* and a multicentre study based in case ascertainment through hospitals, although with backup case ascertainment through cancer registries and other sources. The INTERPHONE study is probably more affected by selection bias due to differential participation between cases and controls, while the findings of both studies are subject to information bias, probably comparable in directionality. The generally null findings in the two large case–control studies for meningioma speak against information bias providing a full explanation for the associations reported for glioma.

Overall, the Working Group reviewed all the available evidence with regard to the use of wireless phones, including both mobile and cordless phones, and the risk of glioma. Time trends were considered, as were several early case-control studies and one cohort study. The evidence from these studies was considered less informative than the results of the INTERPHONE study and the Swedish case-control study. While both of these are susceptible to bias, the Working Group concluded that these findings could not be dismissed as reflecting bias alone, and that a causal interpretation was possible.

(b) Other tumours of the central nervous system: acoustic neuroma

Several early case-control studies and one cohort study from Denmark found no association. The major sources of evidence for acoustic neuroma were essentially the same as for glioma, as was the general pattern of findings. The case numbers, however, were substantially smaller than for glioma. The study from Sweden provided positive results with estimates quite similar to those observed for glioma. The pattern of findings from the INTERPHONE study also paralleled that for glioma, with a decreased risk overall, and an indication of a possibly increased risk in the stratum with the longest cumulative call time. A case-case study in Japan published in 2011 also found some evidence of an increased risk of acoustic neuroma associated with ipsilateral mobile-phone use.

In considering the evidence on acoustic neuroma, the Working Group considered the same methodological concerns as for glioma, but concluded that bias was not sufficient to explain the positive findings, particularly those of the study from Sweden.

(c) Meningioma

For meningioma, the same two studies mentioned above provided the key evidence. Overall, in each, the findings generally indicated no increase in risk.

(d) Leukaemia/lymphoma

The Working Group reviewed results of four studies of mobile-phone use and leukaemia, including two cohort and two case-control studies. Two population-based case-control studies addressed lymphoma. The Working Group found the evidence to be insufficient to reach a conclusion as to the potential association of mobile-phone use and either leukaemia or lymphoma.

(e) Other malignancies

Evidence to date does not point to a causal association of mobile-phone use with the various additional malignancies addressed, including ocular or cutaneous melanoma, cancer of the testis, cancer of the breast, or tumours of the parotid gland. With the exception of cancer of the breast, all these malignancies have been investigated explicitly in one or more case-control studies. No increased risk was observed for the above-mentioned sites in the 2006 report of the cohort study of Danish mobile-phone subscribers.

5.2.2 Occupational exposure

(a) Tumours of the brain

Four independent case-control studies investigated the association of occupational exposure to RF radiation with risk of brain tumours through specific assessment of individual RF exposure. One study was based on death certificates, the others were population-based studies. Two nested case-control studies (one from the USA and another from Canada and France) also investigated this association. For

the category of highest exposure in each study – determined with the best exposure measure reported, i.e. some form of expert assessment of work history in each case – the odds ratios were above unity, but with wide confidence intervals, thus suggesting that occupational exposure to RF radiation might increase the risk of tumours of the brain. Only two studies (a nested case-control analysis from the USA and a case-control study from Australia) provided dose-response assessments, and neither of these showed more than moderate evidence of a dose-response relationship. In addition, only two studies examined the possibility of confounding by other occupational exposures. A study from Germany adjusted the odds ratios for exposure to ionizing radiation and a study from the USA, based on death certificates, evaluated the sensitivity of the observed positive association of exposure to RF radiation with cancer of the brain with respect to confounding with known coexposures: solder fumes, lead and organic solvents. The observed odds ratio of 1.7 (95% CI, 1.1–2.7) for classification of RF exposure based on expert assessment decreased to 1.4 (95% CI, 0.7–3.1) when men exposed to solder fumes and lead were excluded from the exposed group, and dropped further to 0.4 when those exposed to organic solvents were also removed (although only two exposed cases and five exposed controls were left in the analysis). Chance and/or confounding cannot be ruled out as likely explanations for the observed association between occupational exposure to RF radiation and cancer of the brain.

Eight cohort studies (including the two nested case-control studies mentioned above) and a Polish cross-sectional study examined the relationship between occupational exposure to RF radiation and risk of tumours of the brain. Relative risks for the categories of highest exposure in all but three of the studies were close to or below unity. Among the three exceptions, one study from Italy was based on only one death from cancer of the brain; the cross-sectional

study from Poland showed a relative risk of 1.91 (95% CI, 1.08–3.47) but had methodological limitations that could explain the apparent increase in risk; and an American study had only a weakly increased relative risk (OR, 1.39; 95% CI, 0.93–2.00). On balance, therefore, the cohort studies did not suggest a positive association between exposure to RF radiation and cancer of the brain. Their exposure measures, however, were generally of less quality than those in the case-control studies.

While the association of exposure to RF radiation with cancer of the brain has been examined in a substantial number of studies, exposure misclassification and insufficient attention to possible confounding limit the interpretation of the findings. Thus, there is no clear indication of an association of occupational exposure to RF radiation with risk of cancer of the brain.

(b) Leukaemia/lymphoma

Seven cohort studies and one cross-sectional analysis examined the relationship between occupational exposure to RF radiation and risk of lymphoma and leukaemia. Most studies were based on small numbers of cases and limited exposure assessments. Increased standardized mortality ratios (SMRs) were seen for lymphomas and some leukaemias in a study of radio amateurs in the USA, but there was no association with an exposure-level surrogate (licence class). A substantially increased risk was also seen among Belgian military personnel who had worked with moveable radar, based on 11 cases, but exposure to RF radiation was not characterized individually and may have been confounded by ionizing radiation. In addition, follow-up of the cohort was problematic. The largest and most informative study was that of male United States navy veterans of the Korean War. Increased relative risks for leukaemia (in particular, acute myeloid and acute non-lymphocytic leukaemia) were seen among subjects with the highest compared with the lowest exposure. The highest odds ratio

was seen among technicians in aviation electronics, judged by the authors to be those with highest potential exposure. There was, however, no adjustment for potential confounders.

In summary, while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF radiation, the limited exposure assessment and possible confounding make these results difficult to interpret.

(c) Other malignancies

Studies of occupational groups with potential exposure to RF radiation have addressed several additional types of malignancy including uveal melanoma, and cancers of the testis, breast, lung, and skin. The Working Group noted that these studies had methodological limitations and the results were inconsistent.

5.2.3 Environmental exposure

(a) Cancer of the brain

Ecological studies and case-control studies have been carried out to investigate potential associations of brain cancer with RF emissions from transmission antennae. These studies are generally limited by reliance on measures of geographical proximity to the antennae as an exposure surrogate. Substantial exposure misclassification is unavoidable.

Taken together, the ecological studies do not suggest a positive association between RF emissions from fixed transmission sources and cancer of the brain.

There have been five case-control studies of environmental exposure to RF radiation and risk of cancer of brain. Cohort studies have not been reported. In all of the case-control studies, exposure estimation was based on residential proximity to RF-transmitter antennae. Two of these studies used estimates of exposure based on recorded locations of subjects' residences relative to recorded locations of AM radio-transmitters

or mobile-phone base-station antennae. Neither found convincing indications of an increase in risk of brain cancer with increasing estimated exposure to RF radiation. A hospital-based study from France depended on subjects' recall of the proximity of their residence to a mobile-phone base station and found no evidence of an increased risk with closer proximity. However, the hospital-based controls may not represent exposure in the general population. The fourth study assessed proximity of subjects' beds to base stations of DECT cordless phones in the home. It found a weak and imprecise increase in risk of brain cancer associated with sleeping near a base station. Another study found high risks for brain, breast and other cancers associated with the place of residence where the highest power density from a nearby base-station antenna was measured, but the results were imprecise and based on only a few cases. Together, these studies provide no indication that environmental exposure to RF radiation increases the risk of brain tumours.

(b) Leukaemia/lymphoma

Ecological studies in which distance was taken as a proxy for exposure consistently showed a pattern of increased risk of adult and childhood leukaemia with closer proximity to the exposure source, while studies that used analytical designs and better exposure assessments (e.g. measured and modelled) showed no increased risk. In adults, the evidence of an association indicating increased risk was weak at most, and effect estimates were generally imprecise. There was no evidence of an increased risk of childhood leukaemia. Consequently, from the limited data available no conclusions could be drawn on the risk of leukaemia or lymphoma from environmental exposure to RF radiation.

(c) *Other malignancies*

The Working Group identified five studies that addressed other malignancies and environmental exposure to RF radiation, and found the available evidence uninformative.

5.3 Animal carcinogenicity data

Four classes of cancer bioassays in animals were reviewed and assessed by the Working Group. These studies involved a variety of animal models, exposure metrics, durations of exposure, and other criteria on which the evaluation of carcinogenicity was based.

Seven two-year cancer bioassays of RF radiation were reported, two in mice and five in rats; six studies were performed to examine the effects of exposure to mobile-phone RF metrics, and one study involved exposure to pulsed RF radiation. When compared with sham controls, no statistically significant increases in the incidence of benign or malignant neoplasms at any organ site were identified in animals exposed to mobile-phone RF radiation in any study. In the study with exposure to pulsed RF radiation, an increased incidence of total malignant tumours (all sites combined) was observed in rats; however, the Working Group considered this finding to be of limited biological significance since it resulted from pooling of non-significant changes in tumour incidence at several sites. Exposure to RF radiation did not increase total tumour incidence in any of the other six studies that were evaluated. The Working Group concluded that the results of the 2-year cancer bioassays provided no evidence that long-term exposure to RF radiation increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats.

The Working Group evaluated twelve studies that used four different tumour-prone animal models; two of these studies demonstrated an increased incidence of tumours in animals

exposed to RF radiation. The first study with positive results demonstrated an increased incidence of lymphoma in *Eμ-Pim1*-transgenic mice exposed to GSM mobile-phone RF radiation at 900 MHz; however, two subsequent studies by other investigators using the same model system failed to confirm this finding. In the second study with positive results, an increased incidence of tumours of the mammary gland was observed in C3H/HeA mice exposed to RF radiation at 2450 MHz; although two later studies using the same exposure metric did not confirm this finding, these follow-on studies were performed at lower levels of exposure. The Working Group concluded that the results of studies in three tumour-prone animal models (the *Eμ-Pim1* mouse model of lymphoma, the AKR mouse model of lymphoma, and the *Patched1*^{+/-} mouse model of brain cancer) do not support the hypothesis that the incidence of tumours in the brain or lymphoid tissue would increase as a result of exposure to RF radiation.

The Working Group evaluated 16 studies of initiation and promotion that were performed with animal models of tumorigenesis in skin, mammary gland, brain, and lymphoid tissue. None of the five studies in models of skin cancer and none of the six studies in models of brain cancer showed an association with exposure to RF radiation. One of four studies with the model of mammary-gland tumour in Sprague-Dawley rats gave positive results; the other three studies – one with a nearly identical protocol – did not show an association, although they used the same experimental model and the same conditions of exposure to RF radiation. Likewise, the study with the model of lymphoma was negative. The Working Group concluded that the evidence from these studies of initiation and promotion failed to demonstrate a consistent pattern of enhancement of carcinogenesis by exposure to RF radiation in any of the tissues studied.

The Working Group evaluated six co-carcinogenesis studies involving five different animal models. Four positive responses were reported.

Two studies giving positive results, one in Wistar rats continuously exposed to drinking-water containing MX – a by-product of water disinfection – and another study in pregnant B6C3F₁ mice given a single dose of ethyl-nitrosourea, involved exposures to mobile-phone RF radiation at 900 and 1966 MHz, respectively. The other two studies with positive results involved coexposure of BALB/c mice to RF radiation at 2450 MHz and benzo[a]pyrene. Although the value of two of these studies was weakened by their unknown relevance to cancer in humans, the Working Group concluded that they did provide some additional evidence supporting the carcinogenicity of RF radiation in experimental animals.

5.4 Other relevant data

The data to evaluate the mechanisms by which RF radiation may cause or enhance carcinogenesis are extensive and diverse. Studies in humans from occupational cohorts, mobile-phone users and controlled exposures in experimental settings provide information on effects in various tissues, including blood and brain. Studies in animals have been focused on a variety of organs and tissues. Assays *in vitro* in human cells, other mammalian cells, and cells from other organisms provide the largest set of data from which to evaluate mechanisms. Many studies were confounded by significant increases in the temperature of the cells, leading to thermal effects that could not be dissociated from non-thermal RF-induced changes. The conclusions presented in this section for results *in vivo* and *in vitro* pertain only to those studies for which the Working Group concluded that thermal confounding did not occur.

5.4.1 Genetic and related effects of exposure

Multiple studies in humans were conducted on the possible genetic damage associated with exposure to RF radiation. Most of these studies were of occupational exposure and the others evaluated mobile-phone users. Several common exposures to the general population that are likely to be confounders were generally not considered, including tobacco use and age. In addition, other occupational exposures that might have contributed to the findings were rarely discussed. Most of the occupational studies that suggested a positive association of the effect with exposure to RF radiation involved workers from the same facility, included small numbers of subjects, and provided no indication of the extent to which the same individuals were sampled in multiple studies. Virtually all the large studies did not show an association with exposure to RF radiation, for any type of genetic damage. Finally, there were methodological flaws and weaknesses in reporting in many studies, including the failure to actually measure exposure to RF radiation, the use of small numbers of cells for evaluating genetic damage, the failure to use proper controls while culturing cells, incomplete reporting, and improper interpretation of results.

A few studies in *Drosophila* that addressed mutagenicity after exposure to RF radiation gave negative results.

Approximately half of the laboratory studies of genetic damage in mammalian systems, generally rats and mice, had limitations related to reporting on the exposure system, small sample sizes and exposures that induced thermal effects, or that were so low as to be no challenge to the animals. Of the remaining studies, many were satisfactory and of comparable quality, but showed contradictory results. Some were attempts to repeat original laboratory findings. Also these studies provided mixed and sometimes contradictory results. Some of the discrepancies could be due to differences in species or

exposure conditions, but others were in direct contrast.

Roughly half of the studies of human cells *in vitro* were done in lymphocytes cultured from the blood of donors. Short-term, high-intensity exposures to RF radiation resulted in consistently positive results for DNA damage, but the Working Group felt that thermal effects were the likely cause of these effects. A large number of studies on DNA strand breaks and the studies on sister chromatid exchange generally gave negative results. Exposures to RF radiation in the non-thermal range also generally gave negative results.

The remaining in-vitro studies with human cells and the in-vitro studies with non-human cells also involved short-term, high-intensity exposures that consistently gave positive results for DNA damage. The Working Group considered that these results were likely due to thermal effects. There were acceptable reports showing both positive and negative results in the remaining studies with exposures in the non-thermal range. In addition, studies showing aneuploidy and spindle disturbances in human-hamster hybrid A_L cells, and studies at low exposures showing DNA single-strand breaks were of concern. While RF radiation has insufficient energy to produce these types of direct genetic damage, other changes such as oxidative stress and production of reactive oxygen species may explain these results.

The remaining few studies that gave positive results for genetic damage at lower doses could not be replicated after multiple attempts in different laboratories, raising serious questions regarding the original findings. A single study showing altered microtubule structures at low exposures remains a concern.

Overall, the Working Group concluded that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation.

5.4.2 Reaction of the immune system after exposure

Several studies assessed the effects of exposure to RF radiation on indicators of immune function in humans. In two studies, increased concentrations of some immunoglobulins (Ig) and changes in numbers of lymphocytes (T8, natural killer [NK] cells) were observed in blood samples from radar operators and workers at television-transmission stations, but the results were variable and the alterations seemed to be within the normal variation. Two studies among workers exposed to very high frequency RF radiation showed a significant increase in IgG and IgM, and a higher number of NK cells, respectively. Patients with atopic eczema dermatitis showed an increase in allergen-provoked production of IgE when they had been exposed to RF radiation from a mobile phone. Many of these studies used small numbers of subjects and generally did not control for possible confounders.

The available evidence from numerous experimental studies *in vivo* that aimed to assess effects of short-term and prolonged low-level exposure to RF radiation on function and status of the immune system, clearly indicates that various shifts in number and/or activity of immunocompetent cells are possible. However, in some cases the same lymphocyte functions are reported to be weakened or enhanced in different single experiments, despite exposures to RF radiation at similar intensities and under similar exposure conditions. Short-term exposure to weak RF fields may temporarily stimulate certain humoral or cellular immune functions, while prolonged irradiation inhibits the same functions. Thus, even though there are indications that changes are occurring, the relevance of these observations in relation to carcinogenicity is unclear.

The effects of RF radiation on various types of human lymphocytes *in vitro* are variable and depend on the mitotic state of the cells during

exposure. A difference was reported between the effects of exposure to continuous-wave and pulsed-wave RF radiation, the latter preferentially stimulating the immunogenic and pro-inflammatory activity of monocytes. Many of these studies had weaknesses in the description of experimental procedures and from lack of detail on dosimetry.

Overall, the Working Group concluded that there was insufficient evidence to determine that alterations in immune function induced by exposure to RF radiation affect carcinogenesis in humans.

5.4.3 Effects on genes, proteins and signalling pathways

No studies assessing gene expression in humans exposed to RF radiation were identified, and only one pilot study assessed protein changes in exposed human subjects.

Nearly 30 studies investigated gene/protein changes in rodents exposed to RF radiation. Many of these studies were unreliable due to deficiencies in the exposure system or methodological shortcomings. The data from the remaining studies are limited and present mixed results with no consistent pattern of response.

A large number of studies have assessed the ability of RF radiation to affect gene/protein expression and protein activation in human-derived cell lines *in vitro*. The majority of studies assessing effects of RF radiation on expression and activity of heat-shock proteins reported no effect. A limited number of studies assessed the ability of RF radiation to influence the activity of signal-transduction pathways in human cells *in vitro*. Three studies found changes in MAPK signalling, while another did not. The role of reactive oxygen species in mediating these responses is unclear.

A total of 16 studies used high-throughput genomics/proteomics approaches to evaluate the effect of exposure to RF radiation on human cell lines *in vitro*. Many of these studies had

serious methodological shortcomings related to poor exposure conditions, inadequate statistical analysis, and lack of validation of alternative approaches. The remaining data were limited with no consistent pattern of response, but some studies demonstrated changes in both gene and protein expression, for some proteins in some cell lines.

On the basis of the above considerations, the Working Group concluded that data from studies of genes, proteins and changes in cellular signalling show weak evidence of effects from RF radiation, but did not provide mechanistic information relevant to carcinogenesis in humans.

5.4.4 Other mechanistic end-points

Several potential changes resulting from exposure to RF radiation are summarized here. With the exception of changes in cerebral blood flow, many of the other studies reviewed by the Working Group provided conflicting, negative or very limited information, which made it difficult to draw conclusions, especially in relation to carcinogenesis. These studies focused on electrical activity in the brain, cognitive function, general sensitivity to RF radiation and alterations in brain biochemistry. Even though the relationship between alterations in cerebral blood flow during exposure to RF radiation cannot be directly related to carcinogenesis, the Working Group concluded that the available data were sufficiently consistent to identify them as important findings.

Some studies were conducted in experimental animals to explore the possibility that exposure to RF radiation *in vivo* may induce the production of reactive oxygen species in multiple organs, most frequently brain, but also kidney, liver and eye. Markers of oxidative stress included increases in the concentration of malondialdehyde (related to lipid peroxidation) and nitric oxide, enhanced activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and pro-oxidant enzymes, and reductions in

glutathione. Many of these studies are weakened by methodological shortcomings in design, such as absence of sham-exposed or cage-control groups, use of mobile phones as the exposure source, and lack of dosimetry.

A few studies in human cells *in vitro* evaluated the possible role of exposure to RF radiation in altering levels of intracellular oxidants or activities of antioxidant enzymes. One study showed a marginal effect, while other studies demonstrated an increase in activity with increasing exposures. There were not enough studies to make a reasonable assessment of the consistency of these findings. Additional studies addressed this issue in in-vitro systems with non-human cells. While most of these did not find changes, one study evaluated the formation of DNA adducts from reactive oxygen species (8-hydroxy-deoxyguanosine) and was able to demonstrate reversal of this effect by melatonin. While the overall evidence was inconclusive, the results from in-vitro studies with animal models raise some concern.

Overall, the Working Group concluded that there was weak evidence that exposure to RF radiation affects oxidative stress and alters the levels of reactive oxygen species.

Numerous studies have assessed the function of the blood–brain barrier in rodents exposed to RF radiation at various intensities. Consistent results from one laboratory suggest an increase in the permeability of the blood–brain barrier, but the majority of the studies, many of which aimed at replicating published results, failed to observe any effect on this point from exposure to either continuous or pulsed RF radiation. The evidence that exposure to RF radiation alters the blood–brain barrier was considered weak.

A few studies dealt with alterations induced by RF radiation in cell differentiation or induction of apoptosis in the brain or other organs. While most of the studies showed an association, the Working Group was not convinced that these data were of sufficient scientific rigour to assess

apoptotic effects in these organs. An additional 14 studies focused on apoptosis in cultured human cells. Only two studies demonstrated an increase in apoptosis: one compared the results observed in treated cells with controls that were not subject to the same conditions as the exposed cells, while thermal effects may have had an impact in the other study. Finally, other in-vitro studies with non-human cells gave essentially negative results, with the exception of one study that demonstrated mixed results. The evidence that exposure to RF radiation alters apoptosis was considered weak.

Multiple assays *in vitro* were conducted to test proliferation of primary cells or established cell lines by analysis of cell-cycle progression and thymidine uptake, after exposure to various intensities of RF radiation at various time intervals. Many of these studies used small sample sizes and description of experimental details was lacking in several cases. Studies with positive results showed increases and decreases in cellular replication, and no consistent pattern could be discerned. The evidence that RF radiation alters cellular replication was considered weak.

Ornithine decarboxylase is an enzyme involved in the metabolism of polyamines, which are critical components of cellular replication and differentiation processes. The activity of this enzyme was the object of several studies *in vitro* in human and animal cells exposed to GSM900 and GSM1800 signals. Some of these studies showed significantly increased ornithine decarboxylase activity. The result of one study suggested that ornithine decarboxylase activities may be reduced. It was unclear how these changes in activity relate to human cancer. There was weak evidence from in-vitro studies that exposure to RF radiation alters ornithine decarboxylase activity.

The evidence that exposure to RF radiation, at intensities below the level of thermal effects, may produce oxidative stress in brain tissue and may affect neural functions was considered weak.

6. EVALUATION

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of radiofrequency radiation. Positive associations have been observed between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of radiofrequency radiation.

6.3 Overall evaluation

Radiofrequency electromagnetic fields are *possibly carcinogenic to humans (Group 2B)*.

6.4 Rationale for the evaluation of the epidemiological evidence

The human epidemiological evidence was mixed. Several small early case-control studies were considered to be largely uninformative. A large cohort study showed no increase in risk of relevant tumours, but it lacked information on level of mobile-phone use and there were several potential sources of misclassification of exposure. The bulk of evidence came from reports of the INTERPHONE study, a very large international, multicentre case-control study and a separate large case-control study from Sweden on gliomas and meningiomas of the brain and acoustic neuromas. While affected by selection bias and information bias to varying degrees, these studies showed an association between

glioma and acoustic neuroma and mobile-phone use; specifically in people with highest cumulative use of mobile phones, in people who had used mobile phones on the same side of the head as that on which their tumour developed, and in people whose tumour was in the temporal lobe of the brain (the area of the brain that is most exposed to RF radiation when a wireless phone is used at the ear). The Swedish study found similar results for cordless phones. The comparative weakness of the associations in the INTERPHONE study and inconsistencies between its results and those of the Swedish study led to the evaluation of *limited evidence* for glioma and acoustic neuroma, as decided by the majority of the members of the Working Group. A small, recently published Japanese case-control study, which also observed an association of acoustic neuroma with mobile-phone use, contributed to the evaluation of *limited evidence* for acoustic neuroma.

There was, however, a minority opinion that current evidence in humans was *inadequate*, therefore permitting no conclusion about a causal association. This minority saw inconsistency between the two case-control studies and a lack of exposure-response relationship in the INTERPHONE study. The minority also pointed to the fact that no increase in rates of glioma or acoustic neuroma was seen in a nationwide Danish cohort study, and that up to now, reported time trends in incidence rates of glioma have not shown a trend parallel to time trends in mobile-phone use.

GLOSSARY

Antenna: Device that serves as a transducer between a guided wave (e.g. via a coaxial cable) and a free space wave, or *vice versa*. It can be used either to emit or to receive a radio signal.

Base station: Wireless communications station installed at a fixed location and used to transmit and receive radio signals to and from mobile-phone users. Also used for DECT phones at home.

Cell phone: See “Mobile phone”.

Cellular radio network: Fixed infrastructure comprising multiple base stations deployed across a wide geographical area such that mobile-phone users are able to communicate via the base stations, with the radio signals associated with their calls being transmitted from one base station to another as the users move across cell boundaries.

Conductivity: The ratio of the conduction-current density in a medium to the electric field strength. The unit of conductivity is siemens per metre (S/m).

Cordless phone: (DECT, portable phone) A wireless telephone that communicates via radio waves with a base station connected to a fixed telephone line, usually within a limited range of its base station. The base station is on the premises of the owner, and attached to the wired telephone network in the same way as a corded telephone.

DECT phone: See “Cordless phone”

Effective radiated power (ERP) or equivalent radiated power: is a standardized theoretical measurement of radiofrequency (RF) energy using the SI unit watts, and is determined by subtracting system losses and adding system gains. ERP is similar to EIRP (see below), but may use some other reference antenna than an isotropic antenna, e.g. a half dipole.

Electric-field strength (E): Magnitude of a field vector at a point that represents the force (F) on a small test charge (q) divided by the charge:

$$\vec{E} = \frac{\vec{F}}{q}$$

The magnetic field strength is expressed in units of volt per metre (V/m).

Equivalent isotropically radiated power (EIRP) or effective isotropically radiated power: The amount of power that a theoretical isotropic antenna (which evenly distributes power in all directions) would emit to produce the peak power density observed in the direction of maximum antenna gain. EIRP can take into account the losses in transmission line and connectors and includes the gain of antenna. The EIRP is often expressed in terms of decibels over a reference power emitted by an isotropic radiator with an equivalent signal strength. The EIRP allows comparisons between different emitters regardless of type, size or form. From the EIRP, and with knowledge of a real antenna’s gain, it

is possible to calculate real values for power and field strength.

Equivalent plane-wave power density (plane-wave equivalent power density) (S): A commonly used term associated with any electromagnetic wave, equal in magnitude to the power density of a plane wave having the same electric- (E) or magnetic- (H) field strength. Specifically, the normalized value of the square of the electric- or the magnetic-field strength at a point in the near field of a radiating source. The unit of equivalent plane-wave power density (according to the International System of Units, SI) is the watt per square metre (W/m²) and is computed as follows:

$$S = \frac{|E|^2}{\eta} = \eta |H|^2$$

where:

E and *H* are the root-mean-square (rms) values of the electric- and magnetic-field strengths, respectively

η is the wave impedance ($\cong 377$ ohms in free space).

Note that most field-survey equipment uses this relationship, although it does not apply to the near field. In case of exposure assessment, the independent measurement of *E rms* (or $|E|^2$) and *H rms* (or $|H|^2$) is preferred.

Synonym: equivalent plane-wave power flux density.

Far-field region and near-field region: The far-field region is defined when the fields can be well approximated by the radiating fields, i.e. the E-field vector is perpendicular to the H-field vector, and both are orthogonal to the direction of propagation whereby the ratio of the amplitudes of the E- and H-fields is 377 ohm.

The near-field region is when the above conditions are not met, i.e. when the field is dominated by reactive field components.

Frequency and wavelength: The intensity of electric and magnetic fields can vary periodically over time and space, following a sinusoidal function. In the time domain, the number of cycles of oscillation per second is defined as the frequency, *f*, of the field and is expressed in hertz (Hz). In the spatial domain, the distance between two peaks of one oscillation cycle is called the wavelength. In free space, this is equivalent to:

$$\lambda = \frac{c}{f}$$

where:

c is the velocity of light ($\approx 3.10^8$ m/s).

Magnetic-field strength (H): The magnitude of a field vector in a point that results in a force (F) on a charge *q* moving with the velocity *v*:

$$F = q (v \times \mu H)$$

The magnetic-field strength is expressed in units of ampere per metre (A/m).

Magnetic-flux density (B): The magnitude of a field vector that is equal to the magnetic field strength *H* multiplied by the permeability (μ) of the medium:

$$B = \mu H$$

Magnetic-flux density is expressed in units of tesla (T).

Mobile phone: (cell phone, hand-held phone) Electronic device used to make and receive phone calls across a wide geographical area allowing the user to be mobile. A mobile phone is connected to a cellular network provided by a mobile-network operator.

Modulation: The process, or result of the process, whereby some characteristic of one wave is varied in accordance with another wave or signal. There are three canonical modulation types:

- AM (amplitude modulation): information is imparted to an electromagnetic wave by varying its amplitude
- FM (frequency modulation): information is imparted to an electromagnetic wave by varying its frequency
- ϕ M (phase modulation): information is imparted to an electromagnetic wave by varying its phase

FM and ϕ M are actually closely related to each other, e.g. both can be expressed mathematically in terms of a phase modulation.

Multiple access, or channel multiple access: Multiple-access methods are required to allow multiple devices to operate simultaneously. The following multiple-access methods are available for transmitting a set of individual data streams:

- FDMA: frequency-division multiple access splits the communication spectrum into different frequency domain bands that are assigned to the different data streams.
- TDMA: time-division multiple access splits the communication spectrum into periodically repetitive time slots, each terminal or data stream has a fixed periodic time slot during which data may be transmitted.
- CDMA: code-division multiple access allows multiple transmitters to send data simultaneously, theoretically, in the same frequency and time-domain channels. Communication channels are separated in the code domain by multiplying (spreading) the data streams with mutually orthogonal code vectors. Applying the same code vectors at the receiver allows separation of multiple simultaneous data streams due to the orthogonality of the codes.
- SDMA: space-division multiple access separates different data streams in space.

A prominent example is directional radio systems.

In principle, the same multiple-access methods can be used to divide the forward and return data stream between two terminals. In practice however only time-division duplex (TDD) and frequency-division duplex (FDD) are applied.

Peak spatial SAR (psSAR): Peak spatial SAR values describe the peak SAR of all sSAR (See specific absorption rate [SAR] and spatially averaged SAR [sSAR]).

Peak-to-average power ratio (PAPR): The probability of peak signal power exceeding the average power level by 0.1%. In the case of non-statistical disruptions, PAPR is equivalent to the crest factor, i.e. 2 for a sinusoidal signal, 8.7 for GSM, 3.1–3.3 for UMTS-FDD, 10–20 for WLAN, etc. In the case of pulsed signals, the peak pulse amplitude is PAPR multiplied by the average power.

Penetration depth: For a plane electromagnetic wave incident on the boundary of a medium, the distance from the boundary into the medium along the direction of propagation in the medium, at which the field strengths of the wave have been reduced to $1/e$ (around 37%) of their boundary values. Penetration depth is expressed in metres (m).

Permittivity: The ratio of the electric-flux density in a medium to the electric-field strength at a point. The permittivity of biological tissues is dependent on frequency. Permittivity is expressed in units of farad per metre (F/m).

Polarization: The property of a radiated electromagnetic wave describing the time-varying direction and amplitude of the electric-field vector; specifically, the figure traced as a function of time by the extremity of the E-field vector at a fixed location in space, as observed along the direction of propagation.

Power density (Pd): The radiant power incident perpendicular to a surface, divided by the area of the surface. The power density is expressed in units of watt per square metre (W/m²). Power density can be determined from the field strengths as follows:

$$P_d = E \times H = \frac{E^2}{377\Omega} = 377\Omega H^2$$

Also written as:

$$P_d = E \times H = E^2/377\Omega = 377\Omega H^2$$

Radiation: The emission and propagation of energy in the form of waves or particles through space.

Radiofrequency: Any frequency in the range of 30 MHz to 300 GHz.

Receiver: A device that detects radio signals and extracts useful information that has been encoded onto them through modulation, such as speech, music, data or pictures.

Resonance: The tendency of an object to oscillate with a larger amplitude at certain frequencies.

Root-mean-square (rms): The rms value or effective value is the square root of the mean of the squares of a continuous function:

$$f_{rms} = \sqrt{\frac{1}{T_2 - T_1} \int_{T_1}^{T_2} [f(t)]^2 dt}$$

where:

T is period

t is time

f is frequency

The rms values are important in the context of expressing exposure values averaged over time (see also specific absorption rate, SAR).

Root-sum-square (rss): The rss value is the root of the sum of the squares of the components of a vector.

Sidelobes: Antennae designed to radiate a main beam in particular angular direction also produce weaker beams known as sidelobes in other angular directions.

Spatially averaged SAR (sSAR): Spatially averaged SAR (sSAR) values have been defined to better characterize SAR with respect to potential hazards. Technically, each location of the body is represented with a spatially averaged SAR. Different definitions have been proposed for standard settings and are commonly applied:

- **sSAR-1 g:** spatially averaged SAR values over a mass of 1 g of tissue in the shape of a cube. Special evaluation conditions are applied in case of air interfaces (IEEE C95.3). In practice, each local SAR value in the body is represented by the sSAR-1 g value whereby the cube is grown symmetrically around that location. At higher frequencies, sSAR-1 g is approximately twice the value of sSAR-10 g due to the reduced penetration depth.
- **sSAR-10 g:** spatially averaged SAR values over a mass of 10 g of tissue in the shape of a cube.
- **sSAR-10 g c:** spatially averaged SAR values over a mass of 10 g of contiguous tissue.

Specific absorption rate (SAR): The time derivative of the incremental energy (dW) absorbed by (dissipated in) an incremental mass (dm) contained in a volume element (dV) of given density (ρ):

$$SAR = \frac{d}{dt} \left(\frac{dW}{dm} \right) = \frac{d}{dt} \left(\frac{dW}{\rho dV} \right)$$

The SI unit of SAR is the watt per kilogram (W/kg).

NOTE: SAR can be related to the electric field at a point by:

$$SAR = \frac{\sigma |E|^2}{\rho}$$

where:

σ is conductivity of the tissue (S/m)

ρ is mass density of the tissue (kg/m³)

E is rms electric field strength in tissue (V/m)

NOTE: SAR can be related to the increase in temperature at a point by:

$$SAR = \left. \frac{c \Delta T}{\Delta t} \right|_{t=0}$$

where:

ΔT is the change in temperature (°C)

Δt is the duration of exposure (s)

c is the specific heat capacity (J/kg °C)

This assumes that measurements are made under “ideal” non-thermodynamic circumstances, i.e. no heat loss by thermal diffusion, radiation, or thermoregulation (blood flow, sweating, etc.). Therefore, the third equation is only valid if the exposed body is in thermal equilibrium or a steady thermal state at the beginning of the exposure and either heat exchange processes can be neglected during the measurement interval or the processes are known and corrected such that dT can be correspondingly corrected.

In other words, SAR is proportional to the absorbed energy, square of the induced E-fields or induced current density. However, SAR is not directly proportional to the induced magnetic field.

Specific tissue-averaged SAR (stSAR): The total electromagnetic power absorbed by an organ or specific tissue.

Standing waves: Standing waves are formed where RF fields are contained by reflection back and forth. Energy is stored in the space where reflection occurs, which leads to high field

strengths that are not associated with radiation. Fields associated with standing waves generally deposit much less energy in the body tissues than radiation fields of the same strength.

Time-averaged SAR or temporal-averaged SAR: SAR is usually reported as time-averaged SAR, either over the periodicity of the signal or over any 6 minutes.

Transceiver: A device containing both a transmitter and a receiver, such that it forms one terminal in a duplex communications link.

Transmitter: A device that generates and amplifies a carrier wave, modulates it to carry information, and radiates the resulting signal from an antenna, such that it can be received elsewhere.

UMTS (Universal Mobile Telecommunications System): a third-generation mobile telecommunications technology that uses digitally encoded signals to enable user access.

Whole-body SAR or whole-body averaged SAR (wbSAR): The whole-body SAR is the total electromagnetic power absorbed by a body divided by its mass.

Wi-Fi: a wireless transmission technique for use in local area networks that works in 2.4 GHz and 5 GHz bands. It is a registered trademark of the Wi-Fi Alliance.

WLAN (wireless local area network): a short-range wireless data communications network linking two or more devices.

WPAN (wireless personal area networks): a short-range wireless communications network for personal devices located near to the individual, e.g. Bluetooth.

LIST OF ABBREVIATIONS

AMPS	advanced mobile phone system
CMB	cosmic microwave background
CDMA	code-division multiple access
CW	continuous wave
DAB	digital audio broadcasting
D-AMPS	digital advanced mobile phone system
DECT	digital enhanced cordless telecommunications
DCS	digital cellular system
DMH	dimethylhydrazine
DTX	discontinuous transmission
EIRP	equivalent isotropically radiated power
EMF	electromagnetic field
ENU	<i>N</i> -ethyl- <i>N</i> -nitrosourea
ERP	effective radiated power
FDD	frequency-division duplex
FDMA	frequency-division multiple access
FDTD	finite-difference time-domain
FEM	finite-element method
GPRS	general packet radio service
GSH-Px	glutathione peroxidase
GSM	Global System for Mobile communications
HAN	home area network
HF	high frequency
ICNIRP	International Council on Non-Ionizing Radiation Protection
iDEN	integrated Digital Enhanced Network
IRP	spherically-integrated radiated power
ISM	industrial, scientific and medical
LAN	local area network
LF	low frequency
LPS	lipopolysaccharide
LTE	long-term evolution
MF	medium frequency
MoM	method of moment
MPE	maximum permissible exposures
MRI	magnetic resonance imaging

MX	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone
NAC	<i>N</i> -acetyl cysteine
NO	nitric oxide
ODC	ornithine decarboxylase
OFDM	orthogonal frequency-division multiplexing
PCI	peripheral component interconnect
PDC	personal digital cellular
PHA	phytohaemagglutinin
PMA	phorbol 12-myristate 13-acetate
PMR	private mobile radio
PTT	push-to-talk
pps	pulses per second
PVC	polyvinyl chloride
PW	pulsed wave
MMC	mitomycin C
NMT	Nordic Mobile Telephony
RF	radiofrequency
ROS	reactive oxygen species
RTL	radial transmission line
RT-PCR	reverse-transcriptase polymerase chain reaction
SAM	specific anthropometric mannequin
SAR	specific absorption rate
SD	standard deviation
SMS	short message service
SOD	superoxide dismutase
TAC	total antioxidant capacity
TACS	total-access communication systems
TCSE	total cumulative specific energy
TDMA	time-division multiple access
TEM	transverse electromagnetic
TETRA	Terrestrial Trunked Radio
TNF	tumour necrosis factor
TPA	12- <i>O</i> -tetradecanoylphorbol-13-acetate
UMTS	Universal Mobile Telecommunications System
<i>vs</i>	<i>versus</i>
WCDMA	wideband code-division multiple access
Wi-Fi	standard wireless local area network (WLAN) technology
WiMax	worldwide interoperability for microwave access
WLAN	wireless local area network
XO	xanthine oxidase

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1,2-Epoxybutane	47 (1989); 71 (1999)
1-Epoxyethyl-3,4-epoxycyclohexane (see 4-Vinylcyclohexene diepoxide)	
3,4-Epoxy-6-methylcyclohexylmethyl-3,4-epoxy-6-methyl-cyclohexane carboxylate	11 (1976); Suppl. 7 (1987); 71 (1999)
<i>cis</i> -9,10-Epoxy stearic acid	11 (1976); Suppl. 7 (1987); 71 (1999)
Epstein-Barr virus	70 (1997); 100B (2012)
<i>d</i> -Equilenin	72 (1999)
Equilin	72 (1999)
Erionite	42 (1987); Suppl. 7 (1987); 100C (2012)
Estazolam	66 (1996)
Estradiol	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Estradiol-17 β (see Estradiol)	
Estradiol 3-benzoate (see Estradiol)	
Estradiol dipropionate (see Estradiol)	
Estradiol mustard	9 (1975); Suppl. 7 (1987)
Estradiol valerate (see Estradiol)	
Estriol	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Estrogen replacement therapy (see Post-menopausal estrogen therapy)	
Estrogens (see Estrogens, progestins and combinations)	
Estrogens, conjugated (see Conjugated estrogens)	
Estrogens, nonsteroidal (see Nonsteroidal estrogens)	
Estrogens, progestins (progestogens) and combinations	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Estrogens, steroidal (see Steroidal estrogens)	
Estrone	6 (1974); 21 (1979) (corr. 42); Suppl. 7 (1987); 72 (1999)
Estrone benzoate (see Estrone)	
Ethanol in alcoholic beverages	41 (2010); 100E (2012)
Ethinylloestradiol	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)

Ethionamide	13 (1977); Suppl. 7 (1987)
Ethyl acrylate	19 (1979); 39 (1986); Suppl. 7 (1987); 71 (1999)
Ethyl carbamate	7 (1974); Suppl. 7 (1987); 96 (2010)
Ethylbenzene	77 (2000)
Ethylene	19 (1979); Suppl. 7 (1987); 60 (1994); 71 (1999)
Ethylene dibromide	15 (1977); Suppl. 7 (1987); 71 (1999)
Ethylene oxide	11 (1976); 36 (1985) (corr. 42); Suppl. 7 (1987); 60 (1994); 97 (2008); 100F (2012)
Ethylene sulfide	11, 257 (1976); Suppl. 7, 63 (1987)
Ethylenethiourea	7 (1974); Suppl. 7 (1987); 79 (2001)
2-Ethylhexyl acrylate	60 (1994)
Ethyl methanesulfonate	7 (1974); Suppl. 7 (1987)
<i>N</i> -Ethyl- <i>N</i> -nitrosourea	1 (1972); 17 (1978); Suppl. 7 (1987)
Ethyl selenac (see also Selenium and selenium compounds)	12 (1976); Suppl. 7 (1987)
Ethyl tellurac	12 (1976); Suppl. 7 (1987)
Ethynodiol diacetate	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Etoposide	76 (2000); 100A (2012)
Eugenol	36 (1985); Suppl. 7 (1987)
Evans blue	8 (1975); Suppl. 7 (1987)
Extremely low-frequency electric fields	80 (2002)
Extremely low-frequency magnetic fields	80 (2002)

F

Fast Green FCF	16 (1978); Suppl. 7 (1987)
Fenvalerate	53 (1991)
Ferbam	12 (1976) (corr. 42); Suppl. 7 (1987)
Ferric oxide	1 (1972); Suppl. 7 (1987)
Ferrochromium (see Chromium and chromium compounds)	
Firefighting	98 (2010)
Fission products, mixtures of	100D (2012)
Fluometuron	30 (1983); Suppl. 7 (1987)
Fluoranthene	32 (1983); Suppl. 7 (1987); 92 (2010)
Fluorene	32 (1983); Suppl. 7 (1987); 92 (2010)
Fluorescent lighting, exposure to (see Ultraviolet radiation)	
Fluorides, inorganic, used in drinking-water	27 (1982); Suppl. 7 (1987)
5-Fluorouracil	26 (1981); Suppl. 7 (1987)
Fluorspar (see Fluorides)	
Fluosilicic acid (see Fluorides)	
Fluroxene (see Anaesthetics, volatile)	
Foreign bodies	74 (1999)
Formaldehyde	29 (1982); Suppl. 7 (1987); 62 (1995) (corr. 65; corr. 66); 88 (2006); 100F (2012)
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	7 (1974) (corr. 42); Suppl. 7 (1987)
Frusemide (see Furosemide)	
Frying, emissions from high-temperature	95 (2010)
Fuel oils (heating oils)	45 (1989) (corr. 47)

Fumonisin B1 (see also Toxins derived from <i>Fusarium moniliforme</i>)	82 (2002)
Fumonisin B2 (see Toxins derived from <i>Fusarium moniliforme</i>)	
Furan	63 (1995)
Furazolidone	31 (1983); Suppl. 7 (1987)
Furfural	63 (1995)
Furniture and cabinet-making	25 (1981)
Furosemide	50 (1990)
2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (see AF-2)	
Fusarenon-X (see Toxins derived from <i>Fusarium graminearum</i> , <i>F. culmorum</i> and <i>F. crookwellense</i>)	
Fusarenone-X (see Toxins derived from <i>Fusarium graminearum</i> , <i>F. culmorum</i> and <i>F. crookwellense</i>)	
Fusarin C (see Toxins derived from <i>Fusarium moniliforme</i>)	

G

Gallium arsenide	86 (2006)
Gamma (γ)-radiation	75 (2000); 100D (2012)
Gasoline	45 (1989) (corr. 47)
Gasoline engine exhaust (see Diesel and gasoline engine exhausts)	
Gemfibrozil	66 (1996)
Glass fibres (see Man-made mineral fibres)	
Glass manufacturing industry, occupational exposures in	58 (1993)
Glass wool (see Man-made vitreous fibres)	
Glass filaments (see Man-made mineral fibres)	
Glu-P-1	403 (1986); Suppl. 7 (1987)
Glu-P-2	40 (1986); Suppl. 7 (1987)
L-Glutamic acid, 5-[2-(4-hydroxymethyl)phenylhydrazide] (see Agaritine)	
Glycidaldehyde	11 (1976); Suppl. 7 (1987); 71 (1999)
Glycidol	77 (2000)
Glycidyl ethers	47 (1989); 71 (1999)
Glycidyl oleate	11 (1976); Suppl. 7 (1987)
Glycidyl stearate	11 (1976); Suppl. 7 (1987)
Griseofulvin	10 (1976); Suppl. 7 (1987); 79 (2001)
Guinea Green B	16 (1978); Suppl. 7 (1987)
Gyromitrin	31 (1983); Suppl. 7 (1987)

H

Haematite	1 (1972); Suppl. 7 (1987)
Haematite and ferric oxide	Suppl. 7 (1987)
Haematite mining, underground, with exposure to radon	1 (1972); Suppl. 7 (1987); 100D (2012)
Hairdressers and barbers, occupational exposure as	57 (1993)
Hair dyes, epidemiology of	16 (1978); 27 (1982)

Halogenated acetonitriles	52 (1991); 71 (1999)
Halothane (see Anaesthetics, volatile)	
HC Blue No. 1	57 (1993)
HC Blue No. 2	57 (1993)
α-HCH (see Hexachlorocyclohexanes)	
β-HCH (see Hexachlorocyclohexanes)	
γ-HCH (see Hexachlorocyclohexanes)	
HC Red No. 3	57 (1993)
HC Yellow No. 4	57 (1993)
Heating oils (see Fuel oils)	
<i>Helicobacter pylori</i> , infection with	61 (1994); 100B (2012)
Hepatitis B virus	59(1994); 100B (2012)
Hepatitis C virus	59 (1994); 100B5 (2012)
Hepatitis D virus	59 (1994)
Heptachlor (see also Chlordane and Heptachlor)	5 (1974); 20 (1979)
Hexachlorobenzene	20 (1979); Suppl. 7 (1987); 79 (2001)
Hexachlorobutadiene	20 (1979); Suppl. 7 (1987); 73 (1999)
Hexachlorocyclohexanes	5 (1974); 20 (1979) (corr. 42); Suppl. 7 (1987)
Hexachlorocyclohexane, technical-grade (see Hexachlorocyclohexanes)	
Hexachloroethane	20 (1979); Suppl. 7 (1987); 73 (1999)
Hexachlorophene	20 (1979); Suppl. 7 (1987)
Hexamethylphosphoramide	15 (1977); Suppl. 7 (1987); 71 (1999)
2,4-Hexadienal	101 (2012)
Hexestrol (see also Nonsteroidal estrogens)	Suppl. 7 (1987)
Hormonal contraceptives, progestogens only	72 (1999)
Human herpesvirus 8	70 (1997)
Human immunodeficiency viruses	67 (1996); 100B (2012)
Human papillomaviruses	64 (1995) (corr. 66); 90 (2007); 100B (2012)
Human T-cell lymphotropic viruses	67 (1996); 100B (2012)
Hycanthone mesylate	13 (1977); Suppl. 7 (1987)
Hydralazine	24 (1980); Suppl. 7, (1987)
Hydrazine	4 (1974); Suppl. 7 (1987); 71 (1999)
Hydrochloric acid	54 (1992)
Hydrochlorothiazide	50 (1990)
Hydrogen peroxide	36 (1985); Suppl. 7 (1987); 71 (1999)
Hydroquinone	15 (1977); Suppl. 7 (1987); 71 (1999)
1-Hydroxyanthraquinone	82 (2002)
4-Hydroxyazobenzene	8 (1975); Suppl. 7 (1987)
17α-Hydroxyprogesterone caproate (see also Progestins)	21 (1979) (corr. 42)
8-Hydroxyquinoline	13 (1977); Suppl. 7 (1987)
8-Hydroxysenkirkine	10 (1976); Suppl. 7 (1987)
Hydroxyurea	76 (2000)
Hypochlorite salts	52 (1991)

I

Implants, surgical	74 (1999)
Indeno[1,2,3- <i>cd</i>]pyrene	3 (1973); 32 (1983); Suppl. 7 (1987); 92 (2010)
Indium phosphide	86 (2006)
Inorganic acids (see Sulfuric acid and other strong inorganic acids, occupational exposures to mists and vapours from)	
Inorganic lead compounds	Suppl. 7 (1987); 87 (2006)
Insecticides, occupational exposures in spraying and application of	53 (1991)
Insulation glass wool (see Man-made vitreous fibres)	
Involuntary smoking (see Tobacco, Second-hand smoke)	
Ionizing radiation (all types)	100D (2012)
IQ	40 (1986); Suppl. 7 (1987); 56 (1993)
Iron and steel founding	34 (1984); Suppl. 7 (1987); 100F (2012)
Iron-dextran complex	2 (1973); Suppl. 7 (1987)
Iron-dextrin complex	2 (1973) (corr. 42); Suppl. 7 (1987)
Iron oxide (see Ferric oxide)	
Iron oxide, saccharated (see Saccharated iron oxide)	
Iron sorbitol-citric acid complex	2 (1973); Suppl. 7 (1987)
Isatidine	10 (1976); Suppl. 7 (1987)
Isoflurane (see Anaesthetics, volatile)	
Isoniazid (see Isonicotinic acid hydrazide)	
Isonicotinic acid hydrazide	4 (1974); Suppl. 7 (1987)
Isophosphamide	26 (1981); Suppl. 7 (1987)
Isoprene	60 (1994); 71 (1999)
Isopropanol	15 (1977); Suppl. 7 (1987); 71 (1999)
Isopropanol manufacture (strong-acid process)	Suppl. 7 (1987); 100F (2012)
(see also Isopropanol; Sulfuric acid and other strong inorganic acids, occupational exposures to mists and vapours from)	
Isopropyl oils	15 (1977); Suppl. 7 (1987); 71 (1999)
Isosafrole	1 (1972); 10 (1976); Suppl. 7 (1987)

J

Jacobine	10 (1976); Suppl. 7 (1987)
Jet fuel	45 (1989)
Joinery (see Carpentry and joinery)	

K

Kaempferol	31 (1983); Suppl. 7 (1987)
Kaposi sarcoma herpesvirus	70 (1997); 100B (2012)
Kepone (see Chlordecone)	
Kojic acid	79 (2001)

L

Lasiocarpine	10 (1976); Suppl. 7 (1987)
Lauroyl peroxide	36 (1985); Suppl. 7 (1987); 71 (1999)
Lead acetate (see Lead and lead compounds)	
Lead and lead compounds (see also Foreign bodies).....	1 (1972) (corr. 421); 2 (1973); 12 (1976); 23 (1980); Suppl. 7 (1987); 87 (2006)
Lead arsenate (see Arsenic and arsenic compounds)	
Lead carbonate (see Lead and lead compounds)	
Lead chloride (see Lead and lead compounds)	
Lead chromate (see Chromium and chromium compounds)	
Lead chromate oxide (see Chromium and chromium compounds)	
Lead compounds, inorganic and organic.....	Suppl. 7 (1987); 87 (2006)
Lead naphthenate (see Lead and lead compounds)	
Lead nitrate (see Lead and lead compounds)	
Lead oxide (see Lead and lead compounds)	
Lead phosphate (see Lead and lead compounds)	
Lead subacetate (see Lead and lead compounds)	
Lead tetroxide (see Lead and lead compounds)	
Leather goods manufacture	25 (1981); Suppl. 7 (1987); 100C (2012)
Leather industries	25 (1981); Suppl. 7 (1987); 100C (2012)
Leather tanning and processing	25 (1981); Suppl. 7 (1987); 100C (2012)
Ledate (see also Lead and lead compounds).....	12 (1976)
Levonorgestrel	72 (1999)
Light Green SF	16 (1978); Suppl. 7 (1987)
<i>d</i> -Limonene	56 (1993); 73 (1999)
Lindane (see Hexachlorocyclohexanes)	
Liver flukes (see <i>Clonorchis sinensis</i> ; <i>Opisthorchis felinus</i> ; and <i>Opisthorchis viverrini</i>)	
Lucidin (see 1,3-Dihydro-2-hydroxymethylantraquinone)	
Lumber and sawmill industries (including logging)	25 (1981); Suppl. 7 (1987)
Luteoskyrin	10 (1976); Suppl. 7 (1987)
Lynoestrenol.....	21 (1979); Suppl. 7 (1987); 72 (1999)

M

Madder root (see also <i>Rubia tinctorum</i>).....	82 (2002)
Magenta	4 (1974) (corr. 42); Suppl. 7 (1987); 57 (1993); 100F (2012)
Magenta, manufacture of (see also Magenta).....	Suppl. 7 (1987); 57 (1993); 100F (2012)
Malathion.....	30 (1983); Suppl. 7 (1987)
Maleic hydrazide	4 (1974) (corr. 42); Suppl. 7 (1987)
Malonaldehyde	36 (1985); Suppl. 7 (1987); 71 (1999)
Malondialdehyde (see Malonaldehyde)	
Maneb	12 (1976); Suppl. 7 (1987)
Man-made mineral fibres (see Man-made vitreous fibres)	

Man-made vitreous fibres	43 (1988); 81 (2002)
Mannomustine	9 (1975); Suppl. 7 (1987)
Mate	51 (1991)
MCPA	30 (1983)
(see also Chlorophenoxy herbicides; Chlorophenoxy herbicides, occupational exposures to)	
MeA- α -C	40 (1986); Suppl. 7 (1987)
Medphalan	9 (1975); Suppl. 7 (1987)
Medroxyprogesterone acetate	6 (1974); 21 (1979) (corr. 42); Suppl. 7 (1987); 72 (1999)
Megestrol acetate	Suppl. 7 (1987); 72 (1999)
MelQ	40 (1986); Suppl. 7 (1987); 56 (1993)
MelQx	40 (1986); Suppl. 7 (1987) 56 (1993)
Melamine	39 (1986); Suppl. 7 (1987); 73 (1999)
Melphalan	9 (1975); Suppl. 7 (1987); 100A (2012)
6-Mercaptopurine	26 (1981); Suppl. 7 (1987)
Mercuric chloride (see Mercury and mercury compounds)	
Mercury and mercury compounds	58 (1993)
Merphalan	9 (1975); Suppl. 7 (1987)
Mestranol	6 (1974); 21 (1979) (corr. 42); Suppl. 7 (1987); 72 (1999)
Metabisulfites (see Sulfur dioxide and some sulfites, bisulfites and metabisulfites)	
Metallic mercury (see Mercury and mercury compounds)	
Methanearsonic acid, disodium salt (see Arsenic and arsenic compounds)	
Methanearsonic acid, monosodium salt (see Arsenic and arsenic compounds)	
Methimazole	79 (2001)
Methotrexate	267 (1981); Suppl. 7 (1987)
Methoxsalen (see 8-Methoxypsoralen)	
Methoxychlor	5 (1974); 20 (1979); Suppl. 7 (1987)
Methoxyflurane (see Anaesthetics, volatile)	
5-Methoxypsoralen	407 (1986); Suppl. 7 (1987)
8-Methoxypsoralen (see also 8-Methoxypsoralen plus ultraviolet radiation)	24 (1980)
8-Methoxypsoralen plus ultraviolet radiation	Suppl. 73 (1987); 100A (2012)
Methyl acrylate	19 (1979); 39 (1986); Suppl. 7 (1987); 71 (1999)
5-Methylangelicin plus ultraviolet radiation	Suppl. 7 (1987)
(see also Angelicin and some synthetic derivatives)	
2-Methylaziridine	9 (1975); Suppl. 7 (1987); 71 (1999)
Methylazoxymethanol acetate (see also Cycasin)	1 (1972); 10 (1976); Suppl. 7 (1987)
Methyl bromide	41 (1986) (corr. 45); Suppl. 7 (1987); 71 (1999)
Methyl tert-butyl ether	73 (1999)
Methyl carbamate	12 (1976); Suppl. 7 (1987)
Methyl-CCNU (see 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea)	
Methyl chloride	41 (1986); Suppl. 7 (1987); 71 (1999)
1-, 2-, 3-, 4-, 5- and 6-Methylchrysenes	32 (1983); Suppl. 7 (1987); 92 (2010)
N-Methyl-N,4-dinitrosoaniline	1 (1972); Suppl. 7 (1987)
4,4'-Methylene bis(2-chloroaniline)	4 (1974) (corr. 42); Suppl. 7 (1987); 57 (1993); 100F (2012)
4,4'-Methylene bis(N,N-dimethyl)benzenamine	27 (1982); Suppl. 7 (1987)
4,4'-Methylene bis(2-methylaniline)	4 (1974); Suppl. 7 (1987)
4,4'-Methylenedianiline	4 (1974) (corr. 42); 39 (1986); Suppl. 7 (1987)

4,4'-Methylenediphenyl diisocyanate	19 (1979); Suppl. 7 (1987); 71 (1999)
Methyleugenol	101 (2012)
2-Methylfluoranthene	32 (1983); Suppl. 7 (1987); 92 (2010)
3-Methylfluoranthene	32 (1983); Suppl. 7 (1987); 92 (2010)
Methylglyoxal	51 (1991)
2-Methylimidazole	101 (2012)
4-Methylimidazole	101 (2012)
Methyl iodide	15 (1977); 41 (1986); Suppl. 7 (1987); 71 (1999)
Methyl isobutyl ketone	101 (2012)
Methylmercury chloride (see Mercury and mercury compounds)	
Methylmercury compounds (see Mercury and mercury compounds)	
Methyl methacrylate	19 (1979); Suppl. 7 (1987); 60 (1994)
Methyl methanesulfonate	7 (1974); Suppl. 7 (1987); 71 (1999)
2-Methyl-1-nitroanthraquinone	27 (1982); Suppl. 7 (1987)
<i>N</i> -Methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine	4 (1974); Suppl. 7 (1987)
3-Methylnitrosaminopropionaldehyde [see 3-(<i>N</i> -Nitrosomethylamino)-propionaldehyde]	
3-Methylnitrosaminopropionitrile [see 3-(<i>N</i> -Nitrosomethylamino)-propionitrile]	
4-(Methylnitrosamino)-4-(3-pyridyl)-1-butanal [see 4-(<i>N</i> -Nitrosomethyl-amino)-4-(3-pyridyl)-1-butanal]	
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone [see 4-(<i>N</i> -Nitrosomethyl-amino)-1-(3-pyridyl)-1-butanone]	
<i>N</i> -Methyl- <i>N</i> -nitrosourea	1 (1972); 17 (1978); Suppl. 7 (1987)
<i>N</i> -Methyl- <i>N</i> -nitrosourethane	4 (1974); Suppl. 7 (1987)
<i>N</i> -Methylolacrylamide	60 (1994)
Methyl parathion	30 (1983); Suppl. 7 (1987)
1-Methylphenanthrene	32 (1983); Suppl. 7 (1987); 92 (2010)
7-Methylpyrido[3,4- <i>c</i>]psoralen	40 (1986); Suppl. 7 (1987)
Methyl red	8 (1975); Suppl. 7 (1987)
Methyl selenac (see also Selenium and selenium compounds)	12 (1976); Suppl. 7 (1987)
α -Methylstyrene	101 (2012)
Methylthiouracil	7 (1974); Suppl. 7 (1987); 79 (2001)
Metronidazole	13 (1977); Suppl. 7 (1987)
Microcystin-LR	94 (2010)
Microcystis extracts	94 (2010)
Mineral oils	3 (1973); 33 (1984) (corr. 42); Suppl. 7 (1987); 100F (2012)
Mirex	5 (1974); 20 (1979) (corr. 42); Suppl. 7 (1987)
Mists and vapours from sulfuric acid and other strong inorganic acids	54 (1992); 100F (2012)
Mitomycin C	10 (1976); Suppl. 7 (1987)
Mitoxantrone	76 (2000)
MNNG (see <i>N</i> -Methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine)	
MOCA (see 4,4'-Methylene bis(2-chloroaniline))	
Modacrylic fibres	19 (1979); Suppl. 7 (1987)
Monochloramine (see Chloramine)	
3-Monochloro-1,2-propanediol	101 (2012)
Monocrotaline	10 (1976); Suppl. 7 (1987)
Monuron	12 (1976); Suppl. 7 (1987); 53 (1991)
MOPP and other combined chemotherapy including alkylating agents ..	Suppl. 7 (1987); 100A (2012)
Mordanite (see Zeolites)	

Morinda officinalis (see also Traditional herbal medicines)	82 (2002)
Morpholine	47 (1989); 71 (1999)
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone	7 (1974); Suppl. 7 (1987)
Musk ambrette	65 (1996)
Musk xylene	65 (1996)
Mustard gas	9 (1975) (corr. 42); Suppl. 7 (1987); 100F (2012)
Myleran (see 1,4-Butanediol dimethanesulfonate)	

N

Nafenopin	24 (1980); Suppl. 7 (1987)
Naphthalene	82 (2002)
1,5-Naphthalenediamine	27 (1982); Suppl. 7 (1987)
1,5-Naphthalene diisocyanate	19 (1979); Suppl. 7 (1987); 71 (1999)
Naphtho[1,2- <i>b</i>]fluoranthene	92 (2010)
Naphtho[2,1- <i>a</i>]fluoranthene	92 (2010)
Naphtho[2,3- <i>e</i>]pyrene	92 (2010)
1-Naphthylamine	4 (1974) (corr. 42); Suppl. 7 (1987)
2-Naphthylamine	4 (1974); Suppl. 7 (1987); 100F (2012)
1-Naphthylthiourea	30 (1983); Suppl. 7 (1987)
Neutron radiation	75 (2000); 100D (2012)
Nickel acetate (see Nickel and nickel compounds)	
Nickel ammonium sulfate (see Nickel and nickel compounds)	
Nickel and nickel compounds (see also Implants, surgical)	2 (1973) (corr. 42); 11 (1976); Suppl. 7 (1987) (corr. 45); 49 (1990) (corr. 67); 100C (2012)
Nickel carbonate (see Nickel and nickel compounds)	
Nickel carbonyl (see Nickel and nickel compounds)	
Nickel chloride (see Nickel and nickel compounds)	
Nickel-gallium alloy (see Nickel and nickel compounds)	
Nickel hydroxide (see Nickel and nickel compounds)	
Nickelocene (see Nickel and nickel compounds)	
Nickel oxide (see Nickel and nickel compounds)	
Nickel subsulfide (see Nickel and nickel compounds)	
Nickel sulfate (see Nickel and nickel compounds)	
Niridazole	13 (1977); Suppl. 7 (1987)
Nithiazide	31 (1983); Suppl. 7 (1987)
Nitrate or nitrite, ingested, under conditions that result in endogenous nitrosation	94 (2010)
Nitrilotriacetic acid and its salts	48 (1990); 73 (1999)
Nitrite (see Nitrate or nitrite)	
5-Nitroacenaphthene	16 (1978); Suppl. 7 (1987)
5-Nitro- <i>ortho</i> -anisidine	27 (1982); Suppl. 7 (1987)
2-Nitroanisole	65 (1996)
9-Nitroanthracene	33 (1984); Suppl. 7 (1987)
7-Nitrobenz[<i>a</i>]anthracene	46 (1989)
Nitrobenzene	65 (1996)

6-Nitrobenzo[<i>a</i>]pyrene	33 (1984); Suppl. 7 (1987); 46 (1989)
4-Nitrobiphenyl	4 (1974); Suppl. 7 (1987)
6-Nitrochrysene	33 (1984); Suppl. 7 (1987); 46 (1989)
Nitrofen, technical-grade	30 (1983); Suppl. 7 (1987)
3-Nitrofluoranthene	33 (1984); Suppl. 7 (1987)
2-Nitrofluorene	46 (1989)
Nitrofural	7 (1974); Suppl. 7 (1987); 50 (1990)
5-Nitro-2-furaldehyde semicarbazone (see Nitrofural)	
Nitrofurantoin	50 (1990)
Nitrofurazone (see Nitrofural)	
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone	7 (1974); Suppl. 7 (1987)
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	1 (1972); 7 (1974); Suppl. 7 (1987)
Nitrogen mustard	9 (1975); Suppl. 7 (1987)
Nitrogen mustard <i>N</i> -oxide	9 (1975); Suppl. 7 (1987)
Nitromethane	77 (2000)
1-Nitronaphthalene	46 (1989)
2-Nitronaphthalene	46 (1989)
3-Nitroperylene	46 (1989)
2-Nitro- <i>para</i> -phenylenediamine (see 1,4-Diamino-2-nitrobenzene)	
2-Nitropropane	29 (1982); Suppl. 7 (1987); 71 (1999)
1-Nitropyrene	33 (1984); Suppl. 7 (1987); 46 (1989)
2-Nitropyrene	46 (1989)
4-Nitropyrene	46 (1989)
<i>N</i> -Nitrosatable drugs	24 (1980) (corr. 42)
<i>N</i> -Nitrosatable pesticides	30 (1983)
<i>N'</i> -Nitrosoanabasine (NAB)	37 (1985); Suppl. 7 (1987); 89 (2007)
<i>N'</i> -Nitrosoanatabine (NAT)	37 (1985); Suppl. 7 (1987); 89 (2007)
<i>N</i> -Nitrosodi- <i>n</i> -butylamine	4 (1974); 17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrosodiethanolamine	17 (1978); Suppl. 7 (1987); 77 (2000)
<i>N</i> -Nitrosodiethylamine	1 (1972) (corr. 42); 17 (1978) (corr. 42); Suppl. 7 (1987)
<i>N</i> -Nitrosodimethylamine	1 (1972); 17 (1978) (corr. 42); Suppl. 7 (1987)
<i>N</i> -Nitrosodiphenylamine	27 (1982); Suppl. 7 (1987)
<i>para</i> -Nitrosodiphenylamine	27 (1982) (corr. 42); Suppl. 7 (1987)
<i>N</i> -Nitrosodi- <i>n</i> -propylamine	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitroso- <i>N</i> -ethylurea (see <i>N</i> -Ethyl- <i>N</i> -nitroso-urea)	
<i>N</i> -Nitrosofolic acid	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrosoguvacine	37 (1985); Suppl. 7 (1987); 85 (2004)
<i>N</i> -Nitrosoguvacoline	37 (1985); Suppl. 7 (1987); 85 (2004)
<i>N</i> -Nitrosohydroxyproline	17 (1978); Suppl. 7 (1987)
3-(<i>N</i> -Nitrosomethylamino)propionaldehyde	37 (1985); Suppl. 7 (1987); 85 (2004)
3-(<i>N</i> -Nitrosomethylamino)propionitrile	37 (1985); Suppl. 7 (1987); 85 (2004)
4-(<i>N</i> -Nitrosomethylamino)-4-(3-pyridyl)-1-butanal	37 (1985); Suppl. 7 (1987)
4-(<i>N</i> -Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	37 (1985); Suppl. 7 (1987); 89 (2007); 100E (2012)
<i>N</i> -Nitrosomethylethylamine	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitroso- <i>N</i> -methylurea (see <i>N</i> -Methyl- <i>N</i> -nitroso-urea)	

<i>N</i> -Nitroso- <i>N</i> -methylurethane (see <i>N</i> -Methyl- <i>N</i> -nitrosourethane)	
<i>N</i> -Nitrosomethylvinylamine	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrosomorpholine	17 (1978); Suppl. 7 (1987)
<i>N</i> '-Nitrosornicotine (NNN)	17 (1978); 37 (1985); Suppl. 7 (1987); 89 (2007); 100E (2012)
<i>N</i> -Nitrosopiperidine	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrosoproline	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrosopyrrolidine	17 (1978); Suppl. 7 (1987)
<i>N</i> -Nitrososarcosine	17 (1978); Suppl. 7 (1987)
Nitrosoureas, chloroethyl (see Chloroethyl nitrosoureas)	
5-Nitro- <i>ortho</i> -toluidine	48 (1990)
2-Nitrotoluene	65 (1996); 101 (2012)
3-Nitrotoluene	65 (1996)
4-Nitrotoluene	65 (1996)
Nitrous oxide (see Anaesthetics, volatile)	
Nitrovin	31 (1983); Suppl. 7 (1987)
Nivalenol (see Toxins derived from <i>Fusarium graminearum</i> , <i>F. culmorum</i> and <i>F. crookwellense</i>)	
NNK (see 4-(<i>N</i> -Nitrosomethylamino)-1-(3-pyridyl)-1-butanone)	
NNN (see <i>N</i> '-Nitrosornicotine)	
Nodularins	94 (2010)
Nonsteroidal estrogens	Suppl. 7 (1987)
Norethisterone	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Norethisterone acetate	72 (1999)
Norethynodrel	6 (1974); 21 (1979) (corr. 42); Suppl. 7 (1987); 72 (1999)
Norgestrel	6 (1974); 21 (1979); Suppl. 7 (1987); 72 (1999)
Nylon 6	19 (1979); Suppl. 7 (1987)

O

Ochratoxin A	10 (1976); 31 (1983) (corr. 42); Suppl. 7 (1987); 56 (1993)
Oil Orange SS	8 (1975); Suppl. 7 (1987)
Oestrogen and Oestrogen-type compounds (see Estrogen)	
<i>Opisthorchis felineus</i> , infection with	61 (1994)
<i>Opisthorchis viverrini</i> , infection with	61 (1994); 100B (2012)
Oral contraceptives, sequential (see Sequential oral contraceptives)	
Orange I	8 (1975); Suppl. 7 (1987)
Orange G	8 (1975); Suppl. 7 (1987)
Organic lead compounds	Suppl. 7 (1987); 87 (2006)
Organolead compounds (see Organic lead compounds)	
Oxazepam	13 (1977); Suppl. 7 (1987); 66 (1996)
Oxymetholone (see also Androgenic (anabolic) steroids)	13 (1977)
Oxyphenbutazone	13 (1977); Suppl. 7 (1987)

P

Paint manufacture and painting, occupational exposures in	47 (1989); 98 (2010); 100F (2012)
Palygorskite	42 (1987); Suppl. 7 (1987); 68 (1997)
Panfuran S (see also Dihydroxymethylfuratrizine)	24 (1980); Suppl. 7 (1987)
Paper manufacture (see Pulp and paper manufacture)	
Paracetamol	50 (1990); 73 (1999)
Parasorbic acid	10 (1976) (corr. 42); Suppl. 7 (1987)
Parathion	30 (1983); Suppl. 7 (1987)
Patulin	10 (1976); 40 (1986); Suppl. 7 (1987)
Paving and roofing with coal-tar pitch	92 (2010)
Penicillic acid	10 (1976); Suppl. 7 (1987)
Pentachloroethane	41 (1986); Suppl. 7 (1987); 71 (1999)
Pentachloronitrobenzene (see Quintozene)	
Pentachlorophenol	20 (1979); 53 (1991)
(see also Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	
Permethrin	53 (1991)
Perylene	32 (1983); Suppl. 7 (1987); 92 (2010)
Petasitenine	31 (1983); Suppl. 7 (1987)
Petasites japonicus (see also Pyrrolizidine alkaloids)	10 (1976)
Petroleum refining, occupational exposures in	45 (1989)
Petroleum solvents	47 (1989)
Phenacetin	13 (1977); 24 (1980); Suppl. 7 (1987); 100A (2012)
Phenanthrene	32 (1983); Suppl. 7 (1987); 92 (2010)
Phenazopyridine hydrochloride	8 (1975); 24 (1980) (corr. 42); Suppl. 7 (1987)
Phenelzine sulfate	24 (1980); Suppl. 7 (1987)
Phenicarbazide	12 (1976); Suppl. 7 (1987)
Phenobarbital and its sodium salt	13 (1977); Suppl. 7 (1987); 79 (2001)
Phenol	47 (1989) (corr. 50); 71 (1999)
Phenolphthalein	76 (2000)
Phenoxyacetic acid herbicides (see Chlorophenoxy herbicides)	
Phenoxybenzamine hydrochloride	9 (1975); 24 (1980); Suppl. 7 (1987)
Phenylbutazone	13 (1977); Suppl. 7 (1987)
meta-Phenylenediamine	16 (1978); Suppl. 7 (1987)
para-Phenylenediamine	16 (1978); Suppl. 7 (1987)
Phenyl glycidyl ether (see also Glycidyl ethers)	71 (1999)
N-Phenyl-2-naphthylamine	16 (1978) (corr. 42); Suppl. 7 (1987)
ortho-Phenylphenol	30 (1983); Suppl. 7 (1987); 73 (1999)
Phenytoin	13 (1977); Suppl. 7 (1987); 66 (1996)
Phillipsite (see Zeolites)	
PhIP	56 (1993)
Phosphorus-32 as phosphate	100D (2012)
Picene	92 (2010)
Pickled vegetables	56 (1993)
Picloram	53 (1991)

Piperazine oestrone sulfate (see Conjugated estrogens)	
Piperonyl butoxide	30 (1983); Suppl. 7 (1987)
Pitches, coal-tar (see Coal-tar pitches)	
Plutonium-239	100D (2012)
Polyacrylic acid	19 (1979); Suppl. 7 (1987)
Polybrominated biphenyls	18 (1978); 41 (1986); Suppl. 7 (1987)
Polychlorinated biphenyls	7 (1974); 18 (1978) (corr. 42); Suppl. 7 (1987)
Polychlorinated camphenes (see Toxaphene)	
Polychlorinated dibenzo- <i>para</i> -dioxins (other than 2,3,7,8-tetrachlorodibenzodioxin)	69 (1997)
Polychlorinated dibenzofurans	69 (1997)
Polychlorophenols and their sodium salts	71 (1999)
Polychloroprene	19 (1979); Suppl. 7 (1987)
Polyestradiol phosphate (see Estradiol-17 β)	
Polyethylene (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Poly(glycolic acid) (see Implants, surgical)	
Polymethylene polyphenyl isocyanate (see also 4,4'-Methylenediphenyl diisocyanate)	19 (1979); Suppl. 7 (1987)
Polymethyl methacrylate (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polypropylene (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polystyrene (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polytetrafluoroethylene (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polyurethane foams (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polyvinyl acetate (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polyvinyl alcohol (see also Implants, surgical)	19 (1979); Suppl. 7 (1987)
Polyvinyl chloride (see also Implants, surgical)	7 (1974); 19 (1979); Suppl. 7 (1987)
Polyvinyl pyrrolidone	19 (1979); Suppl. 7 (1987); 71 (1999)
Ponceau MX	8 (1975); Suppl. 7 (1987)
Ponceau 3R	8 (1975); Suppl. 7 (1987)
Ponceau SX	8 (1975); Suppl. 7 (1987)
Post-menopausal estrogen therapy	Suppl. 7 (1987); 72 (1999); 100A (2012)
Potassium arsenate (see Arsenic and arsenic compounds)	
Potassium arsenite (see Arsenic and arsenic compounds)	
Potassium bis(2-hydroxyethyl)dithiocarbamate	12 (1976); Suppl. 7 (1987)
Potassium bromate	40 (1986); Suppl. 7 (1987); 73 (1999)
Potassium chromate (see Chromium and chromium compounds)	
Potassium dichromate (see Chromium and chromium compounds)	
Prazepam	66 (1996)
Prednimustine	50 (1990)
Prednisone	26 (1981); Suppl. 7 (1987)
Printing processes and printing inks	65 (1996)
Procarbazine hydrochloride	26 (1981); Suppl. 7 (1987)
Proflavine salts	24 (1980); Suppl. 7 (1987)
Progesterone (see also Progestins; Combined oral contraceptives)	6 (1974); 21 (1979) (corr. 42)
Progestins (see Progestogens)	
Progestogens	Suppl. 7 (1987); 72 (1999)

Pronetalol hydrochloride	13 (1977) (corr. 42); Suppl. 7 (1987)
1,3-Propane sultone	4 (1974) (corr. 42); Suppl. 7 (1987); 71 (1999)
Propam.	12 (1976); Suppl. 7 (1987)
β -Propiolactone	4 (1974) (corr. 42); Suppl. 7 (1987); 71 (1999)
<i>n</i> -Propyl carbamate	12 (1976); Suppl. 7 (1987)
Propylene	19 (1979); Suppl. 7 (1987); 60 (1994)
Propyleneimine (see 2-Methylaziridine)	
Propylene oxide	11 (1976); 36 (1985) (corr. 42); Suppl. 7 (1987); 60 (1994)
Propylthiouracil	7 (1974); Suppl. 7 (1987); 79 (2001)
Ptaquiloside (see also Bracken fern)	40 (1986); Suppl. 7 (1987)
Pulp and paper manufacture	25 (1981); Suppl. 7 (1987)
Pyrene	32 (1983); Suppl. 7 (1987); 92 (2010)
Pyridine	77 (2000)
Pyrido[3,4- <i>c</i>]psoralen	40 (1986); Suppl. 7 (1987)
Pyrimethamine	13 (1977); Suppl. 7 (1987)
Pyrrolizidine alkaloids (see Hydroxysenkirkine; Isatidine; Jacobine; Lasiocarpine; Monocrotaline; Retrorsine; Riddelliine; Seneciphylline; Senkirkine)	

Q

Quartz (see Crystalline silica)	
Quercetin (see also Bracken fern)	31 (1983); Suppl. 7 (1987); 73 (1999)
<i>para</i> -Quinone	15 (1977); Suppl. 7 (1987); 71 (1999)
Quintozene	5 (1974); Suppl. 7 (1987)

R

Radiation (see gamma-radiation, neutrons, ultraviolet radiation, X-radiation)	
Radiofrequency electromagnetic fields	102 (2013)
Radionuclides, internalized, that emit α -particles	78 (2001); 100D (2012)
Radionuclides, internalized, that emit β -particles	78 (2001); 100D (2012)
Radioisotopes of iodine, short-lived, including Iodine-131	100D (2012)
Radium-224, radium-226, radium-228	100D (2012)
Radon-222 with its decay products	43 (1988) (corr. 45); 100D (2012)
Refractory ceramic fibres (see Man-made vitreous fibres)	
Reserpine	10 (1976); 24 (1980) (corr. 42); Suppl. 7 (1987)
Resorcinol	15 (1977); Suppl. 7 (1987); 71 (1990)
Retrorsine	10 (1976); Suppl. 7 (1987)
Rhodamine B	16 (1978); Suppl. 7 (1987)
Rhodamine 6G	16 (1978); Suppl. 7 (1987)
Riddelliine	10 (1976); Suppl. 7 (1987); 82 (2002)
Rifampicin	24 (1980); Suppl. 7 (1987)
Ripazepam	66 (1996)

Rock (stone) wool (see Man-made vitreous fibres)
 Rubber industry 28 (1982) (corr. 42); Suppl. 7 (1987) ; 100F (2012)
Rubia tinctorum (see also Madder root; Traditional herbal medicines) 82 (2002)
 Rugulosin 40 (1986); Suppl. 7 (1987)

S

Saccharated iron oxide 2 (1973); Suppl. 7 (1987)
 Saccharin and its salts 22 (1980) (corr. 42); Suppl. 7 (1987); 73 (1999)
 Safrole 1 (1972); 10 (1976); Suppl. 7 (1987)
 Salted fish, Chinese-style 56 (1993); 100E (2012)
 Sawmill industry, including logging
 (see Lumber and sawmill industry, including logging)
 Scarlet Red 8 (1975); Suppl. 7 (1987)
Schistosoma haematobium, infection with 61 (1994); 100B (2012)
Schistosoma japonicum, infection with 61 (1994)
Schistosoma mansoni, infection with 61 (1994)
 Selenium and selenium compounds 9 (1975) (corr. 42); Suppl. 7 (1987)
 Selenium dioxide (see Selenium and selenium compounds)
 Selenium oxide (see Selenium and selenium compounds)
 Semicarbazide hydrochloride 12 (1976) (corr. 42); Suppl. 7 (1987)
Senecio jacobaea L. (see also Pyrrolizidine alkaloids) 10 (1976)
Senecio longilobus 10 (1976); 82 (2002)
 (see also Pyrrolizidine alkaloids; Traditional herbal medicines)
Senecio riddellii (see also Traditional herbal medicines) 82 (1982)
 Seneciphylline 10 (1976); Suppl. 7 (1987)
 Senkirkine 10 (1976); 31 (1983); Suppl. 7 (1987)
 Sepiolite 42 (1987); Suppl. 7 (1987); 68 (1997)
 Sequential oral contraceptives Suppl. 7 (1987)
 (see also Estrogens, progestins and combinations)
 Shale-oils 35 (1985); Suppl. 7 (1987); 100F (2012)
 Shiftwork 98 (2010)
 Shikimic acid (see also Bracken fern) 40 (1986); Suppl. 7 (1987)
 Shoe manufacture and repair (see Boot and shoe manufacture and repair)
 Silica (see also Amorphous silica; Crystalline silica) 42 (1987); 100C (2012)
 Silicone (see Implants, surgical)
 Simazine 53 (1991); 73 (1999)
 Slag wool (see Man-made vitreous fibres)
 Sodium arsenate (see Arsenic and arsenic compounds)
 Sodium arsenite (see Arsenic and arsenic compounds)
 Sodium cacodylate (see Arsenic and arsenic compounds)
 Sodium chloride 52 (1991)
 Sodium chromate (see Chromium and chromium compounds)
 Sodium cyclamate (see Cyclamates)
 Sodium dichromate (see Chromium and chromium compounds)

Sodium diethyldithiocarbamate	12 (1976); Suppl. 7 (1987)
Sodium equilin sulfate (see Conjugated estrogens)	
Sodium estrone sulfate (see Conjugated estrogens)	
Sodium fluoride (see Fluorides)	
Sodium monofluorophosphate (see Fluorides)	
Sodium <i>ortho</i> -phenylphenate	30 (1983); Suppl. 7 (1987); 73 (1999)
(see also <i>ortho</i> -Phenylphenol)	
Sodium saccharin (see Saccharin)	
Sodium selenate (see Selenium and selenium compounds)	
Sodium selenite (see Selenium and selenium compounds)	
Sodium silicofluoride (see Fluorides)	
Solar radiation	55 (1992); 100D (2012)
Soots	3 (1973); 35 (1985); Suppl. 7 (1987); 100F (2012)
Special-purpose glass fibres such as E-glass and '475' glass fibres (see Man-made vitreous fibres)	
Spirolactone.....	24 (1980); Suppl. 7 (1987); 79 (2001)
Stannous fluoride (see Fluorides)	
Static electric fields.....	80 (2002)
Static magnetic fields.....	80 (2002)
Steel founding (see Iron and steel founding)	
Steel, stainless (see Implants, surgical)	
Sterigmatocystin	1 (1972); 10(1976); Suppl. 7 (1987)
Steroidal estrogens	Suppl. 7 (1987)
Streptozotocin	4 (1974); 17 (1978); Suppl. 7 (1987)
Strobane® (see Terpene polychlorinates)	
Strong-inorganic-acid mists containing sulfuric acid (see Mists and vapours from sulfuric acid and other strong inorganic acids)	
Strontium chromate (see Chromium and chromium compounds)	
Styrene	19 (1979) (corr. 42); Suppl. 7 (1987); 60 (1994) (corr. 65); 82 (2002)
Styrene-acrylonitrile copolymers	19 (1979); Suppl. 7 (1987)
Styrene-butadiene copolymers	19 (1979); Suppl. 7 (1987)
Styrene-7,8-oxide	11 (1976); 19 (1979); 36 (1985); Suppl. 7 (1987); 60 (1994)
Succinic anhydride	15 (1977); Suppl. 7 (1987)
Sudan I	8 (1975); Suppl. 7 (1987)
Sudan II	8 (1975); Suppl. 7 (1987)
Sudan III	8 (1975); Suppl. 7 (1987)
Sudan Brown RR.....	8 (1975); Suppl. 7 (1987)
Sudan Red 7B	8 (1975); Suppl. 7 (1987)
Sulfadimidine (see Sulfamethazine)	
Sulfafurazole	24 (1980); Suppl. 7 (1987)
Sulfallate.....	30 (1983); Suppl. 7 (1987)
Sulfamethazine and its sodium salt	79 (2001)
Sulfamethoxazole	24 (1980); Suppl. 7 (1987); 79 (2001)
Sulfites (see Sulfur dioxide and some sulfites, bisulfites and metabisulfites)	
Sulfur dioxide and some sulfites, bisulfites and metabisulfites.....	54 (1992)
Sulfur mustard (see Mustard gas)	
Sulfuric acid and other strong inorganic acids, occupational exposures to mists and vapours from ..	54 (1992)

Sulfur trioxide	54 (1992)
Sulphisoxazole (see Sulfafurazole)	
Sunset Yellow FCF	8 (1975); Suppl. 7 (1987)
Symphytine	31 (1983); Suppl. 7 (1987)

T

2,4,5-T	15 (1977)
(see also Chlorophenoxy herbicides; Chlorophenoxy herbicides, occupational exposures to)	
Talc	42 (1987); Suppl. 7 (1987)
Talc, inhaled, not containing asbestos or asbestiform fibres	93 (2010)
Talc-based body powder, perineal use of	93 (2010)
Tamoxifen	66 (1996); 100A (2012)
Tannic acid	10 (1976) (corr. 42); Suppl. 7 (1987)
Tannins (see also Tannic acid)	10 (1976); Suppl. 7 (1987)
TCDD (see 2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin)	
TDE (see DDT)	
Tea	51 (1991)
Temazepam	66 (1996)
Teniposide	76 (2000)
Terpene polychlorinates	5 (1974); Suppl. 7 (1987)
Testosterone (see also Androgenic (anabolic) steroids)	6, (1974); 21 (1979)
Testosterone oenanthate (see Testosterone)	
Testosterone propionate (see Testosterone)	
2,2',5,5'-Tetrachlorobenzidine	27 (1982); Suppl. 7 (1987)
2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin	15 (1977); Suppl. 7 (1987); 69 (1997); 100F (2012)
1,1,1,2-Tetrachloroethane	41 (1986); Suppl. 7 (1987); 71 (1999)
1,1,2,2-Tetrachloroethane	20 (1979); Suppl. 7 (1987); 71 (1999)
Tetrachloroethylene	20 (1979); Suppl. 7 (1987); 63 (1995) (corr. 65)
2,3,4,6-Tetrachlorophenol (see Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	
Tetrachlorvinphos	30 (1983); Suppl. 7 (1987)
Tetraethyllead (see Lead and lead compounds)	
Tetrafluoroethylene	19 (1979); Suppl. 7 (1987); 71 (1999)
Tetrakis(hydroxymethyl)phosphonium salts	48 (1990); 71 (1999)
Tetramethyllead (see Lead and lead compounds)	
Tetranitromethane	65 (1996)
Textile manufacturing industry, exposures in	48 (1990) (corr. 51)
Theobromine	51 (1991)
Theophylline	51 (1991)
Thioacetamide	7 (1974); Suppl. 7 (1987)
4,4'-Thiodianiline	16 (1978); 27 (1982); Suppl. 7 (1987)
Thiotepa	9 (1975); Suppl. 7 (1987); 50 (1990); 100A (2012)
Thiouracil	7 (1974); Suppl. 7 (1987); 79 (2001)
Thiourea	7 (1974); Suppl. 7 (1987); 79 (2001)

Thiram	12 (1976); Suppl. 7 (1987); 53 (1991)
Thorium-232 (as Thorotrast)	100D (2012)
Titanium (see Implants, surgical)	
Titanium dioxide	47 (1989); 93 (2010)
Tobacco	
– Second-hand tobacco smoke	83 (2004); 100E (2012)
– Smokeless tobacco	37 (1985) (corr. 42; 52); Suppl. 7 (1987); 89 (2007); 100E (2012)
– Tobacco smoking	38 (1986) (corr. 42); Suppl. 7 (1987); 83 (2004); 100E (2012)
<i>ortho</i> -Tolidine (see 3,3'-Dimethylbenzidine)	
2,4-Toluene diisocyanate (see also Toluene diisocyanates)	19 (1979); 39 (1986)
2,6-Toluene diisocyanate (see also Toluene diisocyanates)	19 (1979); 39 (1986)
Toluene	47 (1989); 71 (1999)
Toluene diisocyanates	39 (1986) (corr. 42); Suppl. 7 (1987); 71 (1999)
Toluenes, α -chlorinated (see α -Chlorinated toluenes and benzoyl chloride)	
<i>ortho</i> -Toluenesulfonamide (see Saccharin)	
<i>ortho</i> -Toluidine	16 (1978); 27 (1982) (corr. 68); Suppl. 7 (1987); 77 (2000)
Toremifene	66 (1996)
Toxaphene	20 (1979); Suppl. 7 (1987); 79 (2001)
T-2 Toxin (see Toxins derived from <i>Fusarium sporotrichioides</i>)	
Toxins derived from <i>Fusarium graminearum</i> , <i>F. culmorum</i> and <i>F. crookwellense</i>	11 (1976); 31, 279 (1983); Suppl. 7 (1987); 56 (1993)
Toxins derived from <i>Fusarium moniliforme</i>	56 (1993)
Toxins derived from <i>Fusarium sporotrichioides</i>	31 (1983); Suppl. 7 (1987); 56 (1993)
Traditional herbal medicines	82 (2002); 100A (2012)
Tremolite (see Asbestos)	
Treosulfan	26 (1981); Suppl. 7 (1987); 100A (2012)
Triaziquone (see Tris(aziridinyl)- <i>para</i> -benzoquinone)	
Trichlorfon	30 (1983); Suppl. 7 (1987)
Trichlormethine	9 (1975); Suppl. 7 (1987); 50 (1990)
Trichloroacetic acid	63 (1995) (corr. 65); 84 (2004)
Trichloroacetonitrile (see also Halogenated acetonitriles)	71 (1999)
1,1,1-Trichloroethane	20 (1979); Suppl. 7 (1987); 71 (1999)
1,1,2-Trichloroethane	20 (1979); Suppl. 7 (1987); 52 (1991); 71 (1999)
Trichloroethylene	11 (1976); 20 (1979); Suppl. 7 (1987); 63 (1995) (corr. 65)
2,4,5-Trichlorophenol	20 (1979)
(see also Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	
2,4,6-Trichlorophenol	20 (1979)
(see also Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	
(2,4,5-Trichlorophenoxy)acetic acid (see 2,4,5-T)	
1,2,3-Trichloropropane	63 (1995)
Trichlorotriethylamine-hydrochloride (see Trichlormethine)	
T2-Trichothecene (see Toxins derived from <i>Fusarium sporotrichioides</i>)	
Tridymite (see Crystalline silica)	
Triethanolamine	77 (2000)

Triethylene glycol diglycidyl ether	11 (1976); Suppl. 7 (1987); 71 (1999)
Trifluralin	53 (1991)
4,4',6'-Trimethylangelicin plus ultraviolet radiation	Suppl. 7 (1987)
(see also Angelicin and some synthetic derivatives)	
2,4,5-Trimethylaniline	27 (1982); Suppl. 7 (1987)
2,4,6-Trimethylaniline	27 (1982); Suppl. 7 (1987)
4,5',8'-Trimethylpsoralen	40 (1986); Suppl. 7 (1987)
Trimustine hydrochloride (see Trichlormethine)	
2,4,6-Trinitrotoluene	65 (1996)
Triphenylene	32 (1983); Suppl. 7 (1987); 92 (2010)
Tris(aziridiny)- <i>para</i> -benzoquinone	9 (1975); Suppl. 7 (1987)
Tris(1-aziridinyl)phosphine-oxide	9 (1975); Suppl. 7 (1987)
Tris(1-aziridinyl)phosphine-sulphide (see Thiotepe)	
2,4,6-Tris(1-aziridinyl)-s-triazine	9 (1975); Suppl. 7 (1987)
Tris(2-chloroethyl) phosphate	48 (1990); 71 (1999)
1,2,3-Tris(chloromethoxy)propane	15 (1977); Suppl. 7 (1987); 71 (1999)
Tris(2,3-dibromopropyl) phosphate	20 (1979); Suppl. 7 (1987); 71 (1999)
Tris(2-methyl-1-aziridinyl)phosphine-oxide	9 (1975); Suppl. 7 (1987)
Trp-P-1	31 (1983); Suppl. 7 (1987)
Trp-P-2	31 (1983); Suppl. 7 (1987)
Trypan blue	8 (1975); Suppl. 7 (1987)
<i>Tussilago farfara</i> L. (see also Pyrrolizidine alkaloids)	10 (1976)

U

Ultraviolet radiation	40 (1986); 55 (1992); 100D (2012)
Underground haematite mining with exposure to radon (see Haematite mining, underground)	
Uracil mustard	9 (1975); Suppl. 7 (1987)
Uranium, depleted (see Implants, surgical)	
Urethane (see Ethyl carbamate)	
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Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds, and Natural Products

1972; 184 pages (out-of-print)

Volume 2

Some Inorganic and Organometallic Compounds

1973; 181 pages (out-of-print)

Volume 3

Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds

1973; 271 pages (out-of-print)

Volume 4

Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents

1974; 286 pages (out-of-print)

Volume 5

Some Organochlorine Pesticides

1974; 241 pages (out-of-print)

Volume 6

Sex Hormones

1974; 243 pages (out-of-print)

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Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals

1974; 326 pages (out-of-print)

Volume 8

Some Aromatic Azo Compounds

1975; 357 pages (out-of-print)

Volume 9

Some Aziridines, N-, S- and O-Mustards and Selenium

1975; 268 pages (out-of-print)

Volume 10

Some Naturally Occurring Substances

1976; 353 pages (out-of-print)

Volume 11

*Cadmium, Nickel, Some Epoxides,
Miscellaneous Industrial Chemicals
and General Considerations on Volatile
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1976; 306 pages (out-of-print)

Volume 12

*Some Carbamates, Thio- carbamates and
Carbazides*

1976; 282 pages (out-of-print)

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*Some Miscellaneous Pharmaceutical
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1977; 255 pages

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1977; 106 pages (out-of-print)

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*Some Fumigants, the Herbicides 2,4-D and
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1977; 354 pages (out-of-print)

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*Some Aromatic Amines and Related Nitro
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1978; 400 pages

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Some N-Nitroso Compounds

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1978; 140 pages (out-of-print)

Volume 19

*Some Monomers, Plastics and Synthetic
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1979; 513 pages (out-of-print)

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Some Halogenated Hydrocarbons

1979; 609 pages (out-of-print)

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1979; 583 pages

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Some Non-Nutritive Sweetening Agents

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Volume 24*Some Pharmaceutical Drugs*

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Volume 25*Wood, Leather and Some Associated Industries*

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Volume 26*Some Antineoplastic and Immunosuppressive Agents*

1981; 411 pages (out-of-print)

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1982; 341 pages (out-of-print)

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1983; 424 pages (out-of-print)

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1983; 314 pages (out-of-print)

Volume 32*Polynuclear Aromatic Compounds, Part 1: Chemical, Environmental and Experimental Data*

1983; 477 pages (out-of-print)

Volume 33*Polynuclear Aromatic Compounds, Part 2: Carbon Blacks, Mineral Oils and Some Nitroarenes*

1984; 245 pages (out-of-print)

Volume 34*Polynuclear Aromatic Compounds, Part 3: Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding*

1984; 219 pages (out-of-print)

Volume 35*Polynuclear Aromatic Compounds, Part 4: Bitumens, Coal-tars and Derived Products, Shale-oils and Soots*

1985; 271 pages

Volume 36*Allyl Compounds, Aldehydes, Epoxides and Peroxides*

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Volume 37

*Tobacco Habits Other than Smoking; Betel-
Quid and Areca-Nut Chewing; and Some
Related Nitrosamines*

1985; 291 pages (out-of-print)

Volume 38

Tobacco Smoking

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*Some Chemicals Used in Plastics and
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Volume 40

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Silica and Some Silicates

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Man-Made Mineral Fibres and Radon

1988; 300 pages (out-of-print)

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Alcohol Drinking

1988; 416 pages

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*Occupational Exposures in Petroleum
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*Diesel and Gasoline Engine Exhausts and
Some Nitroarenes*

1989; 458 pages

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*Some Organic Solvents, Resin Monomers
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Manufacture and Painting*

1989; 535 pages (out-of-print)

Volume 48

*Some Flame Retardants and Textile
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Manufacturing Industry*

1990; 345 pages

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Chromium, Nickel and Welding

1990; 677 pages

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Volume 52*Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds*

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*Some Traditional Herbal Medicines, Some
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2004; 1452 pages

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2006; 478 pages

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Smokeless Tobacco and Some Tobacco-specific N- Nitrosamines
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2010; 853 pages

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Carbon Black, Titanium Dioxide, and Talc
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2008; 510 pages

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2010; 806 pages

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2010; 692 pages

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2012; 501 pages

Volume 100D*Radiation*

2012; 341 pages

Volume 100E*Personal Habits and Indoor Combustions*

2012; 575 pages

Volume 100F*Chemical Agents and Related Occupations*

2012; 599 pages

Volume 101*Some Chemicals Present in Industrial and consumer products, food and drinking-water*

2013 (published online: 2012); 586 pages

Volume 102*Non-ionizing Radiation, Part 2:
Radiofrequency Electromagnetic Fields*

2013; 460 pages

Supplement No. 1*Chemicals and Industrial Processes
Associated with Cancer in Humans (IARC
Monographs, Volumes 1 to 20)*

1979; 71 pages (out-of-print)

Supplement No. 2*Long-term and Short-term Screening Assays
for Carcinogens: A Critical Appraisal*

1980; 426 pages (out-of-print)

(updated as IARC Scientific Publications No. 83, 1986)

Supplement No. 3*Cross Index of Synonyms and Trade
Names in Volumes 1 to 26 of the IARC
Monographs*

1982; 199 pages (out-of-print)

Supplement No. 4*Chemicals, Industrial Processes and
Industries Associated with Cancer in
Humans (IARC Monographs, Volumes 1
to 29)*

1982; 292 pages (out-of-print)

Supplement No. 5*Cross Index of Synonyms and Trade
Names in Volumes 1 to 36 of the IARC
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1985; 259 pages (out-of-print)

Supplement No. 6*Genetic and Related Effects: An Updating of
Selected IARC Monographs from Volumes
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1987; 729 pages (out-of-print)

Supplement No. 7*Overall Evaluations of Carcinogenicity: An
Updating of IARC Monographs Volumes
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1987; 440 pages (out-of-print)

Supplement No. 8*Cross Index of Synonyms and Trade
Names in Volumes 1 to 46 of the IARC
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1990; 346 pages (out-of-print)

Cancer; IARC Press Release: IARC Classifies RF EMFs As Possibly
Carcinogenic to Humans, 2011

International Agency for Research on Cancer

PRESS RELEASE
N° 208

31 May 2011

IARC CLASSIFIES RADIOFREQUENCY ELECTROMAGNETIC FIELDS AS
POSSIBLY CARCINOGENIC TO HUMANS

Lyon, France, May 31, 2011 – The WHO/International Agency for Research on Cancer (IARC) has classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer¹, associated with wireless phone use.

Background

Over the last few years, there has been mounting concern about the possibility of adverse health effects resulting from exposure to radiofrequency electromagnetic fields, such as those emitted by wireless communication devices. The number of mobile phone subscriptions is estimated at 5 billion globally.

From May 24–31 2011, a Working Group of 31 scientists from 14 countries has been meeting at IARC in Lyon, France, to assess the potential carcinogenic hazards from exposure to radiofrequency electromagnetic fields. These assessments will be published as Volume 102 of the IARC *Monographs*, which will be the fifth volume in this series to focus on physical agents, after Volume 55 (Solar Radiation), Volume 75 and Volume 78 on ionizing radiation (X-rays, gamma-rays, neutrons, radio-nuclides), and Volume 80 on non-ionizing radiation (extremely low-frequency electromagnetic fields).

The IARC Monograph Working Group discussed the possibility that these exposures might induce long-term health effects, in particular an increased risk for cancer. This has relevance for public health, particularly for users of mobile phones, as the number of users is large and growing, particularly among young adults and children.

The IARC Monograph Working Group discussed and evaluated the available literature on the following exposure categories involving radiofrequency electromagnetic fields:

- occupational exposures to radar and to microwaves;
- environmental exposures associated with transmission of signals for radio, television and wireless telecommunication; and
- personal exposures associated with the use of wireless telephones.

International experts shared the complex task of tackling the exposure data, the studies of cancer in humans, the studies of cancer in experimental animals, and the mechanistic and other relevant data.

¹ 237 913 new cases of brain cancers (all types combined) occurred around the world in 2008 (gliomas represent 2/3 of these). Source: Globocan 2008

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Results

The evidence was reviewed critically, and overall evaluated as being *limited*² among users of wireless telephones for glioma and acoustic neuroma, and *inadequate*³ to draw conclusions for other types of cancers. The evidence from the occupational and environmental exposures mentioned above was similarly judged inadequate. The Working Group did not quantitate the risk; however, one study of past cell phone use (up to the year 2004), showed a 40% increased risk for gliomas in the highest category of heavy users (reported average: 30 minutes per day over a 10-year period).

Conclusions

Dr Jonathan Samet (University of Southern California, USA), overall Chairman of the Working Group, indicated that "the evidence, while still accumulating, is strong enough to support a conclusion and the 2B classification. The conclusion means that there could be some risk, and therefore we need to keep a close watch for a link between cell phones and cancer risk."

"Given the potential consequences for public health of this classification and findings," said IARC Director Christopher Wild, "it is important that additional research be conducted into the long-term, heavy use of mobile phones. Pending the availability of such information, it is important to take pragmatic measures to reduce exposure such as hands-free devices or texting."

The Working Group considered hundreds of scientific articles; the complete list will be published in the Monograph. It is noteworthy to mention that several recent in-press scientific articles⁴ resulting from the Interphone study were made available to the working group shortly before it was due to convene, reflecting their acceptance for publication at that time, and were included in the evaluation.

A concise report summarizing the main conclusions of the IARC Working Group and the evaluations of the carcinogenic hazard from radiofrequency electromagnetic fields (including the use of mobile telephones) will be published in The Lancet Oncology in its July 1 issue, and in a few days online.

² **'Limited evidence of carcinogenicity'**: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

³ **'Inadequate evidence of carcinogenicity'**: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

⁴ a. 'Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study' (the Interphone Study Group, in Cancer Epidemiology, *in press*)

b. 'Estimation of RF energy absorbed in the brain from mobile phones in the Interphone study' (Cardis et al., Occupational and Environmental Medicine, *in press*)

c. 'Risk of brain tumours in relation to estimated RF dose from mobile phones – results from five Interphone countries' (Cardis et al., Occupational and Environmental Medicine, *in press*)

d. 'Location of Gliomas in Relation to Mobile Telephone Use: A Case-Case and Case-Specular Analysis' (American Journal of Epidemiology, May 24, 2011. [Epub ahead of print]).

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POSSIBLY CARCINOGENIC TO HUMANS

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Link to the audio file posted shortly after the briefing:

http://terrance.who.int/mediacentre/audio/press_briefings/

About IARC

The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

If you wish your name to be removed from our press release e-mailing list, please write to com@iarc.fr.

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ABOUT THE IARC MONOGRAPHS

What are the IARC Monographs?

The IARC Monographs identify environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors. National health agencies use this information as scientific support for their actions to prevent exposure to potential carcinogens. Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer. The principles, procedures, and scientific criteria that guide the evaluations are described in the Preamble to the IARC Monographs.

Since 1971, more than 900 agents have been evaluated, of which approximately 400 have been identified as **carcinogenic or potentially carcinogenic** to humans.

Definitions

Group 1: The agent is **carcinogenic to humans**.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is **probably carcinogenic to humans**.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

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Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans*.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Definitions of evidence, as used in IARC Monographs for studies in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

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Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

NTP; Report of Partial Findings from the National Toxicology
Program Carcinogenesis Studies of Cell Phone Radiofrequency
Radiation in Hsd: Sprague Dawley® SD rats
(Whole Body Exposures); Draft 5-19-2016

Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposures)

Draft 5-19-2016

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Abstract

The US National Toxicology Program (NTP) has carried out extensive rodent toxicology and carcinogenesis studies of radiofrequency radiation (RFR) at frequencies and modulations used in the US telecommunications industry. This report presents partial findings from these studies. The occurrences of two tumor types in male Harlan Sprague Dawley rats exposed to RFR, malignant gliomas in the brain and schwannomas of the heart, were considered of particular interest, and are the subject of this report. The findings in this report were reviewed by expert peer reviewers selected by the NTP and National Institutes of Health (NIH). These reviews and responses to comments are included as appendices to this report, and revisions to the current document have incorporated and addressed these comments. Supplemental information in the form of 4 additional manuscripts has or will soon be submitted for publication. These manuscripts describe in detail the designs and performance of the RFR exposure system, the dosimetry of RFR exposures in rats and mice, the results to a series of pilot studies establishing the ability of the animals to thermoregulate during RFR exposures, and studies of DNA damage.

Capstick M, Kuster N, Kühn S, Berdinas-Torres V, Wilson P, Ladbury J, Koepke G, McCormick D, Gauger J, Melnick R. A radio frequency radiation reverberation chamber exposure system for rodents

Yijian G, Capstick M, McCormick D, Gauger J, Horn T, Wilson P, Melnick RL and Kuster N. Life time dosimetric assessment for mice and rats exposed to cell phone radiation

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- 2 Melnick R, Bucher JR, and McCormick D. Pilot studies of the National Toxicology Program's
- 3 cell phone radiofrequency radiation reverberation chamber exposure system
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- 6 GE, Tice RR, Bucher JR, Witt KL. Evaluation of the genotoxicity of cell phone radiofrequency
- 7 radiation in male and female rats and mice following subchronic exposure

Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposures)

Draft 5-19-2016

SUMMARY

The purpose of this communication is to report partial findings from a series of radiofrequency radiation (RFR) cancer studies in rats performed under the auspices of the U.S. National Toxicology Program (NTP).¹ This report contains peer-reviewed, neoplastic and hyperplastic findings only in the brain and heart of Hsd:Sprague Dawley® SD® (HSD) rats exposed to RFR starting *in utero* and continuing throughout their lifetimes. These studies found low incidences of malignant gliomas in the brain and schwannomas in the heart of male rats exposed to RFR of the two types [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] currently used in U.S. wireless networks. Potentially preneoplastic lesions were also observed in the brain and heart of male rats exposed to RFR.

The review of partial study data in this report has been prompted by several factors. Given the widespread global usage of mobile communications among users of all ages, even a very small increase in the incidence of disease resulting from exposure to RFR could have broad implications for public health. There is a high level of public and media interest regarding the safety of cell phone RFR and the specific results of these NTP studies.

¹ NTP is a federal, interagency program, headquartered at the National Institute of Environmental Health Sciences, part of the National Institutes of Health, whose goal is to safeguard the public by identifying substances in the environment that may affect human health. For more information about NTP and its programs, visit <http://ntp.niehs.nih.gov>

Lastly, the tumors in the brain and heart observed at low incidence in male rats exposed to GSM- and CDMA-modulated cell phone RFR in this study are of a type similar to tumors observed in some epidemiology studies of cell phone use. These findings appear to support the International Agency for Research on Cancer (IARC) conclusions regarding the possible carcinogenic potential of RFR.²

It is important to note that this document reviews only the findings from the brain and heart and is not a complete report of all findings from the NTP's studies. Additional data from these studies in Hsd:Sprague Dawley[®] SD[®] (Harlan) rats and similar studies conducted in B6C3F₁/N mice are currently under evaluation and will be reported together with the current findings in two forthcoming NTP Technical Reports.

STUDY RATIONALE

Cell phones and other commonly used wireless communication devices transmit information via non-ionizing radiofrequency radiation (RFR). In 2013, IARC classified RFR as a *possible human carcinogen* based on “limited evidence” of an association between exposure to RFR from heavy wireless phone use and glioma and acoustic neuroma (vestibular schwannoma) in human epidemiology studies, and “limited evidence” for the carcinogenicity of RFR in experimental animals. While ionizing radiation is a well-accepted human carcinogen, theoretical arguments have been raised against the possibility that non-ionizing radiation could induce tumors (discussed in IARC, 2013). Given the extremely large number of people who use wireless

² IARC (International Agency for Research on Cancer). 2013. Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields. IARC Monogr Eval Carcinog Risk Hum 102. Available: <http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf> [accessed 26 May 2016].

communication devices, even a very small increase in the incidence of disease resulting from exposure to the RFR generated by those devices could have broad implications for public health.

DESCRIPTION OF THE NTP CELL PHONE RFR PROGRAM

RFR emitted by wireless communication devices, especially cell phones, was nominated to the NTP for toxicology and carcinogenicity testing by the U.S. Food and Drug Administration (FDA). After careful and extensive evaluation of the published literature and experimental efforts already underway at that time, the NTP concluded that additional studies were warranted to more clearly define any potential health hazard to the U.S. population. Due to the technical complexity of such studies, NTP staff worked closely with RFR experts from the National Institute of Standards and Technology (NIST). With support from NTP, engineers at NIST evaluated various types of RFR exposure systems and demonstrated the feasibility of using a specially designed exposure system (reverberation chambers), which resolved the inherent limitations identified in existing systems.

In general, NTP chronic toxicity/carcinogenicity studies expose laboratory rodents to a test article for up to 2 years and are designed to determine the potential for the agent tested to be hazardous and/or carcinogenic to humans.³ For cell phone RFR, a program of study was designed to evaluate potential, long-term health effects of whole-body exposures. These studies were conducted in three phases: (1) a series of pilot studies to establish field strengths that do not raise body temperature, (2) 28-day toxicology studies in rodents exposed to various low-level field strengths, and (3) chronic toxicology and carcinogenicity studies. The studies were carried out under contract at IIT Research Institute (IITRI) in Chicago, IL following Good Laboratory

³ Specifications for the Conduct of NTP Studies, http://ntp.niehs.nih.gov/ntp/test_info/finalntp_toxcarspecsjan2011.pdf

Practices (GLP). These studies were conducted in rats and mice using a reverberation chamber exposure system with two signal modulations [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] at two frequencies (900 MHz for rats and 1900 MHz for mice), the modulations and frequency bands that are primarily used in the United States.

STUDY DESIGN

Hsd:Sprague Dawley[®] SD[®] (Harlan) rats were housed in custom-designed reverberation chambers and exposed to cell phone RFR. Experimentally generated 900 MHz RF fields with either GSM or CDMA modulation were continuously monitored in real-time during all exposure periods via RF sensors located in each exposure chamber that recorded RF field strength (V/m). Animal exposure levels are reported as whole-body specific absorption rate (SAR), a biological measure of exposure based on the deposition of RF energy into an absorbing organism or tissue. SAR is defined as the energy (watts) absorbed per mass of tissue (kilograms). Rats were exposed to GSM- or CDMA-modulated RFR at 900 MHz with whole-body SAR exposures of 0, 1.5, 3, or 6 W/kg. RFR field strengths were frequently adjusted based on changes in body weight to maintain desired SAR levels.

Exposures to RFR were initiated *in utero* beginning with the exposure of pregnant dams (approximately 11-14 weeks of age) on Gestation Day (GD) 5 and continuing throughout gestation. After birth, dams and pups were exposed in the same cage through weaning on postnatal day (PND) 21, at which point the dams were removed and exposure of 90 pups per sex per group was continued for up to 106 weeks. Pups remained group-housed from PND 21 until they were individually housed on PND 35. Control and treatment groups were populated with no

more than 3 pups per sex per litter. All RF exposures were conducted over a period of approximately 18 hours using a continuous cycle of 10 minutes on (exposed) and 10 minutes off (not exposed), for a total daily exposure time of approximately 9 hours a day, 7 days/week. A single, common group of unexposed animals of each sex served as controls for both RFR modulations. These control rats were housed in identical reverberation chambers with no RF signal generation. Each chamber was maintained on a 12-hour light/dark cycle, within a temperature range of $72 \pm 3^{\circ}\text{F}$, a humidity range of $50 \pm 15\%$, and with at least 10 air changes per hour. Throughout the studies, all animals were provided *ad libitum* access to feed and water.

RESULTS

In pregnant rats exposed to 900 MHz GSM- or CDMA-modulated RFR, no exposure-related effects were observed on the percent of dams littering, litter size, or sex distribution of pups. Small, exposure-level-dependent reductions (up to 7%) in body weights compared to controls were observed throughout gestation and lactation in dams exposed to GSM- or CDMA-modulated RFR. In the offspring, litter weights tended to be lower (up to 9%) in GSM and CDMA RFR-exposed groups compared to controls. Early in the lactation phase, body weights of male and female pups were lower in the GSM-modulated (8%) and CDMA-modulated (15%) RFR groups at 6 W/kg compared to controls. These weight differences in the offspring for both GSM and CDMA exposures tended to lessen (6% and 10%, respectively) as lactation progressed. Throughout the remainder of the chronic study, no RFR exposure-related effects on body weights were observed in male and female rats exposed to RFR, regardless of modulation.

At the end of the 2-year study, survival was lower in the control group of males than in all groups of male rats exposed to GSM-modulated RFR. Survival was also slightly lower in control females than in females exposed to 1.5 or 6 W/kg GSM-modulated RFR. In rats exposed to CDMA-modulated RFR, survival was higher in all groups of exposed males and in the 6 W/kg females compared to controls.

Brain

A low incidence of malignant gliomas and glial cell hyperplasia was observed in all groups of male rats exposed to GSM-modulated RFR (Table 1). In males exposed to CDMA-modulated RFR, a low incidence of malignant gliomas occurred in rats exposed to 6 W/kg (Table 1). Glial cell hyperplasia was also observed in the 1.5 W/kg and 6 W/kg CDMA-modulated exposure groups. No malignant gliomas or glial cell hyperplasias were observed in controls. There was not a statistically significant difference between the incidences of lesions in exposed male rats compared to control males for any of the GSM- or CDMA-modulated RFR groups. However, there was a statistically significant positive trend in the incidence of malignant glioma ($p < 0.05$) for CDMA-modulated RFR exposures.

Table 1. Incidence of brain lesions in male Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§]

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Malignant glioma ^{†‡}	0*	3 (3.3%)	3 (3.3%)	2 (2.2%)	0	0	3 (3.3%)
Glial cell hyperplasia	0	2 (2.2%)	3 (3.3%)	1 (1.1%)	2 (2.2%)	0	2 (2.2%)

[§] Data presented as number of animals per group with lesions (percentage of animals per group with lesions).

* Significant SAR-dependent trend for CDMA exposures by poly-6 ($p < 0.05$). See appendix B

[†] Poly-6 survival adjusted rates for malignant gliomas were 0/53.48 in controls; GSM: 3/67.96 (4.4%), 3/72.10 (4.2%), and 2/72.65 (2.8%) in the 1.5, 3, and 6 W/kg groups, respectively; CDMA: 0/65.94, 0/73.08, and 3/57.49 (5.2%) for the 1.5, 3, and 6 W/kg groups, respectively.

[‡] Historical control incidence in NTP studies: 11/550 (2.0%), range 0-8%

In females exposed to GSM-modulated RFR, a malignant glioma was observed in a single rat exposed to 6 W/kg, and glial cell hyperplasia was observed in a single rat exposed to 3 W/kg (Table 2). In females exposed to CDMA-modulated RFR, malignant gliomas were observed in two rats exposed to 1.5 W/kg. Glial cell hyperplasia was observed in one female in each of the CDMA-modulation exposure groups (1.5, 3, and 6 W/kg). There was no glial cell hyperplasia or malignant glioma observed in any of the control females. Detailed descriptions of the malignant gliomas and glial cell hyperplasias are presented in Appendix C.

Table 2. Incidence of brain lesions in female Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§]

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Malignant glioma [‡]	0	0	0	1 (1.1%)	2 (2.2%)	0	0
Glial cell hyperplasia	0	0	1 (1.1%)	0	1 (1.1%)	1 (1.1%)	1 (1.1%)

[§] Data presented as number of animals per group with lesions (percentage of animals per group with lesions).

[‡] Historical control incidence in NTP studies: 1/540 (0.18%), range 0-2%

Heart

Cardiac schwannomas were observed in male rats in all exposed groups of both GSM- and CDMA-modulated RFR, while none were observed in controls (Table 3). For both modulations (GSM and CDMA), there was a significant positive trend in the incidence of schwannomas of the heart with respect to exposure SAR. Additionally, the incidence of schwannomas in the 6 W/kg males was significantly higher in CDMA-modulated RFR-exposed males compared to controls. The incidence of schwannomas in the 6 W/kg GSM-modulated RFR-exposed males was higher, but not statistically significant ($p = 0.052$) compared to controls. Schwann cell

hyperplasia of the heart was also observed in three males exposed to 6 W/kg CDMA-modulated RFR. In the GSM-modulation exposure groups, a single incidence of Schwann cell hyperplasia was observed in a 1.5 W/kg male.

Table 3. Incidence of heart lesions in male Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated cell phone RFR[§]

	Control	GSM			CDMA		
	0	1.5	3	6	1.5	3	6
	W/kg	W/kg	W/kg	W/kg	W/kg	W/kg	W/kg
Number examined	90	90	90	90	90	90	90
Schwannoma ^{†‡}	0*	2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6 (6.6%)**
Schwann cell hyperplasia	0	1 (1.1%)	0	2 (2.2%)	0	0	3 (3.3%)

[§] Data presented as number of animals per group with lesions (percentage of animals per group with lesions).

* Significant SAR level-dependent trend for GSM and CDMA by poly-3 ($p < 0.05$). See appendix B

** Significantly higher than controls by poly-3 ($p < 0.05$)

[†] Poly-3 survival adjusted rates for schwannomas were 0/65.47 in controls; GSM: 2/74.87 (2.7%), 1/77.89 (1.3%), and 5/78.48 (6.4%) in the 1.5, 3, and 6 W/kg groups, respectively; CDMA: 2/74.05 (2.7%), 3/78.67 (3.8%), and 6/67.94 (8.8%) for the 1.5, 3, and 6 W/kg groups, respectively.

[‡] Historical control incidence in NTP studies: 9/699 (1.3%) range 0-6%

In females, schwannomas of the heart were also observed at 3 W/kg GSM-modulated RFR and 1.5 and 6 W/kg CDMA-modulated RFR. Schwann cell hyperplasia was observed in one female in each of the CDMA-modulation exposure groups (1.5, 3, and 6 W/kg).

Table 4. Incidence of heart lesions in female Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated cell phone RFR[§]

	Control	GSM			CDMA		
	0	1.5	3	6	1.5	3	6
	W/kg	W/kg	W/kg	W/kg	W/kg	W/kg	W/kg
Number examined	90	90	90	90	90	90	90
Schwannoma [‡]	0	0	2 (2.2%)	0	2 (2.2%)	0	2 (2.2%)
Schwann cell hyperplasia	0	0	0	0	1 (1.1%)	1 (1.1%)	1 (1.1%)

[§] Data presented as number of animals per group with tumors (percentage of animals per group with tumors).

[‡] Historical control incidence in NTP studies: 4/699 (0.6%), range 0-4%

Schwann cells are present in the peripheral nervous system and are distributed throughout the whole body, not just in the heart. Therefore, organs other than the heart were examined for schwannomas and Schwann cell hyperplasia. Several occurrences of schwannomas were observed in the head, neck, and other sites throughout the body of control and GSM and CDMA RFR-exposed male rats. In contrast to the significant increase in the incidence of schwannomas in the heart of exposed males, the incidence of schwannomas observed in other tissue sites of exposed males (GSM and CDMA modulations) was not significantly different than in controls (Table 5). Additionally, Schwann cell hyperplasia was not observed in any tissues other than the heart. The combined incidence of schwannomas from all sites was generally higher in GSM- and CDMA-modulated RFR exposed males, but not significantly different than in controls. The Schwann cell response to RFR appears to be specific to the heart of male rats.

Table 5. Incidence of schwannomas in male Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§]

	Control	GSM				CDMA	
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Heart [‡]	0 [*]	2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6 (6.6%) ^{**}
Other sites [†]	3 (3.3%)	1 (1.1%)	4 (4.4%)	2 (2.2%)	2 (2.2%)	1 (1.1%)	1 (1.1%)
All sites (total)	3 (3.3%)	3 (3.3%)	5 (5.5%)	7 (7.7%)	4 (4.4%)	4 (4.4%)	7 (7.7%)

[§] Data presented as number of animals per group with tumors (percentage of animals per group with tumors).

^{*} Significant SAR level-dependent trend for GSM and CDMA, poly 3 test ($p < 0.05$)

^{**} Significantly higher than controls, poly-3 test ($p < 0.05$)

[‡] Historical control incidence in NTP studies: 9/699 (1.3%), range 0-6%

[†] Mediastinum, thymus, and fat

In female rats, there was no statistically significant or apparent exposure-related effect on the incidence of schwannomas in the heart or the combined incidence in the heart or other sites (Table 6).

Table 6. Incidence of schwannomas in female Hsd:Sprague Dawley[®] SD[®] (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§]

Schwannoma site	Control	GSM				CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg		1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90		90	90	90
Heart [‡]	0	0	2 (2.2%)	0		2 (2.2%)	0	2 (2.2%)
Other sites [†]	4 (4.4%)	1 (1.1%)	3 (3.3%)	1 (1.1%)		0	2 (2.2%)	2 (2.2%)
All sites (total)	4 (4.4%)	1 (1.1%)	5 (5.5%)	2 (2.2%)		2 (2.2%)	2 (2.2%)	4 (4.4%)

[§] Data presented as number of animals per group with tumors (percentage of animals per group with tumors).

[‡] Historical control incidence in NTP studies: 4/699 (0.6%), range 0-4%

[†] Ovary, uterus, vagina, thymus, abdomen, and clitoral gland

DISCUSSION

The two tumor types, which are the focus of this report, are malignant gliomas of the brain and schwannomas of the heart. Glial cells are a collection of specialized, non-neuronal, support cells whose functions include maintenance of homeostasis, formation of myelin, and providing support and protection for neurons of the peripheral nervous system (PNS) and the central nervous system (CNS). In the CNS, glial cells include astrocytes, oligodendrocytes, microglial cells, and ependymal cells. Schwann cells are classified as glial cells of the PNS. In the PNS, Schwann cells produce myelin and are analogous to oligodendrocytes of the CNS. Generally, glial neoplasms in the rat are aggressive, poorly differentiated, and usually classified as malignant.

In the heart, exposure to GSM or CDMA modulations of RFR in male rats resulted in a statistically significant, positive trend in the incidence of schwannomas. There was also a statistically significant, pairwise increase at the highest CDMA exposure level tested compared to controls. Schwann cell hyperplasias also occurred at the highest exposure level of CDMA-

modulated RFR. Schwann cell hyperplasia in the heart may progress to cardiac schwannomas. No Schwann cell hyperplasias or schwannomas of the heart were observed in the single, common control group of male rats. The historical control rate of schwannomas of the heart in male Harlan Sprague Dawley rats is 1.30% (7/539) and ranges from 0-6% for individual NTP studies (Table D2, Appendix D). The 5.5-6.6% observed in the 6 W/kg GSM- and CDMA-modulated RFR groups exceeds the historical incidence, and approaches or exceeds the highest rate observed in a single study (6%). The increase in the incidence of schwannomas in the heart of male rats in this study is likely the result of whole-body exposures to GSM- or CDMA-modulated RFR.

In the brain, there was a significant, positive trend in the incidences of malignant gliomas in males exposed to CDMA-modulated RFR, and a low incidence was observed in males at all exposure levels of GSM-modulated RFR that was not statistically different than in control males. Glial cell hyperplasia, a preneoplastic lesion distinctly different from gliosis, was also observed at low incidences in rats exposed to either GSM or CDMA modulation. Glial cell hyperplasia may progress to malignant glioma. Neither of these lesions was observed in the control group of male rats. Although not observed in the current control group, malignant gliomas have been observed in control male Harlan Sprague Dawley rats from other completed NTP studies. Currently in males, the historical control rate of malignant glioma for those studies is 2.0% (11/550) and ranges from 0-8% for individual studies (Table D1, Appendix D). The 2.2-3.3% observed in all of the GSM-modulation groups and in the 6 W/kg CDMA-modulated group only slightly exceeds the mean historical control rate and falls within the observed range.

The survival of the control group of male rats in the current study (28%) was relatively low compared to other recent NTP studies in Hsd:Sprague Dawley[®] SD[®] (Harlan) rats (average 47%, range 24-72%). If malignant gliomas or schwannomas are late-developing tumors, the absence of these lesions in control males in the current study could conceivably be related to the shorter longevity of control rats in this study. Appendix E lists the time on study for each animal with a malignant glioma or heart schwannoma. Most of the gliomas were observed in animals that died late in the study, or at the terminal sacrifice. However, a relatively high number of the heart schwannomas in exposed groups were observed by 90 weeks into the study, a time when approximately 60 of the 90 control male rats remained alive and at risk for developing a tumor.

CONCLUSIONS

Under the conditions of these 2-year studies, the hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR. There is higher confidence in the association between RFR exposure and the neoplastic lesions in the heart than in the brain. No biologically significant effects were observed in the brain or heart of female rats regardless of modulation.

NEXT STEPS

The results reported here are limited to select findings of concern in the brain and heart and do not represent a complete reporting of all findings from these studies of cell phone RFR. The complete results for all NTP studies on the toxicity and carcinogenicity of GSM and CDMA-modulated RFR are currently being reviewed and evaluated according to the established NTP process and will be reported together with the current findings in two forthcoming NTP

1 Technical Reports. Given the large scale and scope of these studies, completion of this process is
2 anticipated by fall 2017, and the draft NTP Technical Reports are expected to be available for
3 peer review and public comment by the end of 2017. We anticipate that the results from a series
4 of initial studies investigating the tolerance to various power levels of RFR, including
5 measurements of body temperatures in both sexes of young and old rats and mice and in
6 pregnant female rats, will be published in the peer-reviewed literature later in 2016.

APPENDIX A – CONTRIBUTORS

NTP CONTRIBUTORS

Participated in the evaluation and interpretation of results and the reporting of findings.

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APPENDIX B – STATISTICAL ANALYSIS

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of lesion incidence at a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the k th power. This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter, k , for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). A further advantage of the Poly-k method is that it does not require lesion lethality assumptions.

Unless otherwise specified, the NTP uses a value of $k=3$ in the analysis of site-specific lesions (Portier et al., 1986). Bailer and Portier (1988) showed that the Poly-3 test gives valid results if the true value of k is anywhere in the range from 1 to 5. In addition, Portier et al. (1986) modeled a collection of relatively common tumors observed in control animals from two-year NTP rodent carcinogenicity studies, showing that the Weibull distribution with values of k ranging between 1 and 5 was a reasonable fit to tumor incidence in most cases. In cases of early tumor onset or late tumor onset, however, $k=3$ may not be the optimal choice. Tumors with early onset would require a value of k much less than 3, while tumors with late onset would require a value of k much greater than 3. In the current studies, malignant brain gliomas occurred only in animals surviving more than 88% of the length of the study. For these brain tumors, a Weibull distribution with $k=6$ is a better fit to survival time than with $k=3$ (Portier, 1986). Malignant schwannomas of the heart occurred in animals surviving at least 65% of the length of the study; a Weibull distribution with $k=3$ adequately fits these heart tumor incidences. Therefore, poly-6 tests were used for analyses of brain tumors and poly-3 tests were used for schwannomas.

Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-k statistic as recommended by Bieler and Williams (1993) and a continuity correction modified from Thomas et al. (1977) was applied.

Tests of significance for tumors and nonneoplastic lesions included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-k tests were used in the analysis of lesion incidence, and reported P values are one sided.

Body weights and litter weights were compared to the control group using analysis of variance and Dunnett's test (1955). The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). Statistical analyses for possible exposure-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify exposure-related trends. Survival analysis p-values are two-sided.

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APPENDIX C – PATHOLOGY

Pathology data presented in this report on cell phone RFR were subjected to a rigorous peer review process. The primary goal of the NTP peer-review process is to reach consensus agreement on treatment-related findings, confirm the diagnosis of all neoplasms, and confirm any unusual lesions. At study termination, a complete necropsy and histopathology evaluation was conducted on every animal. The initial pathology examination was performed by a veterinary pathologist, who recorded all neoplastic and nonneoplastic lesions. This examination identified several potential treatment-related lesions in target organs of concern (brain and heart), which were chosen for immediate review.¹ The initial findings of glial cell tumors and hyperplasias in the brain and schwannomas, Schwann cell hyperplasia, and schwannomas from all sites were subjected to an expedited, multilevel NTP pathology peer-review process. The data were locked² prior to receipt of the finalized, study-laboratory reports to ensure that the raw data did not change during the review.

The pathology peer review consisted of a quality assessment (QA) review of all slides with tissues from the central nervous system (7 sections of brain and 3 sections of spinal cord), trigeminal nerve and ganglion, and heart. Additionally, the schwannomas of the head and neck region were reviewed. The QA review of the central nervous system and head and neck schwannomas was performed by Dr. Margarita Gruebbel of Experimental Pathology Laboratories, Inc. (EPL), and the QA review of the hearts and trigeminal nerves and ganglia was performed by Dr. Cynthia Shackelford, EPL.

The QA review pathologists then met with Dr. Mark Cesta, NTP pathologist for these studies, and Dr. David Malarkey, head of the NTP Pathology Group, to review lesions and select slides for the Pathology Working Group (PWG) reviews. All PWG reviews were conducted blinded with respect to treatment group and only identified the test articles as “test agent A” or “test

¹ Pathology peer review of remaining lesions from the cell phone RFR studies continues and is not addressed in this report.

² Locking data refers to restricting access to the computer database so the data for a particular study cannot be changed.

agent B". Due to the large number of slides for review, the PWG was held in three separate sessions:

- January 29, 2016, for review of glial lesions in the brain and Schwann cell lesions in the heart
- February 11, 2016, for review of schwannomas of the head and neck
- February 12, 2016, for review of granular cell lesions of the brain

The reviewing PWG pathologists largely agreed on the diagnostic criteria for the lesions and on the diagnoses of schwannomas in the head and neck, and granular cell lesions in the brain.

However, there was much discussion on the criteria for differentiating glial cell hyperplasia from malignant glioma and Schwann cell hyperplasia from schwannoma. The lack of PWG agreement on definitive criteria for the glial cell and Schwann cell lesions, and the requirement for a high level of confidence in the diagnoses prompted NTP to convene two additional PWGs (organized and conducted by the NTP pathologist, Dr. Mark Cesta) with selected experts in the organ under review. These second level PWG reviews were also conducted as noted above and held in two separate sessions:

- February 25, 2016, for review of glial lesions in the brain
- March 3, 2016, for review of cardiac schwannomas, schwannomas in other organs (except the head and neck), and right ventricular degeneration

In both PWGs, the participants came to consensus on the diagnoses of the lesions and the criteria used for those diagnoses. Participants of the individual PWGs are listed below.

Table C-1. NTP Pathology Working Group (PWG) Attendees

PWG member	Affiliation
<i>January 29, 2016 - Evaluated glial lesions in the brain and Schwann cell lesions in the heart</i>	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
G.P. Flake, M.D.	National Institute of Environmental Health Sciences
R.H. Garman, D.V.M.	Consultants in Veterinary Pathology, Inc. Monroeville, PA
M.M. Gruebbel, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
R.A. Herbert, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
J.S. Hoane, D.V.M.	Charles River Laboratories, Inc. Durham, NC (contract study pathologist)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System
R. Kovi, BVSc, MVSc, Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
R.A. Miller, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
J.P. Morrison, D.V.M.	Charles River Laboratories, Inc. Durham, NC

PWG member	Affiliation
A.R. Pandiri, BVSc & AH, Ph.D.	National Institute of Environmental Health Sciences
C.C. Shackelford, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
J.A. Swenberg, D.V.M., Ph.D.	University of North Carolina – Chapel Hill, NC
G. Willson, BVMS, Dip RC Path, FRC Path, MRCVS	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
<i>February 11, 2016 - Evaluated schwannomas of the head and neck</i>	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
G.P. Flake, M.D.	National Institute of Environmental Health Sciences
M.M. Gruebbel, D.V.M., Ph.D.,	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System RTP, NC
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
A.R. Pandiri, BVSc & AH, Ph.D.	National Institute of Environmental Health Sciences
R.R. Maronpot, D.V.M.	Experimental Pathology Laboratories, Inc. RTP, NC
<i>February 12, 2016 - Evaluated granular cell lesions of the brain</i>	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
M.M. Gruebbel, D.V.M., Ph.D.,	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
J.S. Hoane, D.V.M.	Charles River Laboratories, Inc. Durham, NC (contract study pathologist)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System RTP, NC
A.R. Pandiri, BVSc. & AH, Ph.D.	National Institute of Environmental Health Sciences
R.R. Moore, D.V.M.	Integrated Laboratory System RTP, NC
<i>February 25, 2016 - Evaluated glial lesions in the brain</i>	
D. Bigner, M.D., Ph.D.	Duke University Durham, NC
B. Bolon, D.V.M., MS, Ph.D.	GEMpath, Inc. Longmont, CO
V. Chen, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (observer)
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (PWG coordinator, NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences (observer)
G.P. Flake, M.D.	National Institute of Environmental Health Sciences (observer)
J.S. Hardisty, D.V.M.	Experimental Pathology Laboratories, Inc. RTP, NC
R.A. Herbert, D.V.M., Ph.D.,	National Institute of Environmental Health Sciences (observer)
R. Kovi, BVSc, MVSc, Ph.D.	Experimental Pathology Laboratories, Inc. (observer)
P.B. Little, D.V.M.	Experimental Pathology Laboratories, Inc.
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
J.P. Morrison, D.V.M., Ph.D.	Charles River Laboratories, Inc.
A. Sharma, BVSc, MVSc, MS, Ph.D.	Covance
<i>March 3, 2016 - Evaluated heart lesions, and schwannomas in other organs (except head and neck)</i>	
B. Berridge, D.V.M., Ph.D.	GlaxoSmithKline RTP, NC
M.C. Boyle, D.V.M., Ph.D.	Amgen Thousand Oaks, CA
V. Chen, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (observer)
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (PWG coordinator, NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences (observer)
M. Elwell, D.V.M., Ph.D.	Covance Chantilly, VA

PWG member	Affiliation
J.R. Hailey, D.V.M.	Covance Chantilly, VA
M. Novilla, D.V.M., MS, Ph.D.	SNBL Everett, WA

LESION DESCRIPTIONS

Brain

Malignant gliomas were infiltrative lesions, usually of modest size, with indistinct tumor margins. The neoplastic cells were typically very densely packed with more cells than neuropil. The cells were typically small and had round to oval, hyperchromatic nuclei. Mitoses were infrequent. In some of the neoplasms, invasion of the meninges, areas of necrosis surrounded by palisading neoplastic cells, cuffing of blood vessels, and neuronal satellitosis were observed. The malignant gliomas did not appear to arise from any specific anatomic subsite of the brain.

Glial cell hyperplasia consisted of small, proliferative, and poorly demarcated foci of poorly differentiated glial cells that accumulated and invaded into the surrounding parenchyma. In some cases, there was a small amount of perivascular cuffing. The hyperplastic cells appeared morphologically identical to those in the gliomas but were typically less dense with more neuropil than glial cells. There were no necrotic or degenerative elements present, so there was no evidence that the increased number of glial cells was a reaction to brain injury.

Heart

The intracardiac schwannomas were either endocardial or myocardial (intramural). The endocardial schwannomas lined the ventricles and atria and invaded into the myocardium. Two morphologic cell types were observed, but indistinct cell margins and eosinophilic cytoplasm were common to both types. Groups of cells with widely spaced small, round nuclei and moderate amounts of cytoplasm were interspersed among bands or sheets of parallel, elongated cells with thin, spindle-shaped, hyperchromatic nuclei. The myocardial schwannomas were typically less densely cellular and infiltrated amid, sometimes replacing, the cardiomyocytes. The cell types described for the endocardial neoplasms were both present, but in fewer numbers. In both subtypes of schwannomas, there was a minimal amount of cellular pleomorphism. In some larger neoplasms, Antoni type A and B patterns were present.

- 1 The Schwann cell hyperplasias were similar in appearance to the schwannomas, but were smaller
- 2 and had less pleomorphism of the cells. In the case of the endocardial Schwann cell hyperplasia,
- 3 there was no invasion of the myocardium.

APPENDIX D – HISTORICAL CONTROLS

Table D1. Incidence of astrocytoma, glioma, and/or oligodendroglioma in brains of male Harlan Sprague Dawley rats in NTP studies

Chemical	First dose	N	Control incidence
Dibutylphthalate	8/30/2010	49	4%
2-Hydroxy-4-methoxybenzophenone	11/8/2010	50	0%
p-Chloro-a,a,a-trifluorotoluene	1/17/2011	50	4%
Di-(2-ethylhexyl)phthalate	2/17/2011	50	8%
Di-(2-ethylhexyl)phthalate (perinatal)	6/27/2011	50	0%
Tris (chloroisopropyl) phosphate	12/12/2011	50	0%
Sodium tungstate	12/23/2011	50	4%
Resveratrol	5/7/2012	50	0%
Black cohosh	7/2/2012	50	2%
Radiofrequency radiation (GSM/CDMA)	9/16/2012	90	0%

Historical control rate: 11/550 (2.0%)

Table D2. Incidence of schwannoma in the heart of male Harlan Sprague Dawley rats in NTP studies

Chemical	First dose	N	Control incidence
Indole-3-carbinol	3/14/2007	50	2%
Perfluorooctanoic acid	6/19/2009	50	0%
Dietary zinc	9/3/2009	50	0%
Dibutylphthalate	8/30/2010	49	4%
2-Hydroxy-4-methoxybenzophenone	11/8/2010	50	2%
p-Chloro-a,a,a-trifluorotoluene	1/17/2011	50	0%
Di-(2-ethylhexyl)phthalate	2/17/2011	50	6%
Di-(2-ethylhexyl)phthalate (perinatal)	6/27/2011	50	4%
Tris (chloroisopropyl) phosphate	12/12/2011	50	0%
Sodium tungstate	12/23/2011	50	0%
Resveratrol	5/7/2012	50	0%
Black Cohosh	7/2/2012	50	0%
Radiofrequency radiation (GSM/CDMA)	9/16/2012	90	0%

Historical control rate: 9/699 (1.30%)

APPENDIX E – TIME ON STUDY TO APPEARANCE OF TUMORS

Malignant Glioma

SAR (W/kg)	Animal ID number	Time on study (weeks)
GSM-modulated exposed males		
1.5	717	105
	735	102
	786	104
3.0	924	101
	943	105
	1014	93
6.0	1135	104
	1137	102
CDMA-modulated exposed males		
6.0	1795	105
	1799	104
	1852	105
GSM-modulated exposed females		
6.0	1246	96
CDMA-modulated exposed females		
1.5	1463	105
	1474	105

Time to Malignant Schwannoma in Heart

SAR (W/kg)	Animal ID number	Length of survival (weeks)
GSM-modulated exposed males		
1.5	758	104
	801	105
3.0	931	105
6.0	1149	83
	1155	105
	1187	104
	1206	104
	1230	91
CDMA-modulated exposed males		
1.5	1364	105
	1352	105
3.0	1559	92
	1617	105
	1622	104
6.0	1801	76
	1821	70
	1829	104
	1833	89
	1849	104
	1860	105
GSM-modulated exposed females		
3.0	1037	105
	1077	83
CDMA-modulated exposed females		
1.5	1461	106
	1480	93
6.0	1888	105
	1965	106

APPENDIX F – REVIEWER’S COMMENTS

National Toxicology Program

Peer Review Charge and Summary Comments

Purpose: To provide independent peer review of an initial draft of this partial report. The peer reviewers were blind to the test agents under study. Introductory materials on RFR and details of the methods dealing with the field generation and animal housing were redacted from the version sent to the reviewers. The reviewers were provided a study data package, also blinded to test agents, containing basic in life study information such as body weight and survival curves and information concerning the generation of pups from the *in utero* exposures.

Report Title: Draft Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Test Articles A and B (and associated Study Data Package)

Reviewers’ Names:

David Dorman, D.V.M., Ph.D., North Carolina State University
 Russell Cattley, D.V.M., Ph.D., Auburn University
 Michael Pino, D.V.M., Ph.D., Pathology consultant

Charge: To peer review the draft report and comment on whether the scientific evidence supports NTP’s conclusion(s) for the study findings.

1. Scientific criticisms:

- a. Please comment on whether the information presented in the draft report, including presentation of data in any tables, is clearly and objectively presented. Please suggest any improvements.

All three reviewers found the results to be clearly and objectively presented, although there were suggestions to provide historical control information for brain and heart lesions for female Harlan Sprague Dawley rats, clarify statements about the specific statistical tests used and the presence or lack of statistical significance of the brain

gliomas in the Results, and expand the conclusions statements to clarify the basis for the conclusions.

- b. Please comment on whether NTP’s scientific interpretations of the data are objective and reasonable. Please explain why or why not.

The reviewers stated that the NTP had performed an adequate and objective peer review of the pathology data, and the statistical approaches used were consistent with other NTP studies. The methods were described as objective and reasonable. The interpretations of the data, including the limitations, were also reasonable and objective. One reviewer found the data on schwannomas of the heart to be more compelling with respect to an association with treatment than the brain gliomas. This reviewer summarized the findings as:

“In the heart the evidence for a carcinogenic effect can be based on 1) the presence of the tumors in all six of the test article groups versus none in the controls 2) the statistically significant trend for schwannomas with both compounds and the statistically significant increase in incidence in the 4X (top) dose for test article B; 3) the fact that the incidence of the tumors in both 4X dose groups approaches or exceeds the high end of the historical control range; and 4) the tumors in the 4X group of test article B are accompanied by a higher incidence of Schwann cell hyperplasia. Using the NTP’s guide for levels of evidence for carcinogenic activity, I would consider the heart schwannomas as ‘Some Evidence’ of carcinogenic activity.

The proliferative lesions in the brain are more difficult to interpret because 1) their low incidence that was well within the historical control range, 2) lack of clear dose response; and 3) lack of statistical significance (except for the significant exposure-dependent trend for test article B. . . . However, the presence of malignant gliomas and/or foci of glial cell hyperplasia in 5 of 6 test article groups for both sexes vs none in controls of either sex is suggestive of a test

article effect. . . I would consider the malignant gliomas as ‘Equivocal Evidence’ of carcinogenic activity.”

2. Please identify any Information that should be added or deleted:

One reviewer suggested that more information be given on the time when tumors were observed (e.g., at terminal necropsy, or early in the study) to help assess the possible impact of the decreased survival times in the control animals on tumor incidence. This reviewer also suggested a discussion of how the survival of control male rats in this study compared to the historical control data. There was also concern that the diagnostic criteria developed by the PWG and used in the current study would impact the historical control incidence rates reported in Table D.

3. The scientific evidence supports NTP’s conclusion(s) for the study findings:

The NTP’s overall draft conclusion was as follows: “Under the conditions of these studies, the observed hyperplastic lesions and neoplasms outlined in this partial report are considered likely the result of exposures to test article A and test article B. The findings in the heart were statistically stronger than the findings in the brain.”

The reviewers had the option of agreeing, agreeing in principle, or disagreeing with the draft conclusions. All three reviewers agreed in principle, reiterating issues discussed above.

APPENDIX G – NIH REVIEWER’S COMMENTS

National Institutes of Health

Peer Review Charge and Reviewer’s Comments

Purpose: To provide independent peer review of the pathology diagnoses and statistical evaluation of the partial findings from NTP’s studies. Background materials included the draft NTP report, introductory materials on RFR, and details on the methods dealing with the field generation and statistical analyses references and guidance. The reviewers were provided a study data package, containing basic in life study information such as body weight and survival curves, information concerning the generation of pups from the *in utero* exposures, and raw pathology data.

Report Title: Draft Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Test Articles A and B (and associated Study Data Package)

Reviewers’ Names:

Diana C. Haines, D.V.M., Frederick National Laboratory
 Michael S. Lauer, M.D., Office of Extramural Research, NIH
 Maxwell P. Lee, Ph.D., Laboratory of Cancer Biology and Genetics, NCI,
 Aleksandra M. Michalowski, M.Sc., Ph.D., Laboratory of Cancer Biology and Genetics, NCI
 R. Mark Simpson, D.V.M., Ph.D., Laboratory of Cancer Biology and Genetics, NCI
 [Sixth reviewer's name and comments are withheld.]

Charge: To peer review the draft report, statistical analyses, and pathology data and comment on whether the scientific evidence supports NTP’s conclusion(s) for the study findings.

Reviewer’s comments and NTP responses to the comments are provided.

- Appendix G1: Reviewer’s comments
- Appendix G2: NTP’s responses to NIH reviewer’s comments

Reviewer: Diana C. Haines, D.V.M., Frederick National Laboratory

April 5, 2016

Dr. Tabak,

I've always relied on experts, not myself, for statistical analysis, and so do not feel qualified to address the statistical methods used. My training and experience has been in veterinary pathology, including QA review of NTP studies, and serving on PWGs, so will give my opinion on the pathology interpretation (biological significance rather than statistical significance).

Having perused the 3 RFR Draft Report and the raw data, all appears to be in order, including QA of the histopathology (technique) as well as PWG review (diagnosis). Looking at the data, I agree with the report's conclusion: *Under the conditions of these studies, the hyperplastic lesions and neoplasms observed in male rats are considered likely the result of exposures to GSM- an CDMA-modulated RFR. The findings in the heart were statistically stronger than the findings in the brain.* But note, it is "considered likely" not "definitely is".

There may be also several caveats relating to "under the conditions of these studies", including how well the conditions recapitulate actual human exposure: whole body exposure from in utero to old age; 18.5 hours/day (10 min on/10 min off, for total of 9hr actual exposure); and dose^A. I'm not physicist, so have to presume experts analyzed and accepted concept of the reverberation chamber, including "doses"^A as being relevant to human exposure.

^A Dosimetric Assessment paper: "As could be expected in a study following NTP protocols, the exposure levels for the rodents in this project exceed the limits for the wbSAR and psSAR defined in the IEEE Std C95.1-2005 safety standard for human exposure to mobile phone radiation. In the low dose exposure group the exposure level in the organs exceeds or is close to the localized SAR limit for the general public, except for a few low-water content tissues. More specifically, the psSAR over 1 g in the human head, is limited by the safety standards to <2W/kg, whereas, in the low dose rodents the SAR averaged over the whole brain is >2.4 W/kg for mice, and >1.3 W/kg for rats, hence similar to the limit. Furthermore, the psSAR and oSAR have larger uncertainty compared to the wbSAR. Deviations of the exposure level from the target dose, especially during the early exposure period, should be carefully evaluated in the interpretation of the final biological studies.

Results from the companion mouse study will hopefully add some insight.

Diana Copeland Haines, DVM

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Reviewer: Michael S. Lauer, M.D., Office of Extramural Research, NIH

Michael S Lauer, MD (OER)

Review of NTP paper: "Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation (Whole Body Exposures)"
March 20, 2016

Summary of findings:

This is a partial report, a report which is presumably part of a larger set of studies involving 2 species (mice and rats), 2 sexes (male, female), and multiple tissue types, all based on 90-week studies of two different types (GSM and CDMA) of cell phone radiofrequency radiation (RFR). In this partial report, we are given findings regarding brain gliomas and heart schwannomas in male and female Harlan Sprague Dawley rats which were exposed to control or 3 different levels (1.5, 3.0, 6.0) of two types (GSM and CDMA) of RFR. There were 90 rats in each group. Using the poly-3 test with the Bieler-Williams variance adjustment, the authors found a statistically significant increase in the rate of brain gliomas in males exposed to CDMA RFR. Using the poly-6 test, the authors found a statistically significant increase in the rates of heart schwannomas in males exposed to GSM and CDMA. There were no statistically significant differences in rates of gliomas or schwannomas in females; also there was no statistically significant increase in rates of gliomas in males exposed to GSM RFR.

Comments:

- 1) Why aren't we being told, at least at a high level, of the results of other experiments (i.e., male and female mice, tissues other than heart and brain, tumors other than glioma and schwannoma)? Given the multiple comparisons inherent in this kind of work (see pages 27-30 and Table 13 of the FDA guidance document), there is a high risk of false positive discoveries. In the absence of knowing other findings, we must worry about selective reporting bias.
- 2) I was able to reproduce the authors' positive P-value findings (see Appendix 1, R code) using the [MCPAN R package](#). However, I'm getting slightly different values for adjusted denominators (also in Appendix 1).
- 3) I was able to reproduce the authors' findings of longer survival with RFR (see Appendix 1, R code).
- 4) I have a number of questions about the study design:
 - a. Were control rats selected in utero like the exposed rats were?
 - b. Were pregnant dams assigned to different groups by formal randomization? If not, why not?
 - c. Why were pups in the same litter included? Did the authors take any steps in their analyses to account for the resulting absence of i.i.d?
 - d. The authors state that at most 3 pups were chosen per litter. How were the 3 pups chosen (and the others presumably not used for this experiment)? Were the 3 pups that were chosen selected by formal randomization? If not, why not?

- e. Were all analyses based on the intent-to-treat principle? Were there any crossovers? Were all rats accounted for by the end of the experiment and were all rats who started in the experiment included in the final analyses?
 - f. Blinding: The authors state that “All PWG reviewer were conducted blinded with respect to treatment group,” but in the very next phrase write “only identifying the test articles as ‘test agent A’ or ‘test agent B.’” Why was this information (test agent A or B) given? The blinding was not complete.
- 5) Sample size:
- a. Did the authors perform a prospective (that is before initiation of the work) sample size calculation? If so, what were the prior assumptions? In other words, why did the authors choose to study 90 rats in each group and why did they set the maximum duration to 90 weeks (instead of 104 weeks)?
 - b. I used a [publicly available](#) simulation package¹ to calculate the study power for male rats based on the following (see Appendix 2, power calculation simulation studies):
 - i. Control tumor rate of ~1.5%.
 - ii. Risk ratio 2.5 in the group receiving the highest dose
 - iii. 2-sided Alpha = 0.005 (based on Table 13 of the FDA guidance document). Note this low alpha of 0.005 for poly-k trend tests is recommended to minimize the risk of false positive discoveries.
 - iv. Sample size of 90 for each group with one planned sacrifice.
 - v. Low lethality with lethality parameters set according to study duration and Weibull shape parameter (see Table 3 of Moon et al¹). When I re-ran the simulations using intermediate lethality, results were not materially changed.
 - vi. Study duration 90 weeks
 - vii. 5000 simulations
 - viii. Note – I used dose levels of 0,1,2, and 4 because I was unable to adjust these on the web site (despite trying 3 different browsers).
 - c. Based on these inputs, the recommendations in Table 13 of the FDA guidance document, and a sample size of 90 rats in each group, I find very low power (<5%, see Appendix 2). Even allowing for a risk ratio of 5.0 (a level that is clinically unlikely), the power for 2-sided alpha=0.005, k=3 and low lethality is only ~14% (see Appendix 2).
 - d. The low power implies that there is a high risk of false positive findings², especially since the epidemiological literature questions the purported association between cell phone exposure and cancer.³
- 6) Summary: I am unable to accept the authors’ conclusions:
- a. We need to know all other findings of these experiments (mice, other tumor types) given the risk of false positive findings and reporting bias. It would be helpful to have a copy of the authors’ statistical code.
 - b. We need to know whether randomization was employed to assign dams to specific groups (control and intervention).

- c. We need to know whether randomization was employed to determine which pups from each litter were chosen for continued participation in the experiment.
- d. We need to know whether there was a formal power/sample size calculation performed prior to initiation of the experiment. If not, why not? If yes, we need to see the details. In particular, we need to know whether the authors followed the recommendations of the FDA guidance document (in particular Table 13).
- e. I suspect that this experiment is substantially underpowered and that the few positive results found reflect false positive findings.² The higher survival with RFR, along with the prior epidemiological literature, leaves me even more skeptical of the authors' claims.

References:

1. Moon H, Lee JJ, Ahn H, Nikolova RG. A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies. *J Stat Software*; Vol 1, Issue 13 . 2002. doi:10.18637/jss.v007.i13.
2. Ioannidis JPA. Why most published research findings are false. Jantsch W, Schaffler F, eds. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124.
3. Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ*. 2011;343.

Appendix 1: Attempted replication of positive findings

Review of NTP paper on cell phone RFR and certain cancers

Attempt to reproduce the positive findings

Data from Larry Tabak

Code by Mike Lauer

```
setwd("~/Desktop/Files to save")
```

```
library(MCPAN)
```

```
library(rms)
```

```
library(Hmisc)
```

Read in CDMA NTP data

```
CDMA <- read.csv("~/Desktop/Files to save/NTP CDMA Raw Tumor Data.csv")
```

Survival and treatment group, adjusting for sex, by Cox proportional hazards

```
CDMA$status<-1
```

```
CDMA$S<-Surv(CDMA$Removal.Day, CDMA$status)
```

```
f<-cph(S~Treatment+Sex, data=CDMA)
```

```
f
```

Survival greater (better) for 3.0W, P=0.0157, for 6.0W, P=0.0260

Table 1 -- Poly-3 test for malignant glioma in males CDMA

```
males_CDMA<-subset(CDMA, Sex=='M')
```

```
poly3test(time=males_CDMA$Removal.Day, status=males_CDMA$Brain.Glioma.Malignant,
           f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')
```

P=0.039

```
poly3ci(time=males_CDMA$Removal.Day, status=males_CDMA$Brain.Glioma.Malignant,
         f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')
```

Call result:

Sample estimates, using poly- 3 -adjustment

	0	1.5	3	6
x	0.0000	0.0000	0.0000	3.0000
n	90.0000	90.0000	90.0000	90.0000
adjusted n	63.8258	72.3688	76.6821	64.8154
adjusted estimate	0.0000	0.0000	0.0000	0.0463

Table 3 -- Poly-6 test for malignant Schwannoma in males CDMA

```
poly3test(time=males_CDMA$Removal.Day,
           status=males_CDMA$Heart.Schwannoma.Malignant, f=males_CDMA$Dose, k=6,
           type='Williams', method='BW', alternative='greater')
```

P=0.0005

```
poly3ci(time=males_CDMA$Removal.Day,
         status=males_CDMA$Heart.Schwannoma.Malignant, f=males_CDMA$Dose,
         k=3, type='Williams', method='BW')
```

Call result:

Sample estimates, using poly- 3 -adjustment

	0	1.5	3	6
x	0.0000	2.0000	3.0000	6.0000
n	90.0000	90.0000	90.0000	90.0000
adjusted n	63.8258	72.3971	77.0575	66.5582
adjusted estimate	0.0000	0.0276	0.0389	0.0901

Read in GSM NTP data

```
GSM <- read.csv("~/Desktop/Files to save/NTP GSM Raw Tumor data.csv")
```

Survival and treatment group, adjusting for sex, by Cox proportional hazards

```
GSM$status<-1
GSM$S<-Surv(GSM$Removal.Day, GSM$status)
f<-cph(S~Treatment+Sex, data=GSM)
f
```

Survival greater (better) for 6.0W, P=0.0048

```
males_GSM<-subset(GSM, Sex=='M')
```

Table 3 -- Poly-6 test for malignant Schwannomas in males GSM

```
poly3test(time=males_GSM$Removal.Day, status=males_GSM$Heart.Schwannoma.Malignant,
          f=males_CDMA$Dose, k=6, type='Williams', method='BW', alternative='greater')
```

```
# P=0.004
```

```
poly3ci(time=males_GSM$Removal.Day, status=males_GSM$Heart.Schwannoma.Malignant,
         f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')
```

Call result:

Sample estimates, using poly- 3 -adjustment

	0	1.5	3	6
x	0.0000	2.0000	1.0000	5.0000
n	90.0000	90.0000	90.0000	90.0000
adjusted n	63.8258	73.1547	76.1127	77.0723
adjusted estimate	0.0000	0.0273	0.0131	0.0649

Appendix 2: Simulations for power calculations

Power Simulations for NTP Cell Phone RFR paper (from
<https://biostatistics.mdanderson.org/acss/Login.aspx> and
<https://www.jstatsoft.org/article/view/v007i13>)¹

Michael Lauer, MD (OER)

March 19, 2016

- 1) For malignant gliomas (Table 1), $P = 0.005$, $HR = 2.5$, $k=3$

The University of Texas M. D. Anderson Cancer Center

Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power
Estimation in Animal Carcinogenicity Studies."

Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002)¹

*** Input Parameters ***

Selected Seed = 3000

Number of Groups = 4

Dose metric of each group:

0.00 1.00 2.00 4.00

Number of animals in each group

90 90 90 90

Number of sacrifices including a terminal sacrifice = 1

Sacrifice time points in weeks:

Study duration = 90 weeks

Number of INTERIM sacrificed animals in each interval:

Background tumor onset probability at the end of the study = 0.01

Tumor onset distribution assumed: Weibull with a shape parameter 3.00

Hazard ratio(s) of dose vs. control group

1.50 2.00 2.50

Competing Risks Survival Rate (CRSR) for each group:

0.70 0.70 0.70 0.70

Tumor lethality parameter entered = 23.00

Level of the test = 0.01

One-sided or two-sided test = 2 sided test

Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:

average tumor rate = 0.0149

average competing risks survival rate = 0.6990

average lethality = 0.0816

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0002	0.0002	0.0334	0.0000	0.0000
78	0.0003	0.0005	0.0729	0.0000	0.0000
90	0.0005	0.0023	0.1855	0.0094	0.6887

dose group 1:

average tumor rate = 0.0225

average competing risks survival rate = 0.7000

average lethality = 0.0784

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0003	0.0002	0.0325	0.0000	0.0000
78	0.0004	0.0008	0.0720	0.0000	0.0000
90	0.0007	0.0034	0.1851	0.0145	0.6842

dose group 2:

average tumor rate = 0.0297

average competing risks survival rate = 0.6997

average lethality = 0.0772

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0004	0.0003	0.0331	0.0000	0.0000
78	0.0005	0.0012	0.0721	0.0000	0.0000
90	0.0010	0.0045	0.1829	0.0191	0.6790

dose group 3:

average tumor rate = 0.0366

average competing risks survival rate = 0.7007

average lethality = 0.0772

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0005	0.0003	0.0330	0.0000	0.0000

78	0.0006	0.0013	0.0716	0.0000	0.0000
90	0.0012	0.0054	0.1812	0.0238	0.6749

Positive Trend (Power): 0.0238

2) For malignant Schwannomas (Table 3), $P = 0.005$, $HR = 2.5$, $k=6$

The University of Texas M. D. Anderson Cancer Center
Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies."
Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002)¹

*** Input Parameters ***

Selected Seed = 3000

Number of Groups = 4

Dose metric of each group:

0.00 1.00 2.00 4.00

Number of animals in each group

90 90 90 90

Number of sacrifices including a terminal sacrifice = 1

Sacrifice time points in weeks:

Study duration = 90 weeks

Number of INTERIM sacrificed animals in each interval:

Background tumor onset probability at the end of the study = 0.01

Tumor onset distribution assumed: Weibull with a shape parameter 6.00

Hazard ratio(s) of dose vs. control group

1.50 2.00 2.50

Competing Risks Survival Rate (CRSR) for each group:

0.70 0.70 0.70 0.70

Tumor lethality parameter entered = 45.00

Level of the test = 0.01

One-sided or two-sided test = 2 sided test

Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:

average tumor rate = 0.0149

average competing risks survival rate = 0.6990

average lethality = 0.0631

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0001	0.0001	0.0335	0.0000	0.0000
78	0.0002	0.0003	0.0732	0.0000	0.0000
90	0.0005	0.0019	0.1859	0.0096	0.6887

dose group 1:

average tumor rate = 0.0225

average competing risks survival rate = 0.7000

average lethality = 0.0602

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0001	0.0001	0.0326	0.0000	0.0000
78	0.0003	0.0005	0.0723	0.0000	0.0000
90	0.0006	0.0029	0.1856	0.0148	0.6842

dose group 2:

average tumor rate = 0.0297

average competing risks survival rate = 0.6997

average lethality = 0.0582

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0002	0.0001	0.0333	0.0000	0.0000
78	0.0004	0.0007	0.0726	0.0000	0.0000
90	0.0009	0.0038	0.1837	0.0195	0.6790

dose group 3:

average tumor rate = 0.0366

average competing risks survival rate = 0.7007

average lethality = 0.0588

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0003	0.0001	0.0332	0.0000	0.0000
78	0.0005	0.0007	0.0722	0.0000	0.0000
90	0.0011	0.0046	0.1821	0.0243	0.6749

Positive Trend (Power): 0.0230

3) For further consideration, $P = 0.005$, $HR = 5$, $k=3$

The University of Texas M. D. Anderson Cancer Center
Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies."
Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002) In Press.

*** Input Parameters ***

Selected Seed = 3000
Number of Groups = 4
Dose metric of each group:
0.00 1.00 2.00 4.00
Number of animals in each group
90 90 90 90
Number of sacrifices including a terminal sacrifice = 1
Sacrifice time points in weeks:

Study duration = 90 weeks
Number of INTERIM sacrificed animals in each interval:
Background tumor onset probability at the end of the study = 0.01
Tumor onset distribution assumed: Weibull with a shape parameter 3.00
Hazard ratio(s) of dose vs. control group
2.00 3.50 5.00
Competing Risks Survival Rate (CRSR) for each group:
0.70 0.70 0.70 0.70
Tumor lethality parameter entered = 23.00
Level of the test = 0.01
One-sided or two-sided test = 2 sided test
Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:
average tumor rate = 0.0149
average competing risks survival rate = 0.6990

average lethality = 0.0816

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0002	0.0002	0.0334	0.0000	0.0000
78	0.0003	0.0005	0.0729	0.0000	0.0000
90	0.0005	0.0023	0.1855	0.0094	0.6887

dose group 1:

average tumor rate = 0.0301

average competing risks survival rate = 0.7000

average lethality = 0.0743

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0004	0.0003	0.0324	0.0000	0.0000
78	0.0005	0.0011	0.0717	0.0000	0.0000
90	0.0009	0.0045	0.1839	0.0194	0.6789

dose group 2:

average tumor rate = 0.0515

average competing risks survival rate = 0.6997

average lethality = 0.0774

sacrifice time	d	a1	b1	a2	b2
45	0.0002	0.0000	0.0058	0.0000	0.0000
67	0.0007	0.0006	0.0328	0.0000	0.0000
78	0.0009	0.0020	0.0713	0.0000	0.0000
90	0.0017	0.0076	0.1795	0.0331	0.6638

dose group 3:

average tumor rate = 0.0727

average competing risks survival rate = 0.7007

average lethality = 0.0804

sacrifice time	d	a1	b1	a2	b2
45	0.0003	0.0000	0.0059	0.0000	0.0000
67	0.0010	0.0006	0.0327	0.0000	0.0000
78	0.0013	0.0028	0.0701	0.0000	0.0000
90	0.0025	0.0107	0.1755	0.0470	0.6496

Positive Trend (Power): 0.1420

4) For further consideration, same as in baseline (1) but with intermediate lethality

*** Input Parameters ***

Selected Seed = 3000

Number of Groups = 4

Dose metric of each group:

0.00 1.00 2.00 4.00

Number of animals in each group

90 90 90 90

Number of sacrifices including a terminal sacrifice = 1

Sacrifice time points in weeks:

Study duration = 90 weeks

Number of INTERIM sacrificed animals in each interval:

Background tumor onset probability at the end of the study = 0.01

Tumor onset distribution assumed: Weibull with a shape parameter 3.00

Hazard ratio(s) of dose vs. control group

1.50 2.00 2.50

Competing Risks Survival Rate (CRSR) for each group:

0.70 0.70 0.70 0.70

Tumor lethality parameter entered = 225.00

Level of the test = 0.01

One-sided or two-sided test = 2 sided test

Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:

average tumor rate = 0.0149

average competing risks survival rate = 0.6990

average lethality = 0.3936

sacrifice time	d	a1	b1	a2	b2
45	0.0004	0.0000	0.0060	0.0000	0.0000
67	0.0014	0.0001	0.0334	0.0000	0.0000
78	0.0014	0.0004	0.0729	0.0000	0.0000
90	0.0019	0.0015	0.1855	0.0063	0.6887

dose group 1:

average tumor rate = 0.0225

average competing risks survival rate = 0.7000

average lethality = 0.3852

sacrifice time	d	a1	b1	a2	b2
45	0.0006	0.0000	0.0059	0.0000	0.0000
67	0.0022	0.0001	0.0325	0.0000	0.0000
78	0.0020	0.0006	0.0720	0.0000	0.0000
90	0.0029	0.0023	0.1851	0.0097	0.6842

dose group 2:

average tumor rate = 0.0297

average competing risks survival rate = 0.6997

average lethality = 0.3839

sacrifice time	d	a1	b1	a2	b2
45	0.0008	0.0000	0.0059	0.0000	0.0000
67	0.0029	0.0003	0.0331	0.0000	0.0000
78	0.0027	0.0008	0.0721	0.0000	0.0000
90	0.0039	0.0031	0.1829	0.0127	0.6790

dose group 3:

average tumor rate = 0.0366

average competing risks survival rate = 0.7007

average lethality = 0.3897

sacrifice time	d	a1	b1	a2	b2
45	0.0009	0.0000	0.0059	0.0000	0.0000
67	0.0037	0.0003	0.0330	0.0000	0.0000
78	0.0033	0.0009	0.0716	0.0000	0.0000
90	0.0048	0.0037	0.1812	0.0157	0.6749

Positive Trend (Power): 0.0219

References:

1. Moon H, Lee JJ, Ahn H, Nikolova RG. A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies. *J Stat Software*; Vol 1, Issue 13 . 2002. doi:10.18637/jss.v007.i13.
2. Ioannidis JPA. Why most published research findings are false. Jantsch W, Schaffler F, eds. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124.
3. Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ*. 2011;343.

Reviewer: Maxwell P. Lee, Ph.D., Laboratory of Cancer Biology and Genetics, NCI

I think the study was well designed and the analyses and results were clearly presented.

My main concern is the control data. Since the main finding was the increased incidence rates of heart schwannomas and brain gliomas in male Harlan Sprague Dawley rats exposed to GSM- or CDMA-modulated cell phone RFR, my analyses and evaluation below were focused on the male rats.

My concern regarding the control data came from the following two considerations. First, we need to consider sample variation. The incidence rates of the current controls for brain gliomas and heart schwannomas were 0. However, the historical controls were 1.67% for gliomas (range 0-8%) and 1.30% for schwannomas (0-6%). Given that there were substantial variations among the historical controls and the concurrent control is at the lowest end of the range, it is important to evaluate how different estimates of control incidence rates may impact the results of analyses. Supplementary Table S1 shows that for gliomas with 1.7% incidence rate we have 40%, 37%, 17%, and 6% of chance to observe 0 tumor, 1 tumor, 2 tumors, and greater than 2 tumors, respectively; heart schwannomas has similar distribution. Given the low incidence rate and moderate sample size of the control, even after observing 0 tumor in the current study, the 'true' incidence rate may be higher than 0. If we were repeating the experiment, we may see some control studies have 1 or more tumors. Second, it is puzzling why the control had short survival rate. Given that most of the gliomas and heart schwannomas are late-developing tumors, it is possible that if the controls were living longer some tumors might develop. Although the use of poly-3 (or poly-6) test intended to adjust the number of rats used in the study, it is still important to re-evaluate the analysis by considering the incidence rate in controls not being 0.

Therefore I have performed the analyses using the original data as well as the data modified by adding 1 tumor to the control. I implemented the poly-3 (or poly-6) trend test in R using the formula described in the file, Poly3 correction factor[1].docx.

The results are summarized in Table 1 for brain gliomas

Table 1. Incidence of brain gliomas in male rats exposed to GSM- or CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg				pvalue
	0	1.5	3	6	
GSM	0	3	3	2	0.9771
GSM	1	3	3	2	0.8668
CDMA	0	0	0	3	0.0233
CDMA	1	0	0	3	0.1077

Poly-6 adjusted rates were used in the chi-square trend test. The 1st and 3rd rows correspond to the original data with 0 tumor observed in the control group (The numbers in Table 1 here are identical to those in Table 1 in the original report). The test is significant for CDMA exposures (pvalue = 0.0233). However, it is not significant after adding 1 tumor to the control group (pvalue = 0.1077, the 4th row).

Similar analysis was performed for heart schwannomas. The results are summarized in Table 2.

Table 2. Incidence of heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg				pvalue
	0	1.5	3	6	
GSM	0	2	1	5	0.0431
GSM	1	2	1	5	0.1079
CDMA	0	2	3	6	0.0144
CDMA	1	2	3	6	0.0365

Poly-3 adjusted rates were used in the chi-square trend test. The 1st and 3rd rows correspond to the original data with 0 tumor observed in the control group (The numbers in Table 2 here are identical to those in Table 3 in the original report). The tests are significant for both GSM (pvalue = 0.0431) and CDMA (pvalue = 0.0144) exposures. However, only CDMA exposure remains significant after adding 1 tumor to the control group (pvalue = 0.0365, the 4th row).

Since the incidence of heart schwannomas in the 6 W/kg males was significantly higher in CDMA exposed males than the control group in the original report, I also analyzed the impact of adding 1 tumor to the control group

Table 3. Incidence of heart schwannomas in male rats exposed to 6 W/kg CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg		pvalue
	0	6	
CDMA	0	6	0.0381
CDMA	1	6	0.0986

Poly-3 adjusted rates were used in the chi-square trend test. The 1st row corresponds to the original data with 0 tumor observed in the control group. The test was significant for CDMA exposures (pvalue = 0.0381). However, it was not significant after adding 1 tumor to the control group (pvalue = 0.0986, the 2nd row).

Conclusions

Increased incidence of heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR is statistically significant by the chi-square trend test. The evidence is better for CDMA exposure than GSM exposure. I think additional experiments are needed to assess if the incidence of brain gliomas in male rats exposed to GSM- or CDMA-modulated RFR is significantly higher than the control group or not.

My additional comments are summarized below.

1. I compared poly-3 adjusted number from Table 3 in the original report versus the poly-3 adjusted number that I calculated using the raw data from the excel files. Supplementary Figure S1 shows that these two sets of numbers agree with each other in general. This is in contrast to the comparison for poly-6 adjusted number from Table 1 in the original report versus the poly-6 adjusted number that I calculated using the raw data from the excel files (Supplementary Figure S2). In fact, the adjusted rat numbers from Table 1 and Table 3 of the original report look quite similar (Supplementary Figure S3). This suggests that the poly-3 adjusted number was used in the footnotes in both Table 1 and Table 3 in the original report.
2. I noted that in Table S2 the adjusted numbers in from.original.report and poly3 are identical at Dose 0 and 1.5 for both CDMA and GSM as well as at Dose 3 for GSM but differ slightly in the other treatment doses for heart schwannomas. One possible cause of the difference is that the version of the raw data in the excel files differs from that used to generate the original report. The second possibility is typ in the footnote in Table 3. I also generated Table S3 that has the poly-6 adjusted numbers for brain gliomas. The two sets of the poly-6 adjusted numbers are ver different.
3. There are a couple of errors in the footnote of Table in the original report. 2/74.05 (5%) should be 2/74.05 (2.7%). 3/78.67 (4%) should be 3/78.67 (3.8%).

Supplementary Information

Table S1. Expected percentage of observing different numbers of tumors in the controls based on binomial distribution.

	0 tumor	1 tumor	2 tumors	>2 tumors
control for glioma	40%	37%	17%	6%
control for heart schwannoma	43%	37%	15%	5%

The percentage was calculated with 1.7% historical control rate for male rats (gliomas) and with poly-6 adjusted animal number, 53. Similarly, the percentage was calculated with 1.3% historical control rate for male (heart schwannoma) and with poly-3 adjusted animal number, 65.

Table S2. The poly-3 adjusted rat numbers in Table in the original report and those calculated from the raw data.

RFR	Dose	from.original.report	poly3
CDMA	0	65.47	65.47
CDMA	1.5	74.05	74.05
CDMA	3	78.67	78.35
CDMA	6	67.94	66.24
GSM	0	65.47	65.47
GSM	1.5	74.87	74.87
GSM	3	77.89	77.89
GSM	6	78.48	77.66

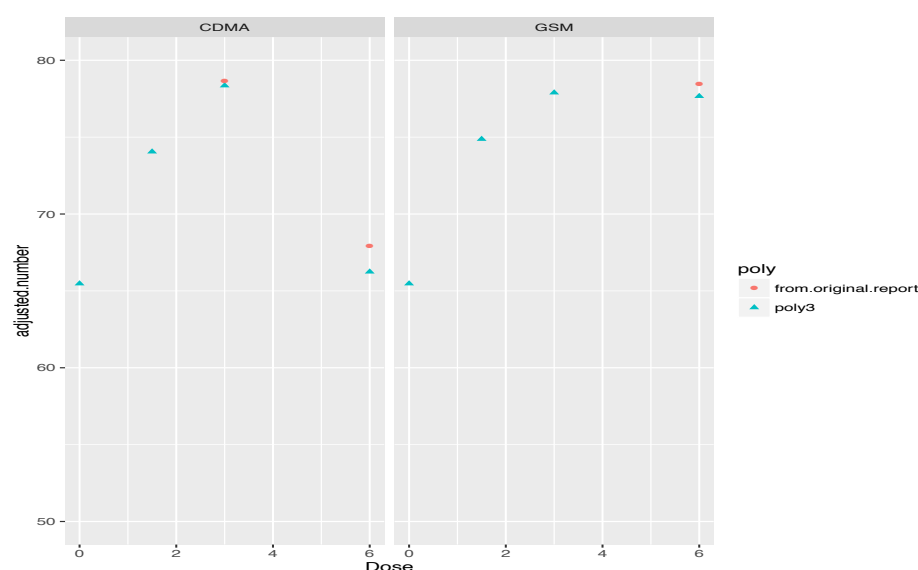
The numbers in from.original.report refers to the poly-3 adjusted rat number from Table 3 in the original report. The numbers in poly3 refers to the poly-3 adjusted rat numbers that I calculated from the raw data for heart schwannoma.

Table S3. The poly-6 adjusted rat numbers in Table in the original report and those calculated from the raw data.

RFR	Dose	from.original.report	poly6
CDMA	0	65.47	53.48
CDMA	1.5	74.05	65.94
CDMA	3	78.35	73.08
CDMA	6	66.24	57.5
GSM	0	65.47	53.48
GSM	1.5	74.93	67.84
GSM	3	78.27	71.43
GSM	6	77.1	72.55

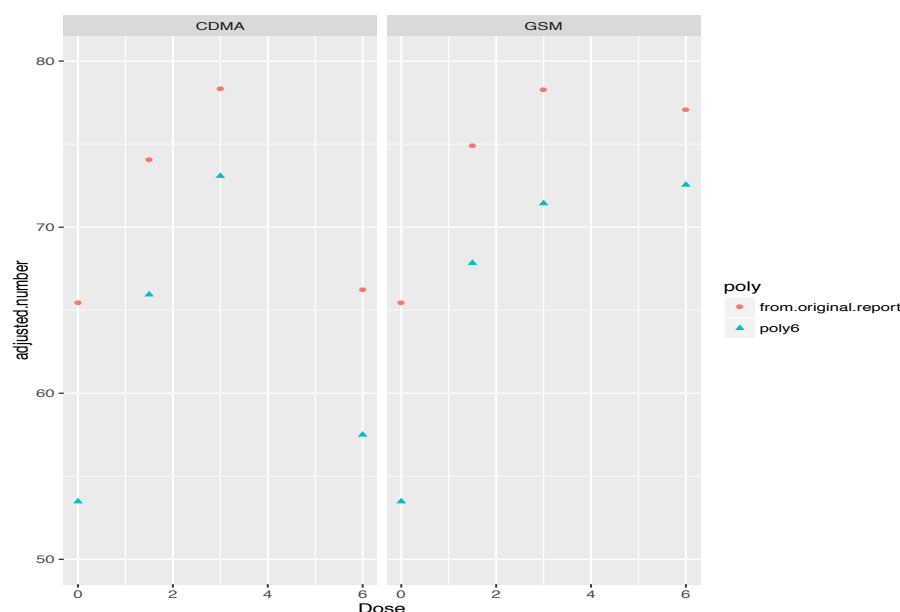
The numbers in from.original.report refers to the poly-6 adjusted rat number from Table 1 in the original report. The numbers in poly6 refers to the poly-6 adjusted rat numbers that I calculated from the raw data for brain gliomas.

Figure S1. Comparison of poly-3 adjusted rat numbers between those from the original report versus those calculated from the raw data.



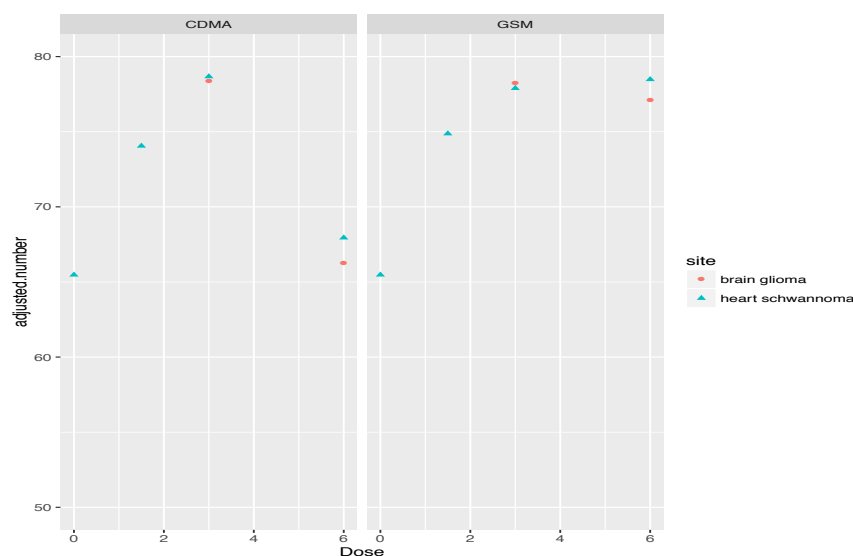
The poly-3 adjusted rat number from Table 3 of the original report is compare with the poly-3 adjusted rat number that I calculated from the raw data for heart schwannomas experiment

Figure S2. Comparison of poly-6 adjusted rat numbers between those from the original report versus those calculated from the raw data.



The poly-6 adjusted rat number from Table 1 of the original report is compared with the poly-6 adjusted rat number that I calculated from the raw data for brain gliomas experiment

Figure S3. Comparison of poly-6 adjusted rat numbers between those from the original report versus those calculated from the raw data.



The adjusted rat numbers from Table 1 and Table 3 of the original report are compared with each other.

Reviewer: Aleksandra M. Michalowski, M.Sc., Ph.D., Laboratory of Cancer Biology and Genetics, NCI

REVIEWER COMMENTS

Reviewer's Name:

Aleksandra M. Michalowski, Ph.D., M.Sc., National Cancer Institute/LCBG

Report Title:

Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation (Whole Body Exposures); Draft 3-16-2016

Charge: To peer review the draft report and comment on whether the scientific evidence supports NTP's conclusion(s) for the study findings.

1. Scientific criticisms:

- a. *Please comment on whether the information presented in the draft report, including presentation of data in any tables, is clearly and objectively presented. Please suggest any improvements.*

Overall, the information included in the report is presented in a comprehensive and accurate manner. Specifically, the experimental design and conditions are sufficiently documented and the choice of statistical approaches is explained; the results are well organized and necessary details are provided.

Nevertheless, a few additions could be suggested:

(1) Appendix tables for all poly-k tests performed could be added. I believe this would enhance the presentation of the adjusted rates and the strength of the statistical evidence. As a possible example I prepared the below table using the R package *MCPAN* and its *poly3test()* function.

poly-3	Heart Schwannoma Malignant, Male				Heart Schwannoma Malignant, Female			
CDMA exposure	0	1.5	3	6	0	1.5	3	6
X	0	2	3	6	0	2	0	2
N	90	90	90	90	90	90	90	90
adjusted n	63.8	72.4	77.1	66.6	67.9	71.8	70.3	78.0
Dunnett contrast	—	1.5 - 0	3 - 0	6 - 0	—	1.5 - 0	3 - 0	6 - 0
Estimate	0	0.03	0.04	0.09	0	0.03	0	0.03
Statistic	—	1.24	1.58	2.45	—	1.26	0	1.24
p-value	—	0.2704	0.1542	0.0209	—	0.2466	0.7992	0.2562
Williams contrast	—	(6,3,1.5) - 0	(6,3) - 0	6 - 0	—	(6,3,1.5) - 0	(6,3) - 0	6 - 0
Estimate	0	0.05	0.06	0.09	0	0.02	0.01	0.03
Statistic	—	2.78	2.75	2.45	—	1.27	0.88	1.24
p-value	—	0.0056	0.0060	0.0138	—	0.1661	0.2871	0.1744

(2) In the portion of the text describing poly-k test results, p-values are given for significant pairwise comparisons; I would also give the p-values estimated for the significant trends (maximum test).

(3) Information could be included regarding the software or programming environment used for the computations.

(4) In the portion of the text describing differences in survival at the end of the study between control and RFR-exposed animals (page 5§2) the compared characteristic is not named (median survival, TSAC?) and also no numerical values of the estimates or the range of differences are given. I would add numbers in the text or an Appendix table showing the group survival estimates described in this paragraph.

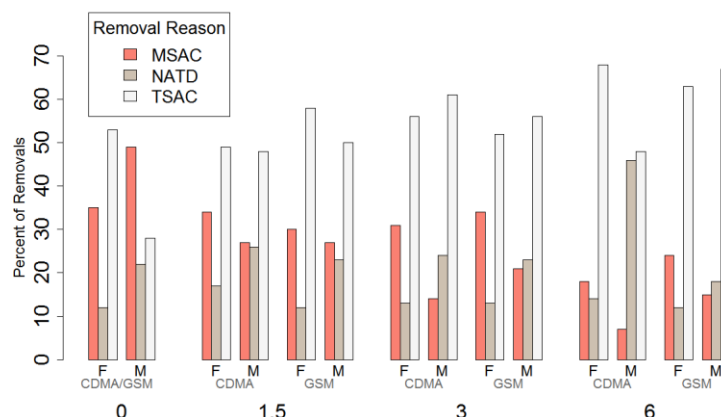
Median survival						TSAC percentage					
CDMA	Female	Male	GSM	Female	Male	CDMA	Female	Male	GSM	Female	Male
0	737	662.5	0	737	662.5	0	53	28	0	53	28
1.5	734	719	1.50	738	729	1.5	49	48	1.5	58	50
3	737	731	3	737	730	3	56	61	3	52	56
6	738.5	717	6	738	731	6	68	48	6	63	67

- b. *Please comment on whether NTP's scientific interpretations of the data are objective and reasonable. Please explain why or why not.*

Appropriate statistical design and methods were applied in accord with the FDA/NTP guidelines for conducting long-term rodent carcinogenicity studies and analyses. The results and limiting issues were objectively discussed. The critical issue of shorter survival in the male control group was addressed with regard to the percentage of animals surviving to terminal sacrifice in historical control data (avg. 47%, range 24% to 72%) and the possible impact of the observed age of tumor occurrence on the statistical inference.

I believe detailed information about animal selection and randomization procedures should be given so that the potential for allocation bias could be judged. As shown in the figure below, the lower survival rate to terminal sacrifice (28%) in the male control is accompanied by the higher rate of moribund sacrifice (49%); in the male group exposed to CDMA with 6 W/kg, a higher rate of natural death was observed (46%).

It has been reported that insufficient randomization can lead to differences in survival rates. As an example, in a carcinogenicity study on aspartame it was suggested that lack of randomization to different rooms may have possibly been the cause of low survival rates (27%) in the control female group due to a high background infection rate (EFSA, 2006; Magnuson, B., Williams, G.M., 2008).



2. Please identify any information that should be added or deleted:

A statement of the required statistical significance level should be added. FDA guidance suggests the use of significance levels of 0.025 and 0.005 for tests for positive trends in incidence rates of rare tumors and common tumors, respectively; for testing pairwise differences in tumor incidence the use of significance levels of 0.05 and 0.01 is recommended for rare and common tumors, respectively. If power calculations to determine the required sample size were performed, the results should also be included.

3. The scientific evidence supports NTP's conclusion(s) for the study findings:

The NTP's overall draft conclusion was as follows: "Under the conditions of these studies, the observed hyperplastic lesions and neoplasms outlined in this partial report are considered likely the result of exposures to test article A and test article B. The findings in the heart were statistically stronger than the findings in the brain."

In my view, the results support the conclusion of likely carcinogenic effect of the RFR-exposure on Schwannoma heart lesions in male Harlan Sprague Dawley rats.

Possible carcinogenic effects in the brain are marginal and are not sufficiently supported by statistical evidence in the male Harlan Sprague Dawley rats.

In the female Harlan Sprague Dawley rats very few lesions were observed in either site and statistical significance was not reached at all.

Reviewer: R. Mark Simpson, D.V.M., Ph.D., Laboratory of Cancer Biology and Genetics, NCI

Analysis of National Toxicology Program (NTP) study evaluating risk in rat lifetime exposure to GSM or CDMA RFR.

Notes:

The NTP study document acknowledges several study limitations [page 10, discussion section]. Potential limitations should prominently factor into considerations regarding the context of the findings, as well as their interpretation and application.

Working list of limitations potentially impacting NTP study interpretations

- Difficulty in achieving diagnostic consensus in lesions classifications of rare, unusual, and incompletely understood lesion association
- Document appears to indicate that the second Pathology Working Group (PWG) empaneled to review and obtain lesion classification consensus, following the inability of the initial PWG to do so, may have reviewed different lesions sets
- No record of clinical disease manifestations due to lesions involving heart and brain [note lesions in heart and brain are mutually exclusive; affected rats have either one or the other and do not appear to have the involvement of both organs together (appendix E)]
- Lesions, including malignancies, do not appear to materially shorten lifespan, except for a subgroup of rats (less than 1/3 of affected rats) with malignant Schwannomas in heart
- Lack of shortened lifespan as a consequence of malignancy for the majority of affected rats contrasts with shortened lifespan of male control rats for which there is absence of attributable cause of death. The survival of the control group of male rats in the current study (28%) was relatively low compared to other recent NTP studies (avg 47%, range 24 to 72%).
Creates greater reliance on statistical controlling for survival disparities and reliance on historical controls
- Reliance on historical controls made up of rats of different genetic strain background, held under different environmental conditions
- Absence of data on incidence of more frequently expected tumor occurrences in rats (background lesions)

Documenting the nature of the brain and cardiac lesions observed in RFR exposed rats and placing them into test article exposure-related context, in contrast to potential for their occurring spontaneously, are important and challenging goals. The NTP study limitations make the interpretation of reasonable risk more complicated. NTP acknowledgements of study limitations appear factored into one of NTP's reviewer's study conclusion, i.e., findings represent "some evidence" for a test article effect in statistically significant trend for Schwannomas; an opinion which is coupled with a conclusion for "equivocal evidence" of an effect in relation to malignant gliomas of the brain [NTP Appendix F, Reviewer Comments].

The summation from Appendix F reviewers regarding existence of test article effect is less than conclusive. The NTP study documents a series of cytoproliferative changes

in heart and brain. The nature of some of the changes is challenging diagnostically and appears to be incompletely understood. These findings are presented in the absence of complete analysis of the entire consequences of the study effects. For example, no potential significance for test article effect context is given to any of granular cell proliferative lesions of the brain, a finding mentioned only as a contrast to what was less well understood pathologically (NTP Appendix C, Pathology). It is noteworthy that the lesion types analyzed in the NTP RFR study under review are uncommon historically in rats, in the organs discussed. Furthermore, the malignancies of neuroglia appear to be paired with the occurrence of poorly understood changes involving neuroglial cell hyperplasias in the central and peripheral nervous systems. Little information can be gleaned from the literature about the nature and significance of these latter proliferative changes, interpreted by NTP as nonneoplastic and non-inflammation-reactive neuroglial cell in nature. Although unclear in the NTP study document, it is plausible that the particular lesion constellation, along with the relative novelty of some lesions, contributed to the lack of consensus regarding the nature of the lesions on the part of the initial PWG study pathologists. Concern raised by one of the reviewers (Appendix F, Reviewer Comments) regarding how this difficulty in ability to classify lesions might impact comparisons to historical control lesion incidence data (NTP Table D) is certainly principled.

The extraordinary PWG process, presumably posed by the difficult diagnostic interpretations, has the potential to influence the reliance on historical controls. In this regard, study limitations concerning determination of whether or not there is a test article effect include the substantially poor survival of male rats in the control group. The survival of the control group of male rats in the study under review (28%) was relatively low compared to other recent NTP studies (avg 47%, range 24 to 72%). This apparently led to greater statistical construction to account for the impact of study matched controls, and created increased reliance upon historical data of rare tumor incidences in control animals taken from other chronic carcinogenicity studies. NTP acknowledges a limitation in using the historical incident data and a small study match control group due to poor survivability. There are potential sources of variability when using historical controls of different rat strains and fluctuating study conditions (environment, vehicle, route of exposure, etc.), as is the case here. It seems less than clear what appropriate background lesion incidence is, as NTP indicates some data involve other strains of rats. The range of lesion incidence in historical controls could mean that the true incidence of some lesions varies considerably and might be considered rare or more common depending upon the incidence rate.

The guidance manual on Statistical Aspects of the Design, Analysis and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals by the FDA provided for this review discusses applying comparisons using historical control lesion incidences at some length [beginning page 27, line 996]. Considering lesions as being rare or more common appears to influence selection of the level of statistical significance for comparisons. It appears that analysis for significant differences in tumor incidence between the control and the dose groups for these NTP studies has been established at the 0.05 level (NTP Tables 1,3,5). Interpretations of trend tests may be influenced by the choice of decision rule applied. Such choices can result in

about twice as large overall false positive error as that associated with control-high pairwise comparison tests [page 28, line 1012-1026]. The FDA guidance manual [page 31, line 1136] highlights concern regarding reliance upon historical control incidence data, stating that using historical control data in the interpretation of statistical test results is not very satisfactory because the range of historical control rates is usually too wide. This is especially true in situations in which the historical tumor rates of most studies used are clustered together, but a few other studies give rates far away from the cluster. When the range of historical control data is simply calculated as the difference between the maximum and the minimum of the historical control rates, the range does not consider the shape of the distribution of the rates. These circumstances may impose some limitations on optimal risk assessment designs.

Somewhat paradoxically then, NTP study limitations including that imposed due to reliance upon less than optimal historical control lesion incidence data for much of the comparisons between treated and untreated rats, is confronted by existence of a difficult to classify and incompletely understood lesion constellation interpreted to include neuroglial cell hyperplasia. Notwithstanding, this confounding proliferative lesion occurring in the context along with malignancies of apparently similar histogeneses, sustains a level of concern for a rare injury mechanism related to test article effect. Additional information about the study together with an assessment of the statistical analyses may enhance the value of this analysis.

R. Mark Simpson, D.V.M., Ph.D.

Appendix G2: NTP's Responses to NIH Reviewer's Comments

NTP Responses to Pathology Reviewer' Comments

April 12, 2016

Reviewers: R. Mark Simpson, D.V.M., Ph.D. and Diana Copeland Haines, D.V.M.

Responses Relating to the Pathology Review Process

Drafts of the PWG reports are provided. As described in the PWG report, the specific task of the first PWG (January 29th 2016) was to: 1) confirm the presence of glial cell hyperplasia and malignant gliomas in the brain and Schwann cell hyperplasia and schwannomas in the heart; 2) develop specific diagnostic criteria in the brain for distinguishing glial cell hyperplasia from malignant glioma and gliosis, and in the heart for distinguishing between Schwann cell hyperplasia and schwannoma. The PWG participants confirmed the malignant gliomas and schwannomas, but the criteria for distinguishing between hyperplasia and neoplasia differed between the participants.

In order to clearly establish specific diagnostic criteria for the differentiation between hyperplastic and neoplastic lesions in the brain and heart, two additional PWGs were convened. The participants for the second (February 25, 2016) and third (March 3, 2016) PWGs were selected based on their distinguished expertise in the fields of neuropathology and cardiovascular pathology, respectively. Some of the participants were leaders in the International Harmonization of Nomenclature and Diagnostic Criteria initiative. The neuropathology experts of the second PWG confirmed the malignant gliomas in the brain, established diagnostic criteria for glial cell hyperplasia, and agreed that the hyperplastic lesions are within a continuum leading to malignant glioma. The cardiovascular pathology experts of the third PWG established specific diagnostic criteria for Schwann cell hyperplasia and schwannoma in the endocardium and myocardium, and reviewed and confirmed all cases of Schwann cell hyperplasia and schwannoma observed in these studies. The outcome of the PWG provided a very high degree of confidence in the diagnoses.

The participants of the first PWG (January 29th 2016) only reviewed a subset of the glial lesions that were observed in the studies. The review for the second PWG (February 25, 2016) included all glial lesions in the studies including the subset that was reviewed in the first PWG.

Responses Relating to Considerations of Historical Control Data

For NTP toxicology and carcinogenicity studies, the concurrent controls are always the primary comparison group. However, historical control information is useful particularly in instances when there is differential survival between controls and exposed groups, as was observed in the RFR studies. Rates for glial cell neoplasms and heart schwannomas from control groups of male Harlan Sprague Dawley rats from other recently completed NTP studies are presented in Appendix D of the 3-16-2016 draft report. While Harlan Sprague Dawley rats are an outbred strain, they are considered a single genetic strain in the same sense as other outbred strains, such as the Long-Evans or Wistar rat. Therefore, these historical control tumor rates are applicable to this study. However, it's important to note that the studies listed in Appendix D were carried out at laboratories other than the RFR studies, and under different housing and environmental conditions. At the time of the 3-16-2016 draft report, not all of these studies had undergone a complete pathology peer review. In the past several weeks NTP pathologists have reviewed brain and heart slides from these male rat control groups, and have confirmed, with few exceptions, the low rates of hyperplastic and neoplastic lesions reported in Appendix D, applying the diagnostic criteria established during the PWGs outlined in Appendix C.

NTP Comments on Statistical Issues Raised by the Reviewers

April 12, 2016

Given the multiple comparisons inherent in this kind of work, there is a high risk of false positive discoveries (Michael S. Lauer).

Although the NTP conducts statistical tests on multiple cancer endpoints in any given study, numerous authors have shown that the study-wide false positive rate does not greatly exceed 0.05 (Fears et al., 1977; Haseman, 1983; Office of Science and Technology Policy, 1985; Haseman, 1990; Haseman and Elwell, 1996; Lin and Rahman, 1998; Rahman and Lin, 2008; Kissling et al., 2014). One reason for this is that NTP's carcinogenicity decisions are not based solely on statistics and in many instances statistically significant findings are not concluded to be due to the test agent. Many factors go into this determination including whether there were pre-neoplastic lesions, whether there was a dose-response relationship, biological plausibility, background rates and variability of the tumor, etc. Additionally, with rare tumors especially, the actual false positive rate of each individual test is well below 0.05, due to the discrete nature of the data, so the cumulative false positive rate from many such tests is less than one person would expect by multiplying 0.05 by the number of tests conducted (Fears et al., 1977; Haseman, 1983; Kissling et al., 2015).

I'm getting slightly different values for poly-k adjusted denominators (Michael S. Lauer).

I compared poly---3 adjusted number from Table 3 in the original report versus the poly---3 adjusted number that I calculated using the raw data from the excel files. Supplementary Figure S1 shows that these two sets of numbers agree with each other in general. This is in contrast to the comparison for poly---6 adjusted number from Table 1 in the original report versus the poly---6 adjusted number that I calculated using the raw data from the excel files (Supplementary Figure S2). In fact, the adjusted rat numbers from Table 1 and Table 3 of the original report look quite similar (Supplementary Figure S3). This suggests that the poly---3 adjusted number was used in the footnotes in both Table 1 and Table 3 in the original report. (Max Lee)

I noted that in Table S2 the adjusted numbers in from.original.report and poly3 are identical at Dose 0 and 1.5 for both CDMA and GSM as well as at Dose 3 for GSM but differ slightly in the other treatment doses for heart schwannomas. One possible cause of the difference is that the version of the raw data in the excel files differs from that used to generate the original report. The second possibility is typo in the footnote in Table 3. I also generated Table S3 that has the poly---6 adjusted numbers for brain gliomas. The two sets of the poly---6 adjusted numbers are very different. (Max Lee)

Information could be included regarding the software or programming environment used for the computations. (Aleksandra M. Michalowski)

The adjusted denominators in Table of the original report were labeled as poly-6 denominators, but were actually poly-3 denominators. This error was noted and brought to Dr Tabak's attention by Dr. Bucher in a March 22 email.

The p-values and adjusted denominators calculated by NTP are correct, except as noted for Table 1, and were calculated using validated poly-k software. This software is coded in Java and is embedded within NTP's TDMSE (Toxicology Data Management System Enterprise) system. Poly-k

calculations conducted by the reviewers in R may vary slightly from the NTP's calculation due to selection of study length and the NTP's use of the Bieler-Williams variance adjustment and a continuity correction. In his calculations, Dr. Lauer used 90 weeks as the study length, whereas the actual study length was 10 weeks. It is not apparent from the R documentation that the Bieler-Williams adjustment or the continuity correction is incorporated into the poly-3 calculations in R. In his calculations, Dr. Lee used two-sided p-values. In NTP statistical tests for carcinogenicity, the expectation is that if the test article is carcinogenic, tumor rates should increase with increasing exposure; thus, the NTP employs one-sided tests and p-values are one-sided. Using one-sided p-values in Dr. Lee's Table 1, the GSM trend if there were brain glioma in the control group remains nonsignificant, but the CDMA trend approaches 0.05 ($p = 0.054$) if there were brain glioma in the control group. In Dr. Lee's Table 2, the one-sided p-value for the GSM trend if there were 1 heart schwannoma in the control group approaches 0.05 ($p = 0.054$) and the one-sided p-value for the CDMA trend in heart schwannomas remains significant at $p = 0.018$ if there were 1 heart schwannoma in the control group. In Dr. Lee's Table 3, the one-sided p-value for the CDMA pairwise comparison is significant at $p = 0.049$ if there were 1 heart schwannoma in the control group.

statement of the required statistical significance level should be added. FDA guidance suggests the use of significance levels of 0.025 and 0.005 for tests for positive trends in incidence rates of rare tumors and common tumors, respectively; for testing pairwise differences in tumor incidence the use of significance levels of 0.05 and 0.01 is recommended for rare and common tumors, respectively. (Aleksandra M. Michalowski)

Although the FDA guidance suggests lowering the significance level for most tests of trend and pairwise differences, this guidance is based on a misunderstanding of findings reported by Haseman (1983). In this paper, Haseman discusses several rules proposed by others for setting the significance level lower than 0.05. *If* these rules are rigidly followed, Haseman showed that study conclusions will be consistent with the NTP's more complex decision-making process, for which 0.05 is the nominal significance level and p-values are taken into consideration along with other factors (outlined above in response to comment 1) in determining whether the tumor increase is biologically significant. The NTP does not strictly adhere to a specific statistical significance level in determining whether a carcinogenic effect is present.

Appendix tables for all poly-k tests performed could be added. (Aleksandra M. Michalowski)

Dr. Michalowski proposed a sample table. The rows corresponding to X, N, adjusted n are already included in the tables or appear the footnotes in the tables. The rows corresponding to "Dunnett contrast" and "Williams contrast" are not appropriate for dichotomous tumor data. Both Dunnett's test and Williams' test assume that the data are continuous and normally distributed.

In the portion of the text describing poly-k test results, p-values are given for significant pairwise comparisons; I would also give the p-values estimated for the significant trends. (Aleksandra M. Michalowski)

Indicators of significant trends are given in the tables in the form of asterisks next to control group tumor counts.

There are a couple of errors in the footnote of Table 3 in the original report. 2/74.05 (5%) should be 2/74.05 (2.7%). 3/78.67 (4%) should be 3/78.67 (3.8%). (Max Lee)

Thank you for pointing this out. The percentages will be corrected in our final report.

Were control rats selected in utero like the exposed rats were? Were pregnant dams assigned to different groups by formal randomization? How were the pups per litter chosen? (Michael S. Lauer).

believe detailed information about animal selection and randomization procedures should be given so that the potential for allocation bias could be judged. (Aleksandra M. Michalowski)

Pregnant dams were assigned to groups, including the control group, using formal randomization that sought to also equalize mean body weights across groups. The three pups per sex per litter were selected using formal randomization, as well. Tumors in the heart and brain were not observed in littermates, indicating that there was no litter-based bias in the results.

Were all analyses based on the intent-to-treat principle? Were there any crossovers? Were all rats accounted for by the end of the experiment and were all rats who started in the experiment included in the final analyses? (Michael S. Lauer)

The intent-to-treat principle is not relevant to this animal experiment, in which all animals that were assigned to treatment group received the full and equal treatment of that group. There were no crossovers. All animals that started the experiment were accounted for by the end of the experiment and included in the final analyses.

The PWG review blinding was not complete. (Michael S. Lauer)

PWG reviewers were blinded to the identity of the test article and the level of exposure but were not blinded to the fact that there were two different, yet related, test articles (modulations of cell phone RFR), to emphasize the fact that there was a common control group.

Did the authors perform a prospective sample size calculation? (Michael S. Lauer)

If power calculations to determine the required sample size were performed, the results should also be included. (Aleksandra M. Michalowski)

Sample size calculations were conducted for this study. However, for detecting carcinogenesis, sample size and power will depend on the baseline (control) tumor rate and the expected magnitude of the increase in tumors. For example, at 80% power, sample size requirements will be quite different for detecting a 2-fold increase in a rare tumor having a spontaneous occurrence of 0.5% compared to 2-fold increase in a more common tumor having a spontaneous occurrence of 10%. Because many different tumor types having wide range of spontaneous occurrence are involved in these studies, there is no “one-size-fits-all” sample size; rather, the sample size is a

compromise among several factors, including obtaining reasonable power to detect moderate to large increases for most tumor types, while staying within budgets of time, space, and funding. A sample of 90 animals per sex per group was selected as providing as much statistical power as possible across the spectrum of tumors, under the constraints imposed by the exposure system.

The NTP's carcinogenicity studies are similar in structure to the OECD's 45 Guideline for carcinogenicity studies and the FDA's guidance for rodent carcinogenicity studies of pharmaceuticals. These guidelines recommend at least 50 animals of each sex per group, but also mention that an increase in group size provides relatively little increase in statistical power. In the NTP's RFR studies, the group sizes were 90 animals of each sex per group, nearly twice as many as the minimum recommendation. Increasing the group sizes further provides diminishing returns, for which additional animals do not substantially increase power.

The low power implies that there is high risk of false positive findings (citing Ioannidis, 2005). ... suspect that this experiment is substantially underpowered and that the few positive results found reflect false positive findings (citing Ioannidis, 2005). (Michael S. Lauer)

It is true that the power is low for detecting moderate increases above a low background tumor rate of approximately — %, as was seen in the brain and heart tumors. However, this low power does not correspond to high risk of false positive findings. The paper by Ioannidis that was cited correctly states that when studies are small or effect sizes are small (i.e., statistical power is low), “the less likely the research findings are to be true.” Research findings can be “not true” if the result is a false positive or a false negative. With low statistical power, false negatives are much more likely than false positives. Therefore, the vast majority of false research findings in a low power situation will result from the failure to detect an effect when it exists. The false positive rate on any properly constructed statistical test will not exceed its significance level, alpha. By definition, the significance level of a statistical test is its false positive rate, and it is typically selected by the researcher, often at a low fixed value such as 0.05 or 5%.

If we were repeating the experiment, we may see some control studies have 1 or more tumors. (Max Lee) (Dr. Lee also presented analyses of the male rat data, inserting hypothetical data on one tumor-bearing animal in the control group.)

In light of the historical control data, Dr. Lee demonstrated that several associations became less or not significant with the insertion of a tumor data point in the control group. While we appreciate that some other studies had one or more tumors, the NTP considers the concurrent control group as the most important comparator to the treated groups. We took the historical control tumor rates into account in a more subjective manner in our interpretation of the findings. In 2010, we asked to adopt more formal method of incorporating historical control data in our statistical testing, but our Board of Scientific Counselors voted against adopting the method.

It is puzzling why the control had short survival rate. Given that most of the gliomas and heart schwannomas are late-developing tumors, it is possible that if the controls were living longer some tumors might develop. Although the use of poly-3 (or poly-6) test intended to adjust the number of rats

used in the study, it is still important to re-evaluate the analysis by considering the incidence rate in controls not being 0. (Max Lee)

We do not know why the male rat control group had a low survival rate. We generally do observe lower survival rates in studies such as the RFR studies in which animals are singly- rather than group housed. While some tumors might possibly have arisen in controls if they lived longer, it was notable that no glial cell or Schwann cell hyperplasias were found in these animals as well.

The poly-k (e.g., poly-3 or poly-6) test was developed to adjust for the fact that not all animals survive to the end of a two-year study, and survival rates may differ among groups. The test is essentially a Cochran-Armitage trend test in which the denominator of the tumor rate in each group is adjusted downward to better reflect the number of animal-years at risk during the study. Each animal that develops the tumor or survives to the end of the study is counted as one animal. Each animal that does not develop the tumor and dies (or is moribund sacrificed) before the end of the study is counted as a fractional animal. The fraction is calculated as the proportion of the study that it survived, raised to the k-th power; $k = 3$ or $k = 6$ in this study. The survival-adjusted tumor rate in each group is then the number of animals having the tumor of interest divided by the total count of animals at risk of developing the tumor in the group. These survival-adjusted rates are used in the Cochran-Armitage formula to provide the poly-k test for dose-related trends and pairwise comparisons with the control group.

The poly-k test has been shown to yield valid inferences about tumor rates in NTP two-year rat and mouse carcinogenicity studies (Bailer and Portier, 1988; Portier and Bailer, 1989; Portier et al., 1986). Its theoretical basis is that tumor incidence, while not directly observed unless the tumor is immediately lethal, follows a Weibull distribution with a shape parameter, k . Verification using NTP studies has shown that if k is between 1 and 5, setting $k = 3$ yields a valid statistical test (Portier and Bailer, 1989; Portier et al., 1986). Thus, most of the time, the NTP uses the poly-3 test. If tumor type is late-occurring, as we observed with the brain gliomas, $k = 6$ is a better fit to the data and the poly-6 test has more validity.

In the portion of the text describing differences in survival at the end of the study between control and RFR-exposed animals the compared characteristic is not named and also no numerical values of the estimates or the range of differences are given. I would add numbers in the text of a Appendix table showing the group survival estimates described in this paragraph. (Aleksandra M. Michalowski)

The Statistical Methods section describes the method for comparing survival distributions between the control and RFR-exposed groups, namely, Tarone's (1975) life table test to identify exposure-related trends in survival and Cox's (1972) method for testing two groups for equality of survival distributions.

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ADDITIONAL RESPONSE:

Dear All,

Thanks again for all your helpful comments on the NTP RFR studies. I did want to follow up on one remaining point of disagreement that Mike Lauer alluded to in his comments about low powered studies. Although we agree that our study design had low power to detect statistically significant neoplastic effects in the brain and heart, which occurred with both RFR modulations in male rats, we disagree over the assertion that low power in and of itself, creates false positive results. We cited a handful of publications outlining the statistical arguments against this with specific respect to the NTP rodent cancer study design in our response to comments document sent earlier. Although Mike referred to the example of positive findings in underpowered epidemiology studies that could not be replicated in larger follow up studies, there is a growing literature alluding to this problem with respect to experimental animal studies as well. An example is a relatively recent article by one of our collaborators in CAMARADES, Malcolm MacLeod.

<http://www.nature.com/news/2011/110928/full/477511a.html>

It's important to distinguish between low power to detect effects, and the constellation of other factors that often accompany low powered experimental animal studies in contributing to this problem. We've addressed this issue in a recent editorial, and these factors are captured in our published systematic review process for evaluating study quality in environmental health sciences (Rooney et al., 2014).

<http://ehp.niehs.nih.gov/wp-content/uploads/122/7/ehp.1408671.pdf>

<http://ehp.niehs.nih.gov/wp-content/uploads/122/7/ehp.1307972.pdf>

Table 1 in the Rooney et al. report outlines risk of bias considerations that commonly plague studies carried out by academic researchers that are accounted for in NTP studies.

I provide these examples to assure you that we are completely cognizant of these issues and take them very seriously. Again, we appreciate the help you've provided in assuring that we appropriately interpret and communicate our findings.

Best

John Bucher

NTP; Commentary on the utility of the National Toxicology Program study on cell phone radiofrequency radiation data for assessing human health risks despite unfounded criticisms aimed at minimizing the findings of adverse health effects.

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Commentary on the utility of the National Toxicology Program study on cell phone radiofrequency radiation data for assessing human health risks despite unfounded criticisms aimed at minimizing the findings of adverse health effects

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ABSTRACT

The National Toxicology Program (NTP) conducted two-year studies of cell phone radiation in rats and mice exposed to CDMA- or GSM-modulated radiofrequency radiation (RFR) at exposure intensities in the brain of rats that were similar to or only slightly higher than potential, localized human exposures from cell phones held next to the head. This study was designed to test the (null) hypothesis that cell phone radiation at non-thermal exposure intensities could not cause adverse health effects, and to provide dose-response data for any detected toxic or carcinogenic effects. Partial findings released from that study showed significantly increased incidences and/or trends for gliomas and glial cell hyperplasias in the brain and schwannomas and Schwann cell hyperplasias in the heart of exposed male rats. These results, as well as the findings of significantly increased DNA damage (strand breaks) in the brains of exposed rats and mice, reduced pup birth weights when pregnant dams were exposed to GSM- or CDMA-modulated RFR, and the induction of cardiomyopathy of the right ventricle in male and female rats clearly demonstrate that the null hypothesis has been disproved. The NTP findings are most important because the International Agency for Research on Cancer (IARC) classified RFR as a “possible human carcinogen” based largely on increased risks of gliomas and acoustic neuromas (which are Schwann cell tumors on the acoustic nerve) among long term users of cell phones. The concordance between rats and humans in cell type affected by RFR strengthens the animal-to-human association. This commentary addresses several unfounded criticisms about the design and results of the NTP study that have been promoted to minimize the utility of the experimental data on RFR for assessing human health risks. In contrast to those criticisms, an expert peer-review panel recently concluded that the NTP studies were well designed, and that the results demonstrated that both GSM- and CDMA-modulated RFR were carcinogenic to the heart (schwannomas) and brain (gliomas) of male rats.

1. Introduction

The US Food and Drug Administration's (FDA) Center for Devices and Radiological Health nominated cell phone radiofrequency radiation (RFR) to the NTP for evaluation of potential toxicity and carcinogenicity. This nomination was made because of the rapidly growing use of cell phones in the 1990s, because exposure guidelines were based on protection from acute injury from thermal effects, and because little was known about possible health effects of long-term exposure to ‘non-thermal’ levels of RFR. Because of the widespread use of cell phones among the general public, even a small increase in cancer risk would have a serious health impact. The FDA nomination noted that “a significant research effort, involving large well-planned animal

experiments is needed to provide the basis to assess the risk to human health of wireless communications devices” (FDA, 1999).

Radiofrequency (RF) fields are part of the electromagnetic (EM) spectrum; however, unlike ionizing radiation, electromagnetic waves at frequencies used in mobile phones do not have sufficient energy to break chemical bonds or ionize molecules (Moulder et al., 1999). Tissue heating at high exposure intensities is the most firmly established mechanism for effects of RFR in biological systems. Consequently, it has been hypothesized that there is little theoretical basis for anticipating that nonionizing RFR at power levels used by mobile phones would have a significant effect on biological processes, such as causing direct DNA damage or inducing tumor formation by non-thermal mechanisms (Adair, 2003; Moulder et al., 2005).

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In the United States, the Federal Communications Commission (FCC) limits for maximum permissible exposure to RF fields are designed to protect against adverse effects that might occur due to increases in tissue or body temperature of 1 °C resulting from acute exposures. FCC exposure limits for controlled occupational exposure to cell phone RFR are 0.4 W/kg SAR averaged over the whole body and spatial peaks not to exceed 8 W/kg averaged over any 1 g of tissue; for the uncontrolled general population, exposure limits are 0.08 W/kg SAR averaged over the whole body and spatial SARs not to exceed 1.6 W/kg averaged over any 1 g of tissue (FCC, 1997). The SAR, or specific absorption rate, is a measure of the rate of RF energy absorbed per unit mass, and is expressed as W/kg or mW/g.

This commentary describes the general design and partial results of the NTP study on cell phone RFR and addresses several unfounded criticisms that have been promoted to minimize the findings of adverse health effects of cell phone RFR and the utility of the experimental data for assessing human health risks.

2. Design of the NTP study on cell phone radiofrequency radiation

Because little was known about possible health effects of long-term exposure to non-thermal or minimally thermal levels of cell phone RFR, and because guidelines for cell phone RFR are based largely on protection from acute injury due to thermal effects, the NTP study was designed to test the (null) hypothesis that cell phone radiation at non-thermal exposure intensities could not cause adverse health effects, and to provide dose-response data for any detected toxic or carcinogenic effects for health risk assessments.

In order to expose unrestrained animals to cell phone RFR in individual cages and for durations well beyond 2 h/day, the feasibility of using reverberation chambers for the exposure system was demonstrated in collaboration with Perry Wilson and other scientists from the RF fields group at the National Institute of Standards and Technology (NIST) in Boulder, Colorado. A reverberation chamber is a shielded room (shielded from penetrating electromagnetic fields, EMFs) with excitation antennae and ventilation panels. Field exposures emanate from all directions, while rotating paddles distribute the fields to create a statistically homogeneous electromagnetic environment. The feasibility study conducted at NIST showed that a uniform electromagnetic environment could be created in a reverberation chamber with cell phone RFR at two frequencies that are at the centers of the primary cellular bands used in the US (900 and 1900 MHz), and that the emitted power from the antenna was efficiently transmitted into biological simulation fluids located in different regions of the reverberation chamber.

Studies were then conducted for the NTP at IT'IS (Niels Kuster, principal investigator) in Zurich, Switzerland to (a) evaluate the actual absorbed dose and tissue uniformity in anatomical models in relation to animal orientation, animal number, and cage location in reverberation chambers, (b) to determine the influence of plastic animal racks, cages, bedding, and water bottles on animal dosimetry, and (c) to estimate the whole-body and organ-specific dosimetry of RFR in rats and mice exposed over lifetime in reverberation chambers. To eliminate absorption of RF power by the water bottles, a shielded automatic watering system was developed with a choke to prevent RF burns to animals while drinking water during exposures. Descriptions of the RFR reverberation chamber exposure system (Capstick et al., 2017) and the lifetime dosimetry assessment for rats and mice (Gong et al., 2017) have been published. The studies of RFR in anatomical models of rats and mice showed that the organ-specific SAR values compared to whole-body SARs was more uniform in rats exposed to 900 MHz RFR and in mice exposed to 1900 MHz RFR. Thus, for example, the SAR in the brain was nearly the same as the whole-body SAR in rats exposed to 900 MHz and in mice exposed to 1900 MHz RFR. In tissues with lower conductivity, e.g., fat, the SAR is much lower than the whole-body SAR. Therefore, 900 and 1900 MHz were the frequencies selected for the subsequent

NTP toxicity/carcinogenicity studies in rats and mice, respectively. To simulate actual cell phone use, animals were exposed to GSM (global system for mobile communication) or CDMA (code division multiple access) modulated signals at each frequency.

The NTP study, which was conducted at the IIT Research Institute (IITRI) in Chicago (David McCormick, principal investigator), comprised 4 phases:

Phase 1. Procurement of equipment and materials needed to construct the exposure and RFR monitoring systems, and validation that the systems function appropriately and meet NTP specifications (e.g., ventilation, temperature and humidity control, lighting, noise, EMF shielding, field uniformity, etc.). The NTP chronic studies required a total of 21 reverberation chambers: 3 power levels for mice exposed to 1900 MHz GSM modulated signals, 3 power levels for mice exposed to 1900 MHz CDMA modulated signals, 1 mouse sham chamber, 3 power levels for male and 3 power levels for female rats exposed separately to 900 MHz GSM modulated signals, 3 power levels for male and 3 power levels for female rats exposed separately to 900 MHz CDMA modulated signals, and 1 male and 1 female rat sham chamber. Rat chambers hold 100 rats and mouse chambers hold 200 mice.

Phase 2. Thermal pilot study: to determine the effects of modulated cell phone RFR exposures (whole body SARs ranging from 4 to 12 W/kg) on body temperature, body weight, and survival of rats and mice of varying ages. Body temperature was measured with subcutaneously implanted programmable temperature microchips.

Phase 3. Perinatal/prechronic toxicity study: to determine possible toxic effects of cell phone RFR and to determine appropriate power levels for each species and sex to be used in the chronic toxicity/carcinogenicity study. The study involved exposing pregnant animals beginning on gestation day 6 and continuing exposure of offspring until 7 weeks of age.

Phase 4. Chronic study: to determine chronic effects including carcinogenicity of modulated cell phone RFR in rats exposed *in utero* until 106 weeks of age and in mice exposed for 2 years beginning at 6 weeks of age. During the prechronic and chronic studies, animals were exposed 18 h per day on a continuous cycle of 10 min on and 10 min off. Thus, total daily exposures were 9 h; animal hygiene and collection of clinical signs, body weight and survival data were conducted during the 6-h period when the RFR exposures were shut off. The number of animals per group in the chronic study was 90; this is somewhat larger than typical NTP chronic studies (N = 50) in order to increase the statistical power of the study. Also, blood and brain tissue were collected (N = 10) at 19 weeks of age for micronuclei determinations and analyses of possible DNA strand breaks.

The experimental design was presented to scientists from the Radiofrequency Interagency Work Group (includes FDA, EPA, FCC, NIOSH, and OSHA), to the Toxicology Forum (2003), and at the 25th annual meeting of the Bioelectromagnetics Society (2003). The consensus opinion of participants at these presentations was that the NTP study would trump all studies that have examined the carcinogenic potential of RFR in experimental animals.

3. Partial results from the NTP studies on cell phone radiation

In the design of the NTP studies, the original expectation was that the maximum exposure intensity would be limited to a whole-body SAR of 4 W/kg to avoid increasing body temperature by approximately 1 °C. After all, the FCC limit for maximum permissible exposure to RFR was based on a whole-body SAR of 4 W/kg, in order to protect against adverse effects that might occur due to increases in tissue or body temperature of 1 °C from acute exposures (FCC, 1997). However, results from the NTP thermal pilot and prechronic studies indicated that rats could tolerate daily exposures up to 6 W/kg without significant effects on body temperature, body weights, or induction of tissue damage, while mice could also tolerate 10 W/kg and possibly even higher RFR intensities (Wyde et al., 2018); increases in core body temperature of

rats were less than 1 °C at exposures up to 6 W/kg. The results from these studies provided the basis for the selection of the RFR exposure intensities used in the subsequent chronic studies in rats: SAR = 0 (sham), 1.5, 3.0, and 6.0 W/kg. The maintenance of core body temperature (increases < 1 °C) and the lack of an effect of whole-body RFR exposures at 6 W/kg on rat body weights indicate that these exposure conditions did not create thermal effects that might have impacted the overall physiology of the animal leading to increased tumor incidences in the brain, heart, or other organs of exposed animals.

The histopathology findings from the chronic study in rats underwent rigorous peer review before the diagnoses were finalized. Complete necropsies and histopathology evaluations were conducted on every animal by a veterinary pathologist. The subsequent pathology peer review of the heart and central nervous system was first performed by two quality assessment pathologists, and then by Pathology Working Groups involving 30 pathologists from NTP and external to the program.

In May of 2016, NTP released partial findings from the chronic study of RFR in rats (NTP, 2016). The findings in that report were reviewed by 8 expert peer reviewers selected by the NTP and the NIH. The report focused on two organs in which the incidences of tumors were increased in exposed rats compared to controls; the diagnosed tumors were malignant gliomas in the brain and schwannomas of the heart. In addition, focal hyperplasias in these organs, which are considered to be preneoplastic lesions (i.e., part of a continuum of pathological changes leading to malignant glioma or schwannoma), were also observed in exposed rats. Table 1 shows the incidences of tumors and hyperplasias in the brain and heart of male rats.

Based on significant increases in incidence and trend for hyperplastic lesions and tumors of the brain and heart in RFR-exposed male rats, the NTP concluded “Under the conditions of these 2-year studies, the hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR.” Six of the expert peer reviewers agreed that tumor responses were the result of exposure to modulated RFR, one felt that study limitations complicate interpretations of risk, and one disagreed with the NTP conclusion.

In addition, to the tumor data described above, DNA damage (strand breaks detected with the comet assay) was significantly increased in the brains of rats and mice exposed to GSM- and CDMA-modulated RFR (Wyde, 2016).

The tumor and genotoxicity data (DNA strand breaks), as well as the findings of reduced pup birth weights when pregnant dams were exposed to GSM- or CDMA-modulated RFR and the induction of cardiomyopathy of the right ventricle in male and female rats from the NTP study clearly show that the null hypothesis (i.e., low-level cell phone

radiation at thermally insignificant exposures cannot cause adverse health effects) has been disproved. The NTP findings are most important because, in 2011, IARC classified radio frequency radiation as a “possible human carcinogen” based largely on increased risks of gliomas and acoustic neuromas (which are Schwann cell tumors on the acoustic nerve) among long term users of cell phones (IARC, 2013).

4. Unfounded criticisms and facts concerning the interpretation and utility of the animal data for assessing potential human health risks

After the release of the partial results from the NTP study on cell phone radiation, several unfounded criticisms of that study that were promoted and published in the popular media (e.g., Carroll, 2016; Foster, 2016; Singal, 2016). Most of these criticisms are presented below followed by explanations as to why those comments misrepresent the relevance and utility of the results of the NTP study for assessing potential human health risks.

Criticism 1: This is a rat study and does not represent what might happen in humans.

Fact: Because animals and humans exhibit similarities in biological processes of disease induction, data from studies in experimental animals are used to assess health risks from exposures to environmental or occupational agents. Similarly, the pharmaceutical industry relies on the results of animal studies prior to conducting clinical trials of new drugs in humans. The rationale for conducting carcinogenicity studies in animal models is based on experimental data showing that every agent that is known to cause cancer in humans has been shown to be carcinogenic in animals when adequately tested (IARC, 2006) and that almost one-third of human carcinogens were identified after carcinogenic effects were found in well-conducted animal studies (Huff, 1993). In addition, the careful control of exposure conditions in animal studies can eliminate the potential impact of confounding factors on the interpretation of study results. There is no reason to believe that a physical agent such as RFR would affect animal tissue but not human tissue. The concordance between rats and humans in cell type affected by RFR strengthens the animal-to-human association (US EPA, 2005).

Public health agencies that evaluate human cancer risks, rely on animal carcinogenicity data when there is insufficient or inadequate cancer data from studies in humans. The IARC monographs preamble notes: “it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans;” the US EPA Guidelines for Cancer Risk Assessment (US EPA, 2005) note “the default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans. Thus, if no adequate human or mode of action data are present, positive effects in animal cancer studies are a basis for assessing the carcinogenic hazard to humans.” Because of the long latency for many cancers (clinical manifestation may take as much as 30 years from time of first exposure), animal studies can eliminate the need to wait for sufficient human cancer data before implementing public health protective strategies.

Criticism 2: RFR exposure levels in the NTP study were much higher (19–75 times) than human exposure limits.

Fact: While the exposure limit to RFR for the general population in the US is 0.08 W/kg averaged over the whole body, the localized exposure limit is 1.6 W/kg averaged over any one gram of tissue (FCC, 1997); for occupational exposures, the limit is five times higher (0.4 W/kg and 8 W/kg, respectively). Thus, the whole-body exposure levels in the NTP study were higher than the FCC's whole-body exposure limits. Whole-body SAR, however, provides little information about organ-specific exposure levels (IARC, 2013). When an individual uses a cell phone and holds it next to his or her head, body tissues located nearest to the cell phone antenna receive much higher exposures than parts of

Table 1

Incidence of gliomas and glial cell hyperplasias of the brain, and schwannomas and Schwann cell hyperplasias of the heart in male rats exposed to GSM- or CDMA-modulated RFR.

Organ: lesion	Sham	GSM (SAR, W/kg)			CDMA (SAR, W/kg)		
		0	1.5	3.0	6.0	1.5	3.0
Brain: Incidence, %							
Glioma ^a	0	3.3	3.3	2.2	0	0	3.3
Glial cell hyperplasia	0	2.2	3.3	1.1	2.2	0	2.2
Total proliferative	0	5.5 [*]	6.6 [*]	3.3	2.2	0	5.5 [*]
Heart: Incidence, %							
Schwannoma ^{a,b}	0	2.2	1.1	5.5 [*]	2.2	3.3	6.6 [*]
Schwann cell hyperplasia	0	1.1	0	2.2	0	0	3.3
Total proliferative	0	3.3	1.1	7.7 [*]	2.2	3.3	9.9 [*]

* p < 0.05 compared to sham control.

^a Significant trend CDMA.

^b Significant trend GSM.

the body that are located distant from the antenna. Consequently, the localized exposure level is more important for understanding and assessing human health risks from cell phone RFR. When considering organ-specific risk (e.g., risk to the brain) from cell phone RFR, the important measure of potential human exposure is the local SAR value of 1.6 W/kg (the FCC's SAR limit for portable RF transmitters in the US, FCC, 1997) averaged over any gram of tissue. In the NTP study in which animals were exposed to whole-body RFR at SARs of 1.5, 3, and 6.0 W/kg, exposures in the brain were within 10% of the whole-body exposure levels. Consider the converse scenario. If the brain and whole-body exposures were limited to 0.08 W/kg, then localized exposures in humans from use of cell phones held next to the ear could be 20 times greater than exposures to the brain of rats in the NTP study. Under this condition, a negative study would be uninformative for evaluating organ-specific human health risks associated with exposure to RFR. Therefore, exposure intensities in the brains of rats in the NTP study were similar to or only slightly higher than potential, localized human exposures resulting from cell phones held next to the head.

Criticism 3: Daily exposures in rats were longer than typical human exposures to RFR.

Fact: Experimental carcinogenicity studies are generally conducted in small groups of rodents (e.g., 50 per exposure or control group), and incidence values of adverse effects are used to assess health risks to potentially millions of exposed people. With this relatively small group size, tumor incidence in an exposed group needs to be increased by ~10% compared to controls in order to achieve statistical significance. While an increased incidence of 1–5% in an experimental study would not be statistically significant, a 1–5% increased risk of brain cancers due to RFR exposures among the hundreds of millions of cell phone users in the US would be of epidemic proportions. Thus, to identify a hazardous agent, exposure levels in small groups of experimental animals are often much higher than human exposures, while lower doses are included for analyses of dose-response relationships. Exposure intensities in the NTP study in rats were limited to an SAR of 6 W/kg due to possible thermal effects at higher exposures that might affect the outcome of the study. To increase the statistical power of the chronic NTP study to detect an effect if one truly existed, group size was increased to 90 animals, and daily exposures were increased to 9 h/day. While the exposure pattern in the NTP study may not be typical for most or all cell phone users (though exposures to RFR are occurring from multiple emitting devices), health risk estimates would be based on the response rate (i.e., tumor incidence and/or other adverse effects) as a function of tissue dosimetry (absorbed power \times hours per day of exposure) over the comparable fraction of an exposed lifespan. From these data, cancer risk estimates can be made for any pattern of cell phone use, while actual risks would be related to a number of factors including cell phone emission values, side of head use of the phone, distance from the body that the phone is held, exposure to other RF emitting devices, etc.

Criticism 4: The tumor findings may have been affected by the longer survival of exposed rats compared to controls.

Fact: This comment is an inaccurate portrayal and interpretation of the data for at least two reasons: (1) there was no statistical difference in survival between control male rats and the exposure group with the highest rate of gliomas and heart schwannomas (CDMA-exposed male rats, SAR = 6.0 W/kg), and (2) no glial cell hyperplasias (potential precancerous lesions) or heart schwannomas were observed in any control rat, even though glial cell hyperplasia was detected in exposed rats as early as week 58 of the 2-year study and heart schwannoma was detected as early as week 70 in exposed rats. Thus, survival was sufficient to detect tumors or pre-cancerous lesions in the brain and heart of control rats.

Criticism 5: It is odd that increased incidences of gliomas and heart schwannomas were seen only in male rats and not in female rats.

Fact: Actually, there were gliomas and heart schwannomas in female

rats exposed to RFR but none in female controls; however, the incidences of these tumors in exposed female rats did not reach statistical significance. Gender differences in tumor incidence occur frequently in experimental toxicity and carcinogenicity studies (<https://ntp.niehs.nih.gov/results/index.html>), and gender differences in cancer rates also exist in humans (<https://seer.cancer.gov/faststats/selections.php?series=cancer>). For example, brain cancer mortality rates are approximately 50% higher in men than in women, and for many human cancers (e.g., colorectal, liver, soft tissue including heart, kidney, non-Hodgkin lymphoma, etc.) the incidence and mortality rates are much higher in men than in women. Thus, the different response rates between male and female rats in the NTP study of RFR does not diminish the human relevance of the cancer findings.

Criticism 6. Control rats oddly had low rates of tumors, and the incidence of gliomas and of heart schwannomas in controls were below the rates seen in studies in the past.

Fact: Control rats did have tumors (63% of males and 92% of control female rats); however, the tumor responses associated with exposure to RFR (gliomas and schwannomas of the heart) were not detected in controls. Gliomas and schwannomas of the heart are uncommon tumors that occur rarely in control Sprague-Dawley rats. It is not unusual to observe a zero incidence of uncommon tumors in groups of 50–90 control rats. In experimental carcinogenicity studies, the most important control group is the concurrent control group. As mentioned above, the uniquely designed reverberation chambers used in the NTP study were fully shielded from external EMFs. The housing of rats in the RFR shielded reverberation chambers could affect tumor rates in control animals. No data are available on expected tumor rates in control rats of the same strain (Hsd: Sprague Dawley rats) held under these specific environmental conditions.

Criticism 7. Because the study had low statistical power, it is likely to have an increased risk of being a false positive.

Fact: Having low statistical power means that there is a greater chance for a false negative rather than a false positive result (the chance of a false positive result is 5%). That is, with low statistical power there is a high probability of accepting the no-effect hypothesis even when a true effect exists.

Criticism 8. The pathology evaluations were not done blinded with respect to controls or exposed animals; exposed groups were analyzed first and then the unexposed group.

Fact: The reviews of the histopathology slides and final diagnoses of lesions in the RFR studies by the pathology working groups were conducted similar to all other NTP studies in that the pathologists did not know whether the slides they were examining came from an exposed or an unexposed animal (Maronpot and Boorman, 1982). In fact, the reviewing pathologists didn't even know that the test agent was RFR. For anyone questioning the diagnosis of any tissue in this study, all of the slides are available for examination at the NTP archives.

5. Discussion and conclusions

In 2011, an IARC expert working group of international scientists classified RFR as a possible human carcinogen based on *limited evidence* of carcinogenicity in humans and in experimental animals (IARC, 2013). Although associations had been observed between exposure to RFR from wireless phones and increased risks of glioma and acoustic neuroma (Schwann cell tumors on the acoustic nerve) among long term human users of cell phones, the positive case-control studies were considered to provide limited evidence of carcinogenicity in humans because of possible selection and recall bias. *Limited evidence* of carcinogenicity means that a causal interpretation for observed associations between exposure to the agent and cancer is credible, but that other explanations (e.g., chance, bias, or confounding) could not be fully ruled out. However, a recent re-analysis of the Canadian data that was included in the Interphone study showed that there was no effect on the risk of glioma after adjustments were made for selection and recall

biases; the odds ratios (OR) for glioma were significantly increased when comparing the highest quartile of use to those who were not regular users whether or not adjustments were made: OR = 2.0, 95% confidence interval 1.2–2.4 without adjustment; OR = 2.2 95% confidence interval 1.3–4.1 with adjustments (Momoli et al., 2017). Evidently, selection and recall biases do not explain the elevated brain cancer risk associated with use of cell phones.

The IARC working group also concluded that there was *limited evidence* in experimental animals for the carcinogenicity of RFR; chronic studies available at that time provided no evidence for induction of tumors by RFR in conventional animal models, but positive co-carcinogenic effects suggested that RFR may increase the potency of environmental carcinogens to which people are exposed. Mechanistic studies available at that time had minimal impact on the cancer evaluation of RFR; evidence was considered to be weak for RFR causing genotoxic effects, altering gene or protein expression, inducing changes in cell signaling, causing oxidative stress, or altering cell replication. Much of the available mechanistic data showed mixed results or inconsistency in response to RFR exposures.

The results from the NTP carcinogenicity studies clearly demonstrate the induction of proliferative lesions (tumors and hyperplasias in the brain and heart) by RFR in conventional animal models. Recently, Falcioni et al. (2018) from the Ramazzini Institute reported a significant increase in heart schwannomas in male Sprague-Dawley rats exposed to GSM-modulated RFR at a field strength of 50 V/m. The incidence of heart Schwann cell hyperplasia was also increased in that exposure group. The combined incidence of schwannomas and preneoplastic Schwann cell hyperplasias is highly significant ($p = 0.01$). These findings are consistent with the results from the NTP study and demonstrate that the proliferative effect of modulated RFR in heart Schwann cells is a reproducible finding. This consistency is further supported by the fact that Schwann cells are myelin-forming glial cells of the peripheral nervous system and are analogous to oligodendrocytes of the central nervous system (Herbert and Monk, 2017).

The concordance between the tumor types that were increased in the NTP studies and those showing increased risks in human studies strengthens the animal-to-human association for the induction of gliomas and schwannomas from exposure to RFR. Health risk estimates of cell phone RFR should be based on response rates (i.e., incidence of tumors and preneoplastic lesions) as a function of tissue dosimetry (absorbed power times hours per day of exposure) and duration of exposure in animals extrapolated to RFR dosimetry in exposed human. Even a small increase in cancer risk could have a serious health impact due to the widespread use of cell phones (~300 million in the US and 5 billion worldwide). In the meantime, precautionary principles should be promoted by health and regulatory agencies, especially for children and pregnant women.

In addition, previously reported co-carcinogenic effects of modulated RFR radiation in the liver and lung of mice that had been treated with the carcinogen ethylnitrosourea *in utero* (Tillmann et al., 2010) were replicated at exposure levels of 0.04, 0.4, and 2 W/kg SAR (Lerchl et al., 2015). Lerchl et al. concluded that their “findings are a very clear indication that tumor-promoting effects of life-long RF-EMF exposure may occur at levels supposedly too low to cause thermal effects.” Thus, the reproducibility of the tumor promoting effects of RFR at non-thermal exposure levels has been demonstrated. Also, Yang et al. (2012) showed that exposure to RFR can induce transformation of normal cells to tumor cells; NIH 3T3 cells that were exposed to 916 MHz RFR for 8–12 weeks formed clones in soft agar and tumors when inoculated onto the backs of immunodeficient mice.

Numerous *in vivo* and *in vitro* mechanistic studies on RFR have been conducted since the IARC review in 2011; many of these used improved exposure systems with more accurate measures of RF dosimetry. The majority of more recently published studies demonstrate consistency for the induction of oxidative stress (Yakymenko et al., 2016), while there were many additional positive genotoxicity studies including the

finding of DNA damage induced in brain cells of rats and mice exposed to GSM- or CDMA-modulated RFR in the NTP studies. Oxidative DNA damage can lead to mutations, chromosomal translocations, and genomic instability, which are cellular events that can result in cancer development (Berquist and Wilson, 2012). Induction of oxidative stress, which is a key characteristic of many human carcinogens (Smith et al., 2016), including ionizing radiation and asbestos, may also lead to the genotoxicity and carcinogenicity of nonionizing RFR. Thus, without causing direct DNA damage, RFR may induce oxidative DNA damage and thereby initiate or promote tumor development.

In conclusion, animal studies and mechanistic studies on RFR that have been published since 2011 clearly show that the evidence on the carcinogenicity of RFR is much stronger than it was at the time of the IARC evaluation. If the recent animal and mechanistic findings had been available in 2011, it is likely that RFR would have been classified as a probable human carcinogen.

6. Addendum

After this paper was submitted to *Environmental Research*, the NTP released drafts of the full technical reports on GSM- and CDMA-modulated cell phone RFR in rats and mice. Those reports were peer-reviewed by an external panel of scientists who had expertise in studying biological effects of electromagnetic fields and expertise in interpreting results from experimental carcinogenicity studies (NTP, 2016). The peer-review panel concluded that there was *clear evidence of carcinogenic activity* for heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR, *some evidence of carcinogenic activity* for brain gliomas in male rats (both GSM and CDMA), and *equivocal evidence of carcinogenic activity* for heart schwannomas in female rats (both GSM and CDMA). These categories of evidence are defined in all NTP technical reports: *some evidence of carcinogenic activity* means that the test agent caused an increased incidence in neoplasms, but “the strength of the response was less than that required for clear evidence.” *Equivocal evidence of carcinogenicity* means that there was “a marginal increase in neoplasms that may be test-agent related.” In addition, the studies in rats showed that the prostate gland was a target organ of proliferative lesions (neoplasms and/or preneoplastic epithelial hyperplasias) induced by GSM- and CDMA-modulated cell phone RFR. The peer review panel also concluded that there was *some evidence of carcinogenic activity* in the adrenal gland of male rats exposed to GSM-modulated RFR. The peer review panel concurred with NTP that there was *equivocal evidence of carcinogenic activity* of RFR in the prostate gland, pituitary gland, liver, meninges of the brain, and pancreas in rats, and for lymphoma and neoplasms in the lung, skin, and liver of mice. The expert peer-review panel clearly recognized the validity and biological significance of the adverse health effects produced in the NTP’s studies of cell phone RFR. The overall results from the NTP studies indicate that cell phone RFR is potentially carcinogenic to multiple organs of exposed people.

Declaration of interest

The author has consulted on the design and utility of the NTP study on cell phone radiation.

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NTP; Dr. Hardell and Dr. Carlsberg letter to the NTP, NIH, DHHS, NTP Technical Report On The Toxicology And Carcinogenesis Studies; Mar. 12, 2018

National Toxicology Program
National Institutes of Health
Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

March 12, 2018

Comments on:

NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES IN Hsd:SPRAGUE DAWLEY SD RATS
EXPOSED TO WHOLE-BODY RADIO FREQUENCY RADIATION
AT A FREQUENCY (900 MHz) AND MODULATIONS (GSM AND CDMA) USED BY
CELL PHONES

NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES IN B6C3F1/N MICE EXPOSED
TO WHOLE-BODY RADIO FREQUENCY RADIATION AT A FREQUENCY (1,900
MHz) AND MODULATIONS (GSM AND CDMA) USED BY CELL PHONES

We have read these two reports with interest. They show increased incidence of malignant schwannoma in the heart and brain glioma in male rats exposed either to GSM-modulated or CDMA modulated cell phone radiofrequency (RF) radiation for two years. There are also increased incidences of some other tumor types and diseases. We discuss in the following some of the major findings.

The reports the results on schwannoma and glioma are of special concern since they corroborate human epidemiology findings. Thus, it is noteworthy that similar tumors were found in the NTP study as in epidemiological studies on human use of wireless phones; mobile phones or cordless phones (DECT). Malignant schwannoma in the heart is a similar type of tumor as vestibular schwannoma in humans, also called acoustic neuroma, although acoustic neuroma is usually benign and may rarely undergo malignant transformation.

In the following we give an updated evaluation on the scientific evidence for increased risk for glioma and vestibular schwannoma (acoustic neuroma) associated with use of wireless phones. In our opinion also certain aspects on human epidemiology on this issue need to be further clarified and elaborated in the NTP report.

Our study group has since the end of the 1990's published results from case- control studies on use of wireless phones and brain tumor risk (Hardell et al 1999). An increased risk for brain tumors was found for ipsilateral use of mobile phones, the same side of the brain as the phone was used. A statistically significant increased risk was published for malignant brain tumors (Hardell et al 2002) and vestibular schwannoma (Hardell et al 2003). Further scientific evidence on the association has more recently been discussed by Carlberg and Hardell (2017).

Background

The brain is the main target for exposure to RF radiation during use of handheld wireless phones; both mobile and cordless phones (Cardis et al 2008, Gandhi et al 2012). An increased risk for brain tumors has been of concern for a long time. In May 2011 RF radiation in the frequency range 30 kHz–300 GHz was evaluated to be a Group 2B, i.e. a 'possible' human carcinogen, by the International Agency for Research on Cancer (IARC) at the World Health

Organization (WHO) (Baan et al 2011, IARC 2013). This was based on an increased risk for glioma and acoustic neuroma in human epidemiological studies.

The IARC cancer classification includes all sources of RF radiation. The exposure from mobile phone base stations, Wi-Fi access points, smart phones, laptops and tablets can be long-term, sometimes around the clock, at home, at work place, at school, and in the environment. For children this risk may be accentuated because of a cumulative effect during a long lifetime use (Hedendahl et al 2015).

The exposure guideline used by many agencies was established in 1998 by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and was based only on established short-term thermal (heating) effects from RF radiation neglecting non-thermal biological effects (ICNIRP 1988). The ICNIRP guidelines were updated in 2009 but still do not cover cancer and other long-term or non-thermal effects (ICNIRP 2009), see also Hardell (2017).

ICNIRP gives the guideline 2 to 10 W/m² for RF radiation depending on frequency. This is only based on a short-term immediate thermal effect (ICNIRP 2009). ICNIRP is a private non-governmental organisation (NGO) based in Germany. New expert members can only be elected by members of the organization. Many of the ICNIRP members have ties to the industry that is dependent on the ICNIRP guidelines. The guidelines are of huge economic and strategic importance to the military, telecom/IT and power industry.

In contrast to ICNIRP, the BioInitiative Reports from 2007, updated in 2012, based the evaluation also on non-thermal health effects from RF radiation (BioInitiative Working Group 2007, 2012). The scientific benchmark for possible health risks was defined to be 30 to 60 µW/m². In 2012, the Bioinitiative Working Group proposed a precautionary target level of 3–6 µW/m², using a safety factor of 10. Using the significantly higher guideline by ICNIRP gives a ‘green card’ to roll out the wireless digital technology thereby not considering non-thermal health effects from RF radiation.

Since the IARC evaluation in 2011 more studies have been published that support a causal association between RF radiation and brain and head tumors. Thus, it is impertinent to make an up-dated presentation in the NTP reports on current evidence on cancer risks associated with use of wireless phones.

A Danish cohort study on ‘mobile phone users’ (Johansen et al 2001, Schüz et al 2006) is not included here due to serious methodological shortcomings in the study design, see (Söderqvist et al 2012). The study by Benson et al (2013) is of limited value since use of cordless phones was not included, mobile phone use was assessed only at baseline and no information on tumor laterality including ipsilateral *versus* contralateral use were given. In spite of the many shortcomings an increased risk for acoustic neuroma was reported. The study will not be further discussed below.

First human epidemiology studies on specific tumor types are discussed. Then NTPs-study findings are presented and finally an evaluation of the combined evidence from human and animal studies.

Glioma

Human studies

Glioma is the most common malignant brain tumor and represents about 60 % of all central nervous system (CNS) tumors. Most of these are astrocytic tumors divided into low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). The most common glioma type is glioblastoma multiforme (WHO grade IV) with the peak incidence in the age group 45-75 years and median survival less than one year (Ohgaki, Kleihues 2005). No substantial increasing survival has been obtained during recent years. Three research groups have provided results in case-control studies on glioma, Interphone (Interphone 2010), Coureau et al (2014) and the Hardell group in Sweden (Hardell, Carlberg 2009, 2015a; Hardell et al 2006, 2011a, 2011b).

Random effects model was used for meta-analyses of published studies, based on test for heterogeneity in the overall group ("all mobile"), see also <http://www.bioinitiative.org/>. Note that only our group assessed also use of cordless phones. Thus the reference category in our studies included cases and controls with no use of wireless phones in contrast to the other studies investigating only mobile phone use. Including cordless phone use in the 'unexposed' group would bias the risk estimates towards unity (Hardell et al 2011a)

In Table 1 results for highest cumulative use in hours of mobile phones are given. All studies reported statistically significant increased risk for glioma and the meta-analysis yielded odds ratio (OR) = 1.90, 95 % confidence interval (CI) = 1.31-2.76. For ipsilateral mobile phone use the risk increased further to OR = 2.54, 95 % CI = 1.83-3.52 in the meta-analysis based on 247 exposed cases and 202 exposed controls. Further support for the increased risk of glioma associated with mobile phone use has been obtained in additional analyses of parts of the Interphone study (Cardis et al 2011, Grell et al 2016, Momoli et al 2017).

Table 1. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for glioma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010						
Cumulative use $\geq 1,640$ h	210/154	1.40	1.03 – 1.89	100/62	1.96	1.22 – 3.16
Coureau et al 2014						
Cumulative use ≥ 896 h	24/22	2.89	1.41 – 5.93	9/7	2.11	0.73 – 6.08
Hardell, Carlberg 2015						
Cumulative use $\geq 1,640$ h	211/301	2.13	1.61 – 2.82	138/133	3.11	2.18 – 4.44
Meta-analysis						
Cumulative use $\geq 1,640$ h*	445/477	1.90	1.31 – 2.76	247/202	2.54	1.83 – 3.52

* ≥ 896 h used for Coureau et al.

We analyzed survival of the patients in our studies and found shorter survival in patients with glioblastoma multiforme associated with use of wireless phones compared with patients with no use (Carlberg, Hardell 2014). Interestingly mutation of the p53 gene involved in disease progression has been reported in glioblastoma multiforme in patients with mobile phone use

≥3 hours per day. The mutation was statistically significant correlated with shorter overall survival time (Akhavan-Sigari et al 2014).

NTP study

No increased incidence of glioma was reported in the mice study (*NTP TR 596*).

In male rats (*NTP TR 595*) malignant glioma and glia cell hyperplasia occurred in all groups exposed to GSM-modulated cell phone RF radiation for 2 years. No lesions were seen in sham controls. In female rats glial cell hyperplasia occurred in one rat (3 W/kg) but none in sham controls. One malignant glioma occurred in one rat in the 6 W/kg group but none in sham controls. These results were not statistically significant.

In male rats exposed to CDMA-modulated cell phone RF radiation for 2 years there was an increased incidence of malignant glioma with a statistically significant trend, $p = 0.044$. In females three malignant glioma occurred in the 1.5 W/kg group, but none in the other exposed groups or sham control. Glial cell hyperplasia was seen in most exposed groups, although not statistically significant.

Evaluation

Based on human epidemiology studies and the NTP animal study there is clear evidence that RF radiation causes glioma in humans.

Meningioma

Human studies

Meningioma is an encapsulated, well-demarcated and rarely malignant tumor. It is the most common benign brain tumor that accounts for about 30 % of intracranial neoplasms. It develops from the pia and arachnoid membranes that cover CNS. It is slow growing and gives neurological symptoms by compression of adjacent structures. Most common are headaches and seizures. The incidence is about two times higher in women than in men and meningioma develops mostly among middle aged and older persons (Cea-Soriano et al 2012). The same research groups as for glioma included also meningioma in their case-control studies with a separate publication on meningioma by Carlberg, Hardell (2015). Results of the meta-analyses for cumulative exposure in highest exposure category are given in Table 2. A statistically significant increased risk was obtained for ipsilateral mobile phone use with OR = 1.49, 95 % CI = 1.08-2.06.

Table 2. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for meningioma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010						
Cumulative use ≥1,640 h	130/107	1.15	0.81 – 1.62	46/35	1.45	0.80 – 2.61
Coureau et al 2014						
Cumulative use ≥896 h	13/9	2.57	1.02 – 6.44	6/4	2.29	0.58 – 8.97
Carlberg et al 2013						
Cumulative use ≥1,640 h	141/301	1.24	0.93 – 1.66	67/133	1.46	0.98 – 2.17
Meta-analysis						
Cumulative use ≥1,640 h*	284/417	1.27	0.98 – 1.66	119/172	1.49	1.08 – 2.06

*≥896 h used for Coureau et al.

NTP study

No increased incidence was reported in mice (*NTP TR 596*).

In the rat study (*NTP TR 595*) increased incidence of malignant or benign granular cell tumors occurred in the males exposed to GSM-modulated cell phone RF radiation for 2 years. This was not statistically significant, trend $p = 0.343$. In female rats granular cell tumors malignant or benign were not associated with RF radiation, p trend = 0.594.

Evaluation

Based on human epidemiology studies and the NTP animal study there is equivocal evidence that RF radiation causes meningioma in humans (may be related to exposure).

Rate/incidence of brain tumors

The Swedish Cancer Register has not shown increasing incidence of brain tumors in a study for the time period 1979-2008, and has been used to dismiss epidemiological evidence on a risk (Deltour et al 2012). We have previously published that descriptive studies cannot be used to dismiss results in analytical epidemiology with individual exposure histories such as in case-control studies. We have also published the deficiencies in reporting of brain tumors to the Swedish Cancer Register (Hardell, Carlberg 2015b). Results for more recent time periods have now been published. These articles discuss also results from studies in other countries.

We used the Swedish National Inpatient Register (IPR) and Causes of Death Register (CDR) to study the incidence of brain tumors comparing with the Swedish Cancer Register data for the time period 1998–2013 using joinpoint regression analysis (Hardell, Carlberg 2015b). In the IPR we found a joinpoint in 2007 with Annual Percentage Change (APC) +4.25%, 95% CI +1.98, +6.57% during 2007–2013 for tumors of unknown type in the brain or CNS. Figure 1 shows time trends in IPR for brain tumors of unknown type (D43), red line, and mobile phone communication; number of out-going mobile phone minutes in millions per year (blue line). The figure shows increasing rates of brain tumors with some latency in relation to increasing use of mobile phones.

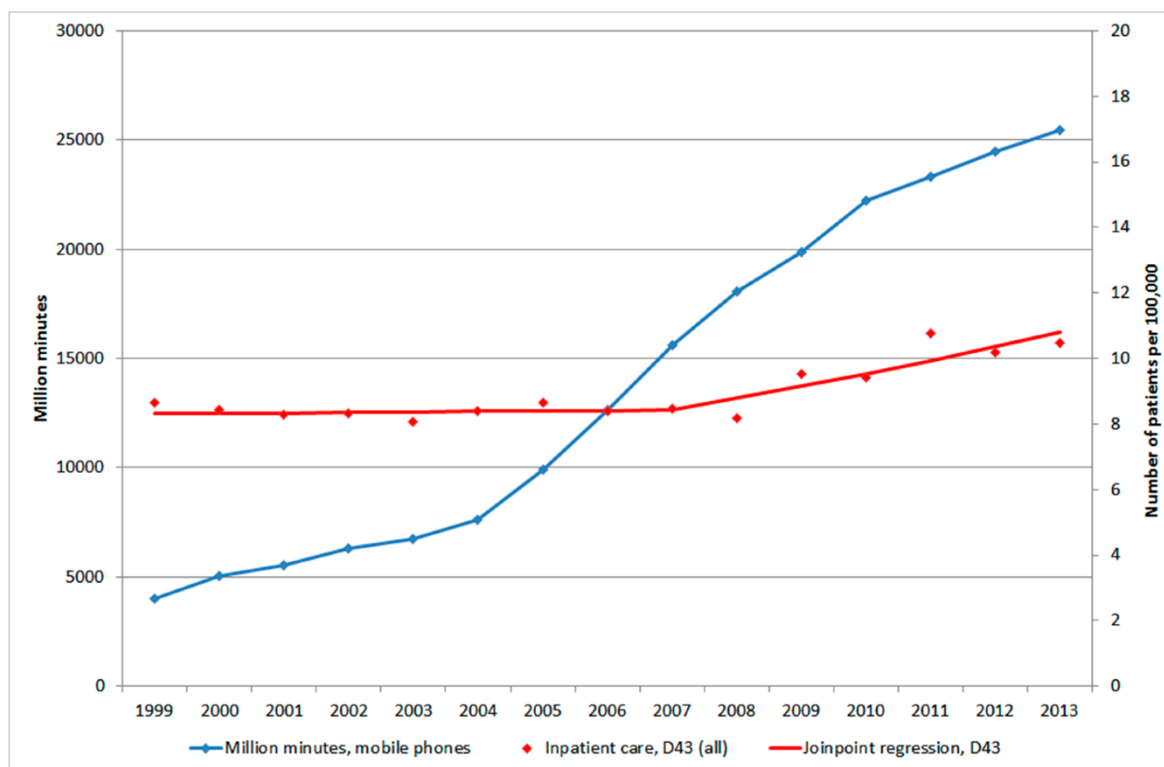


Figure 1. Number of out-going mobile phone minutes in millions during 1999–2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf> ; accessed on 1 April 2015) and joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish National Inpatient Register for all ages during 1999–2013 diagnosed with D43 = tumor of unknown type in the brain or CNS (<http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard> ; accessed on 1 April 2015).

In the Causes of Death Register (CDR) joinpoint regression found one joinpoint in 2008 with APC during 2008–2013 +22.60%, 95% CI +9.68, +37.03%. These tumor diagnoses would be based on clinical examination, mainly CT and/or MRI, but without histopathology or cytology. No statistically significant increasing incidence was found in the Swedish Cancer Register during these years. We postulated that a large part of brain tumors of unknown type are never reported to the Cancer Register. Furthermore, the frequency of diagnoses based on autopsy has declined substantially due to a general decline of autopsies in Sweden adding further to missing cases. We conclude that the Swedish Cancer Register is not reliable to be used to dismiss results in epidemiological studies on the use of wireless phones and brain tumor risk.

In Figure 2 we show rates per 100,000 of deaths in unknown type of brain tumor (D43), red line, and number of out-going mobile phone minutes in millions (blue line) during 1999–2013. We postulate that the increasing rate of patients deceased with brain tumor may be associated with the increasing use of mobile phones.

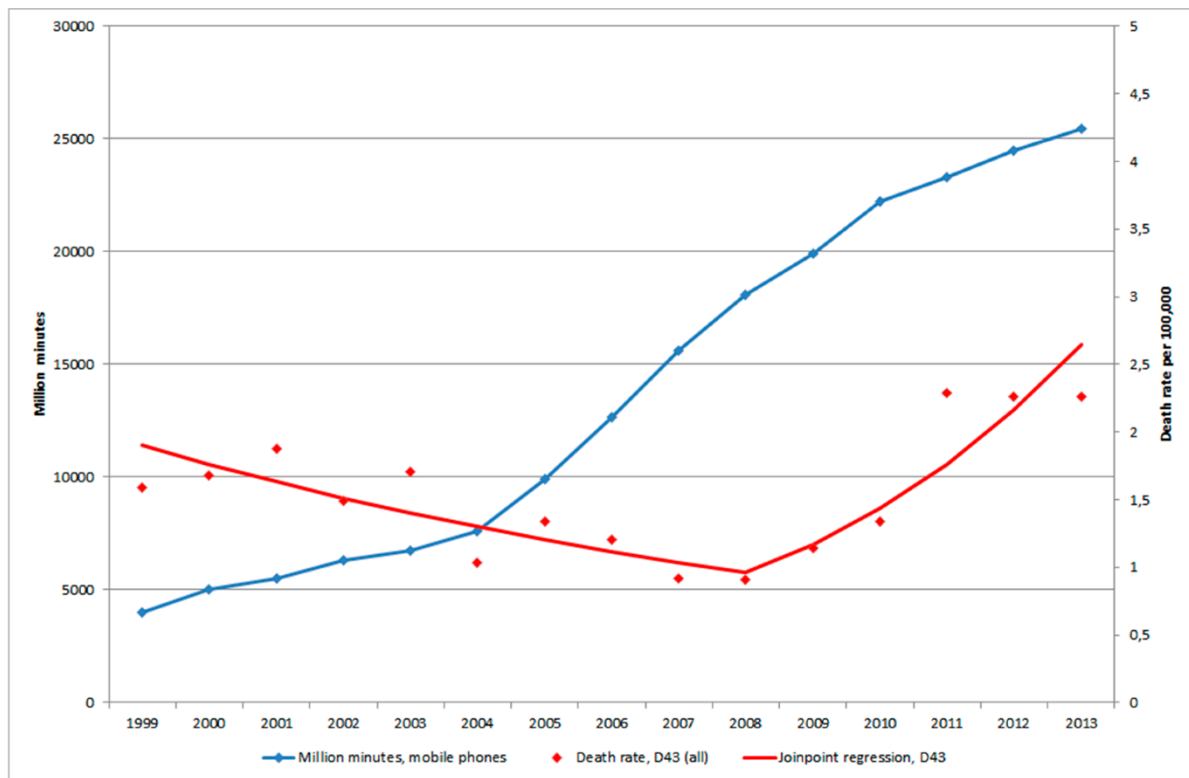


Figure 2. Number of out-going mobile phone minutes in millions during 1999–2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf> ; accessed on 1 April 2015) and joinpoint regression analysis of age-standardized death rates per 100,000 inhabitants according to the Swedish Causes of Death Register for all ages during 1999–2013 diagnosed with D43 = tumor of unknown type in the brain or CNS (<http://www.socialstyrelsen.se/statistik/statistikdatabas/dodsorsaker> ; accessed on 1 April 2015).

In an up-dated further analysis we used the Swedish Inpatient Register (IPR) to analyze rates of brain tumors of unknown type (D43) during 1998-2015 in different age groups (Hardell, Carlberg 2017). Average Annual Percentage Change (AAPC) per 100,000 increased with +2.06 %, 95 % confidence interval (CI) +1.27, +2.86 % in both genders combined. A joinpoint was found in 2007 with APC 1998-2007 of +0.16 %, 95 % CI -0.94, +1.28%, and 2007-2015 of +4.24 %, 95 % CI +2.87, +5.63 %. Highest AAPC was found in the age group 20-39 years.

In the Swedish Cancer Register the age-standardized incidence rate per 100,000 increased for brain tumors, ICD-code 193.0, during 1998-2015 with AAPC in men +0.49 %, 95 % CI +0.05, +0.94 %, and in women +0.33 %, 95 % CI -0.29, +0.45 % (Hardell, Carlberg 2017). The cases with brain tumor of unknown type lack morphological examination. Brain tumor diagnosis was based on cytology/histopathology in 83 % for men and in 87 % for women in 1980. This frequency increased to 90 % in men and 88 % in women in 2015. During the same time period CT and MRI imaging techniques were introduced and morphology is not always necessary for diagnosis. If all brain tumors based on clinical diagnosis with CT or MRI had been reported to the Cancer Register the frequency of diagnoses based on cytology/histology would have decreased in the register. The results indicate underreporting of brain tumor cases to the Cancer Register. The real incidence would be higher. Thus, incidence trends based on

the Cancer Register should be used with caution. Our results support mobile and cordless phones as risk factors for brain tumors with a reasonable latency period.

Figure 3 shows joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015, and Figure 4 results in women.

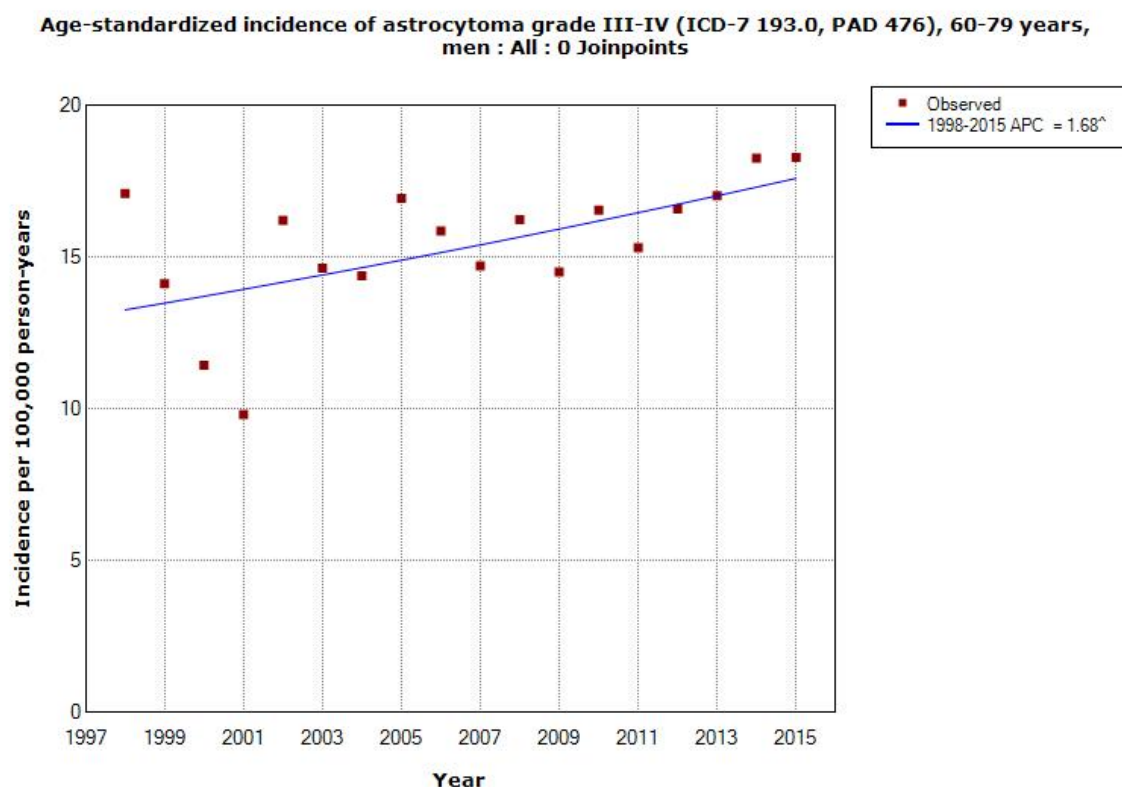


Figure 3. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC +1.68 %, 95 % CI +0.39, +2.99 %. (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>). <https://doi.org/10.1371/journal.pone.0185461.g005>

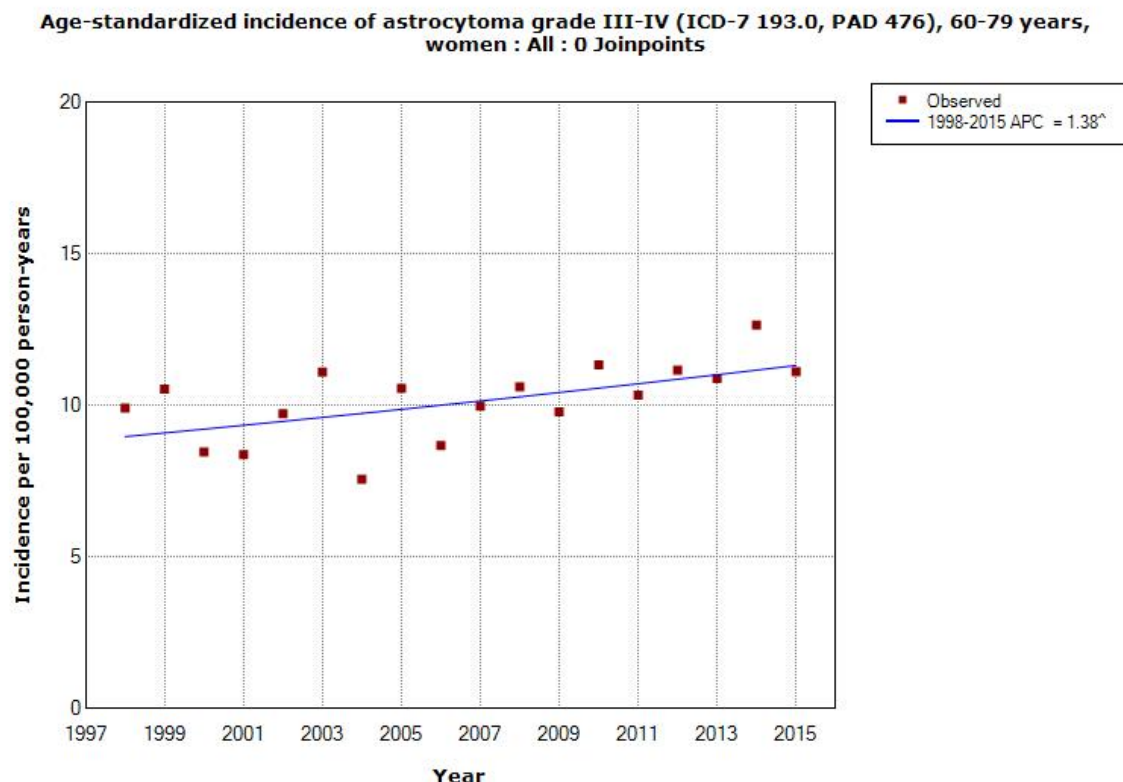


Figure 4. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in women aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC + 1.38 %, 95 % CI +0.32, +2.45 %.

(<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

<https://doi.org/10.1371/journal.pone.0185461.g006>

Evaluation

Increasing rates/incidences of brain tumors in Sweden, a country with among the earliest use of wireless phones in the world, have been published. Similar findings have been reported from other countries. The results give some evidence that RF radiation causes brain tumors in humans.

Acoustic neuroma (vestibular schwannoma)

Human studies

Acoustic neuroma, also called vestibular schwannoma, is a benign tumor located on the eighth cranial nerve from the inner ear to the brain. It is usually encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It grows slowly and due to the narrow anatomical space may give compression of vital brain stem structures. First symptoms of acoustic neuroma are usually tinnitus and hearing problems. Results for use of mobile phones in Interphone (2011) and Hardell et al (2013a) are given in Table 3. Statistically significant increased risk was found for cumulative ipsilateral use $\geq 1,640$ h yielding OR = 2.71, 95 % CI = 1.72-4.28.

Table 3. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for acoustic neuroma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010 Cumulative use $\geq 1,640$ h	77/107	1.32	0.88 – 1.97	47/46	2.33	1.23 – 4.40
Hardell et al 2013 Cumulative use $\geq 1,640$ h	27/301	2.40	1.39 – 4.16	19/133	3.18	1.65 – 6.12
Meta-analysis Cumulative use $\geq 1,640$ h	104/408	1.73	0.96 – 3.09	66/179	2.71	1.72 – 4.28

The study by Moon et al (2014) was not included in the meta-analysis since data on cumulative mobile phone use with numbers of cases and controls were not given. Support of an increased risk was seen in the case-case part of the study (Moon et al 2014), as also reported by Sato et al (2011) in their case-case analysis. Pettersson et al made a case-control study on acoustic neuroma in Sweden not overlapping our study (Pettersson et al 2014). An increased risk for highest category of cumulative use of both mobile phone (≥ 680 h OR = 1.46, 95 % CI = 0.98-2.17) and cordless phone (≥ 900 hours OR = 1.67, 95 % CI = 1.13-2.49) was found. We did not include that study in our meta-analysis due to the many scientific shortcomings in the study, e.g. laterality analysis was not made for cordless phone and the numbers in the laterality analysis for mobile phone are not consistent in text and tables and obviously not correct, and the 'unexposed' reference category included subjects using either mobile or cordless phone (Hardell, Carlberg 2014).

The Danish part of Interphone study reported mean tumor volume 1.66 cm^3 among regular mobile phone users and 1.39 cm^3 for non-users ($p = 0.03$) (Christensen et al 2004). We analyzed percentage change in tumor volume per year of latency and 100 h of cumulative use (Hardell et al 2013). For all types of wireless phones the percentage of tumor volume increased, statistically significant for analogue mobile phones. Moon et al (2014) reported statistically significant larger mean tumor volume for heavy users ($11.32 \pm 15.43 \text{ cm}^3$) compared with light users ($4.88 \pm 5.60 \text{ cm}^3$) based on daily amount of mobile phone use ($p = 0.026$). Similar results were found for cumulative hours of use. Taken together these results support tumor promotion by RF radiation.

NTP study

No malignant schwannoma was reported in the mice study (NTP TR 596).

In the rat study (NTP TR 595) there was an increased incidence of malignant schwannoma in the heart in males exposed to GSM modulated cell phone RF radiation for 2 years; trend $p = 0.041$. The tumor was found in all exposed male rats, whereas no malignant schwannoma was found in sham controls. Endocardial hyperplastic Schwann cell lesions, that are preneoplastic, were found in one 1.5 W/kg and in two 6 W/kg males, but no in sham control. Two female rats were diagnosed with malignant schwannoma in the heart in the 3 w/kg group, no was found in the two other exposure groups or in sham control, p trend = 0.640.

Evaluation

Based on human epidemiology studies and the NTP animal study there is clear evidence that RF radiation causes vestibular schwannoma (acoustic neuroma) in humans

Pituitary tumor

Human studies

In a case-control study from Japan no statistically significant increased risks were found for use of mobile phone (Takebayashi et al 2008). A somewhat increased risk was found in the highest cumulative call time in hours, OR = 1.33, 95 % CI = 0.58-3.09. The cases were aged 30-69 years and diagnosed during 2000-2004.

In a UK case-control study with patients diagnosed during 2001-2005 overall no statistically significant increased risks were found (Schoemaker, Swerdlow 2009). In the group with ≥ 10 years of use a somewhat increased risk was found for analog mobile phone use, OR = 1.2, 95 % CI = 0.6-2.4, and digital mobile phone use with OR = 2.5, 95 % CI = 0.7-9.1.

In a case-control study from China with cases diagnosed 2006-2010 mobile phone use yielded an increased risk for pituitary tumor, OR = 7.6, 95 % CI = 2.6-21.4 and duration of use gave OR = 8.5, 95 % CI = 2.8-24.4 (Leng, Zhang 2016). However no more data were given.

The incidence of pituitary tumors increased during the time period 2004-2009 in USA (Gittleman et al 2014). The incidence is increasing in Sweden especially sine 2000, see Fig 5. There seems to be a drop during the latest year, but this may be explained by a time lag in the reporting to the Swedish Cancer Register.

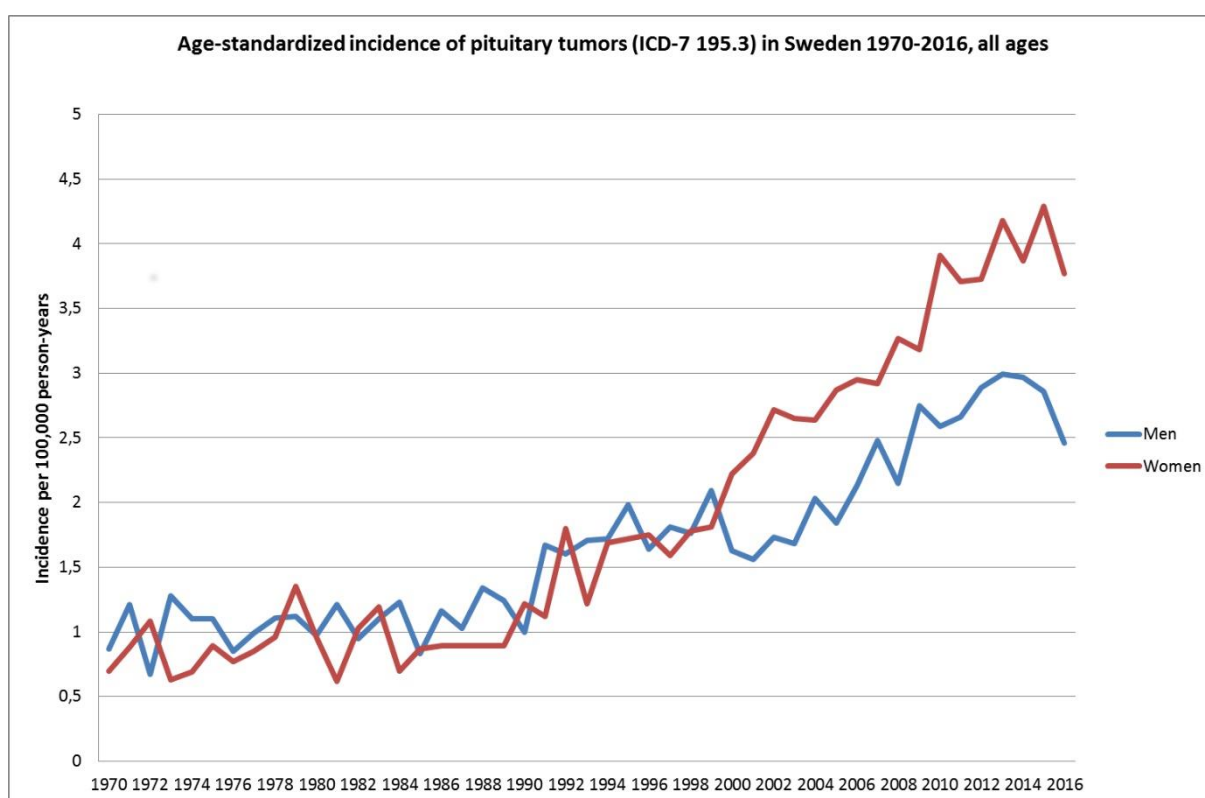


Figure 5. Age-standardized incidence of pituitary tumors (ICD-7 195.3) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

NTP

In male rats exposed to GSM-modulated cell phone RF radiation for 2 years (*NTP TR 595*) increased incidence of pituitary adenoma was found in all exposed groups, although not statistically significant. In females the incidence of adenoma in 1.5 W/kg and 6 W/kg were statistically significant decreased.

In male rats exposed to CDMA-modulated RF radiation for 2 years an increased incidence of pituitary adenoma was found in the 1.5 W/kg ($p=0.208$) and 3W/kg ($p=0.030$). In females there was a statistically decreased incidence of adenoma or carcinoma in the 3 W/kg group ($p=0.030$).

In male mice (*NTP TR 596*) exposed to CDMA-modulated RF radiation for 2 years two adenoma and one carcinoma occurred in pars distalia of the pituitary gland. No carcinoma or adenoma occurred in the sham control or the other two exposure groups. No increased incidence was seen in female mice.

Evaluation:

Based on human epidemiology studies and the NTP animal study there is equivocal evidence that RF radiation causes pituitary tumor in humans (may be related to exposure).

Thyroid cancer**Human studies**

The incidence of thyroid cancer is increasing in many countries, especially the papillary type that is the most radiosensitive type. We used the Swedish Cancer Register to study the incidence of thyroid cancer during 1970-2013 using joinpoint regression analysis (Carlberg et al 2016). In women, the incidence increased statistically significantly during the whole study period; AAPC +1.19 % (95 % CI +0.56, +1.83 %). Two joinpoints were detected, 1979 and 2001, with a high increase of the incidence during the last period 2001-2013 with an APC of +5.34 % (95 % CI +3.93, +6.77 %).

In the age group 20-39 years joinpoint regression analysis of age-standardized incidence of thyroid cancer in women, aged 20–39 years, APC increased with + 10.77 % (95 % CI +5.75, +16.04 %) during the time period 2006-2013, see Figure 6.

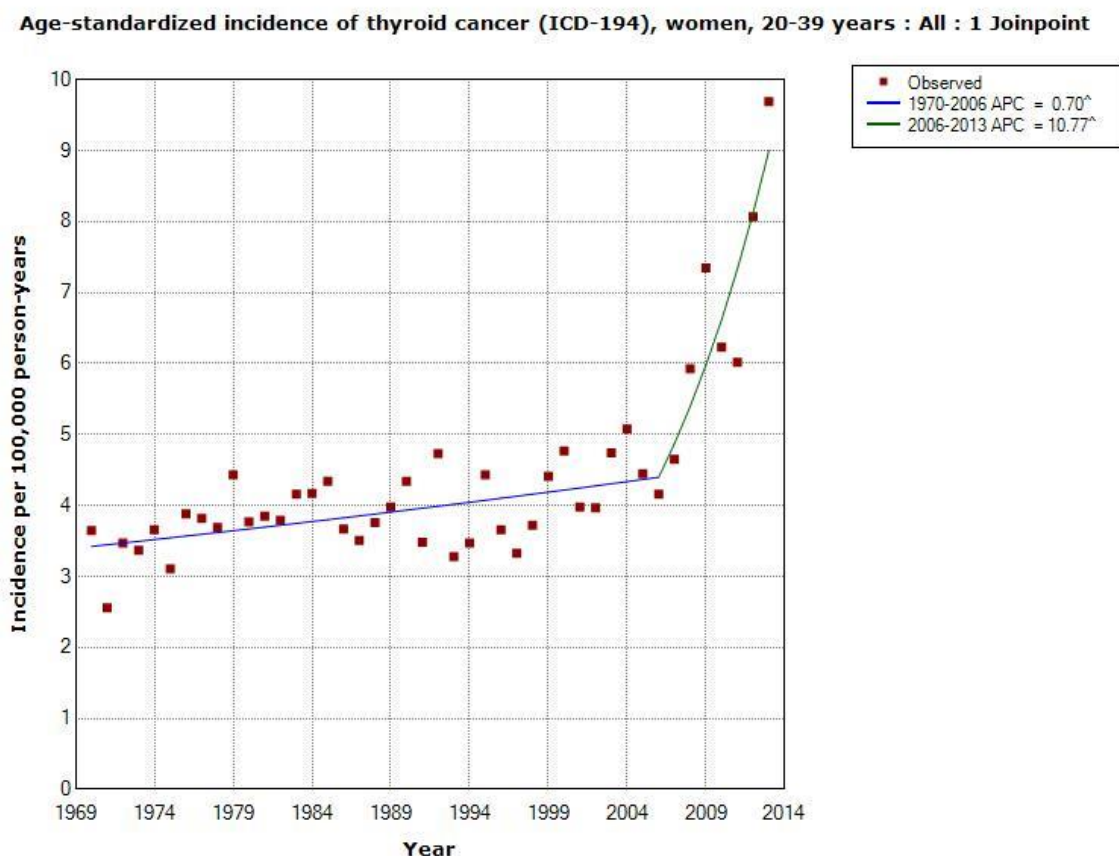


Figure 6. Joinpoint regression analysis of age-standardized incidence of thyroid cancer for women, aged 20–39 years, 1970–2013. Incidence per 100,000 inhabitants for ICD-7 code 194 according to the Swedish Cancer Register
<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>)

Analyses based on data from the Cancer Register showed that the increasing trend in Sweden was mainly caused by thyroid cancer of the papillary type. The incidence increased statistically significantly in women with an AAPC of +4.38 % (95 % CI +2.95, +5.84 %) during 1993-2013, see Figure 7. One joinpoint was detected in 2006; 1993-2006 APC +1.69 % (95 % CI +0.32, +3.08 %), 2006-2013 APC +9.58 % (95 % CI +5.85, +13.44 %). The incidence increased in men during 1993-2013 with an AAPC of +3.95 % (95 % CI +2.20, +5.73%).

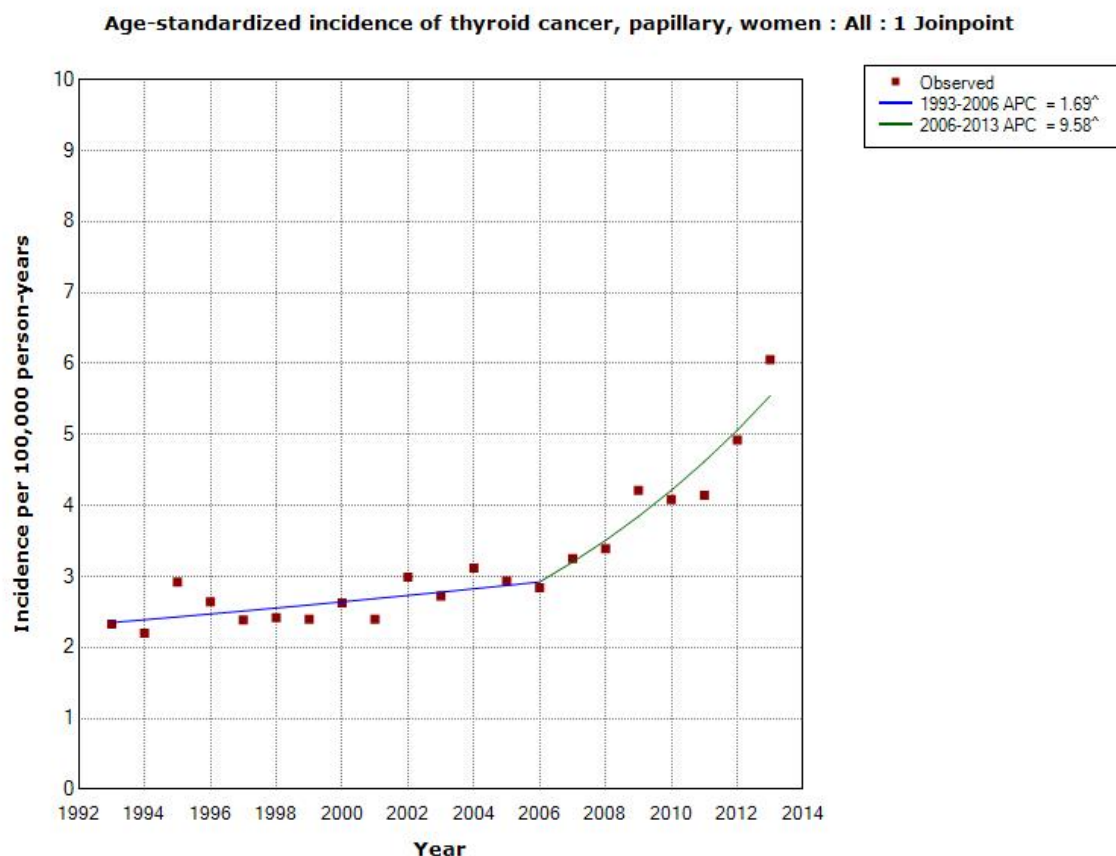


Figure 7. Joinpoint regression analysis of age-standardized incidence of papillary thyroid cancer for women, all ages, 1993–2013. Incidence per 100,000 inhabitants for ICD-7 code 194; data obtained from the Swedish Cancer Register

AAPC for all men during 1970-2013 was +0.77 % (95 % CI -0.03, +1.58 %). One joinpoint was detected in 2005 with a statistically significant increase in incidence during 2005-2013; APC +7.56 % (95 % CI +3.34, +11.96 %). Based on NORDCAN data, there was a statistically significant increase in the incidence of thyroid cancer in the Nordic countries during the same time period. In both women and men a joinpoint was detected in 2006. The incidence increased during 2006-2013 in women; APC +6.16 % (95 % CI +3.94, +8.42 %) and in men; APC +6.84 % (95 % CI +3.69, +10.08 %), thus showing similar results as the Swedish Cancer Register.

We postulate that the whole increase cannot be attributed to better diagnostic procedures. In Figure 8 Swedish data are shown on number of out-going mobile phone minutes during 2001-2013 and the incidence of thyroid cancer in men (green line) and in women (red line). Clearly, with a lag time of some years after the increasing number of out-going calls, the thyroid cancer incidence is-increasing.

Increasing exposure to ionizing radiation, e.g. medical CT scans, and to RF radiation should be further studied as causative factors to this emerging thyroid cancer health problem.

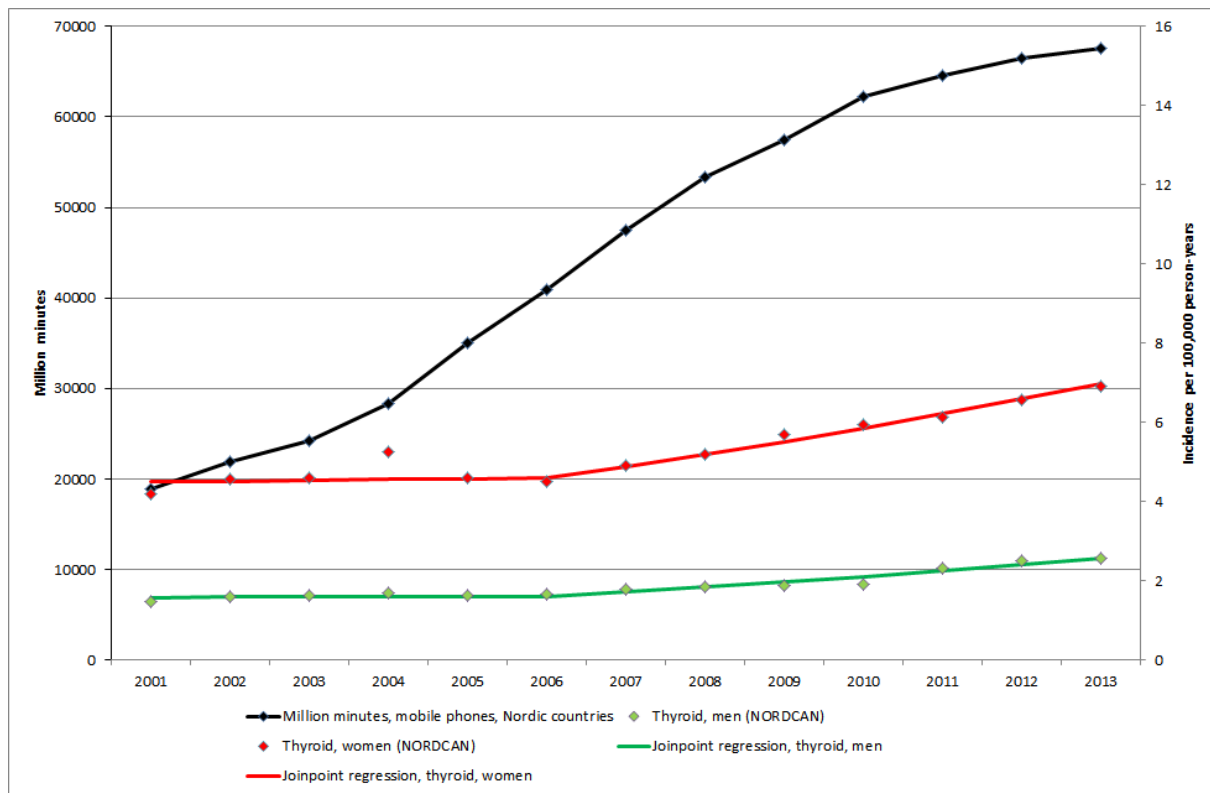


Figure 8. Number of out-going mobile phone minutes and incidence of thyroid cancer 2001–2013. Mobile phone minutes in millions in the Nordic countries (<http://statistik.pts.se/PTSnordic/NordicBaltic2014/>) and incidence per 100,000 person-years for all ages 2001–2013 according to NORDCAN (<http://www-dep.iarc.fr/NORDCAN/english/frame.asp>). Joinpoint regression analyses based on the time period 1970–2013

Figure 9 shows three developments in the antenna design in mobile phones that may be of relevance in thyroid carcinogenesis. The second generation (2G) mobile phones started in the 1990s with the external retractable monopole or helical antennas. The 2G GSM band operated at 800/900 MHz frequency band, later accompanied by 1,800 MHz band. Around the turn of the millennium, the external antennas were starting to disappear, replaced with new phone models with internal planar or microstrip antennas. The first internal antenna was introduced in 1998 and the first dual-band mobile phone, with the internal antenna, was introduced on the market in 1999 (Garg et al 2001). The internal antennas were positioned at the top of the telephone. With the emergence of the smartphones in the mid and late 2000s, the internal antenna location started to shift from the top of the phone to the bottom. Currently, the majority of smartphone models have their antenna positioned at the bottom of the phone, thus closer the thyroid gland (grey in figure). This would have a major impact on increasing radiation to the thyroid gland from smartphones.

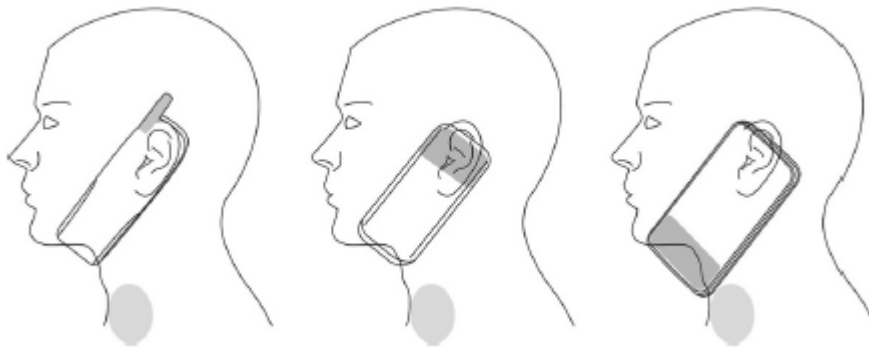


Figure 9. Mobile phone antenna placements in regard to the thyroid gland

Some published laboratory studies are of interest, Radiofrequency radiation at 2.45 GHz at a non-thermal level modified the morphology of the thyroid gland in a study on rats. The central and peripheral follicles presented increased in size and the thickness of peripheral septa decreased. Peripheral follicles increased in size with repeated exposure at 3 W power (Misa-Agustiño et al 2015).

In another study on rats, whole body exposure to 900 MHz pulse-modulated RF radiation that was similar to that emitted by the global system for mobile communications (GSM) mobile phones caused pathological changes in the thyroid gland. The gland structure was altered and caspase-dependent pathways of apoptosis were enhanced (Eşmekaya et al 2010).

NTP studies

In mice (*NTP TR 596*) no increased incidence was reported.

In female rats (*NTP TR 595*) a statistically significant increased incidence of C-cell hyperplasia was found in the 2 years GSM exposed groups (1.5, 3 and 6 W/kg, respectively). In males a statistically non-significant increased incidence was seen in the 1.5 W/kg exposure group.

Evaluation

C-cell hyperplasia as a precursor to familial medullary thyroid cancer in humans is well established. C-cell hyperplasia may be a precursor to other types of thyroid cancer but its role is not well established. Based on human cancer statistics and the NTP animal study there is some evidence that thyroid cancer is caused by RF radiation in humans.

Malignant lymphoma

Human studies

Few studies exist on malignant lymphoma and exposure to RF radiation. In a case-control study male and female subjects aged 18-74 years living in Sweden were included during a period from 1 December 1999 to 30 April 2002 (Hardell et al 2005). Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated. NHL of the B-cell type was not associated with the use of cellular or cordless telephones. Regarding T-cell NHL and >5 year latency period, the use of analogue cellular phones yielded: OR = 1.46, 95%; 95 % CI = 0.58-3.70, digital: OR=1.92, 95%; CI=0.77-4.80 and cordless phones: OR=2.47; 95 % CI=1.09-5.60. The corresponding results for certain, e.g. cutaneous and

leukaemia, T-cell lymphoma for analogue phones were: OR=3.41, 95%; CI=0.78-15.0, digital: OR=6.12, 95%; CI=1.26-29.7 and cordless phones: OR=5.48, 95%; CI=1.26-23.9. The results indicate an association between T-cell NHL and the use of cellular and cordless telephones, however based on low numbers and must be interpreted with caution. Regarding B-cell NHL no association was found.

A case-control study in USA used a questionnaire to assess cellular telephone use in 551 NHL cases and 462 frequency-matched population controls (Linet et al 2006). Compared to persons who had never used cellular telephones, risks were not increased among individuals whose lifetime use was more than 100 times (e.g., regular users, OR = 0.9, 95% CI= 0.6-1.4).

Among regular users compared to those who had never used hand-held cellular telephones, risks of NHL were not statistically significantly associated with minutes per week, duration, cumulative lifetime or year of first use, although NHL was non-significantly higher in men who used cellular telephones for more than 8 years; OR = 2.4, 95 % CI = 0.8-7.0. Little evidence linked use of cellular telephones with total, diffuse large B-cell lymphoma or follicular NHL. No results were presented for T-cell lymphoma.

In USA primary central nervous system lymphoma (PCNSL) rates in immunocompetent men and women aged 65+ years increased statistically significantly (1.7% and 1.6% per year, respectively), but remained stable in other age groups during 1992-2011 (Shiels et al 2016). Thus, the increasing rates could not be related to HIV or immune suppression in organ transplant patients.

In Sweden increasing incidence of PCNSL was reported for the time period 2000-2013 in immunocompetent persons (Eloranta et al 2018). With 359 identified PCNSL cases (median age 66 years), overall incidence was 0.26 (95% CI= 0.24-0.29) and the average annual increase 4% ($p = 0.002$). The increasing trend was primarily observed among elderly individuals (70+ years). Similarly, an increase in incidence of all brain tumors was noted only among the elderly.

No etiologic factor has clearly been defined to explain the increasing incidence of brain lymphoma. However, it has occurred during a time period when RF radiation to the brain from wireless phones has increased.

It should be noted that in transgenic mouse an increased incidence of lymphoma exposed to 900 MHz GSM RF radiation was reported; $p=0.006$ versus sham group (Repacholi et al 1997). No increased risk for malignant lymphoma was found in mice exposed to GSM 900 MHz but the incidence in the sham exposed group was higher than in the Repacholi et al (1997) study (Utteridge et al 2002).

NTP study

In NTP TR 595 no conclusive evidence of increased incidence of malignant lymphoma was reported in rats.

In NTP TR 596 there were in female mice exposed to GSM modulated cell phone RF radiation for 2 years increased incidences of malignant lymphoma in all exposed groups compared to the controls. The increase was statistically significant in the 2.5 W/kg ($p=0.004$) and 5 W/kg groups ($p=0.035$). In the CDMA modulated cell phone RF radiation for 2 years the incidence increased in female mice in all exposed groups compared to the controls, statistically significant in the 2.5 W/kg group ($p=0.035$).

Evaluation

Based on human epidemiology studies and the NTP study there is equivocal evidence that malignant lymphoma is caused by RF radiation in humans (may be related to exposure).

Skin (cutaneous tissue)

Human studies

Few studies exist on RF radiation and the risk for skin tumors. In a Danish cohort on mobile phone subscribers from 1987-1995 followed to 2007 no increased risks of skin cancer was seen (Poulsen et al 2013). The same cohort has also been used for studying brain tumor risk. Due to serious methodological problems including misclassification of exposure it has been evaluated to be uninformative (Söderqvist et al 2012, IARC 2013).

In a Swedish study on cutaneous malignant melanoma diagnosed during 2000-2003 no increased risk was seen overall (Hardell et al 2011c). In the shortest latency period >1-5 years and highest cumulative use > 365 hours wireless phone use (mobile phone and/or cordless phone) yielded OR = 1.6, 95 % CI = 0.96-2.9. For melanoma in the most exposed anatomical area during use of the handheld phone, temporal, ear, cheek, the risk increased to OR = 2.1, 95 % CI = 1.1-3.8. The risk was overall highest for cases with first use of a wireless phone before 20 years of age, OR = 2.7, 95 % CI = 0.6-12, although based on low numbers. No interaction was seen with known risk factors for malignant lymphoma such as hair and eye color, skin type or sunburns as teenager.

Figure 10 displays the rapidly increasing incidence of malignant melanoma in Sweden in both genders. The increase is most marked from early 2000.

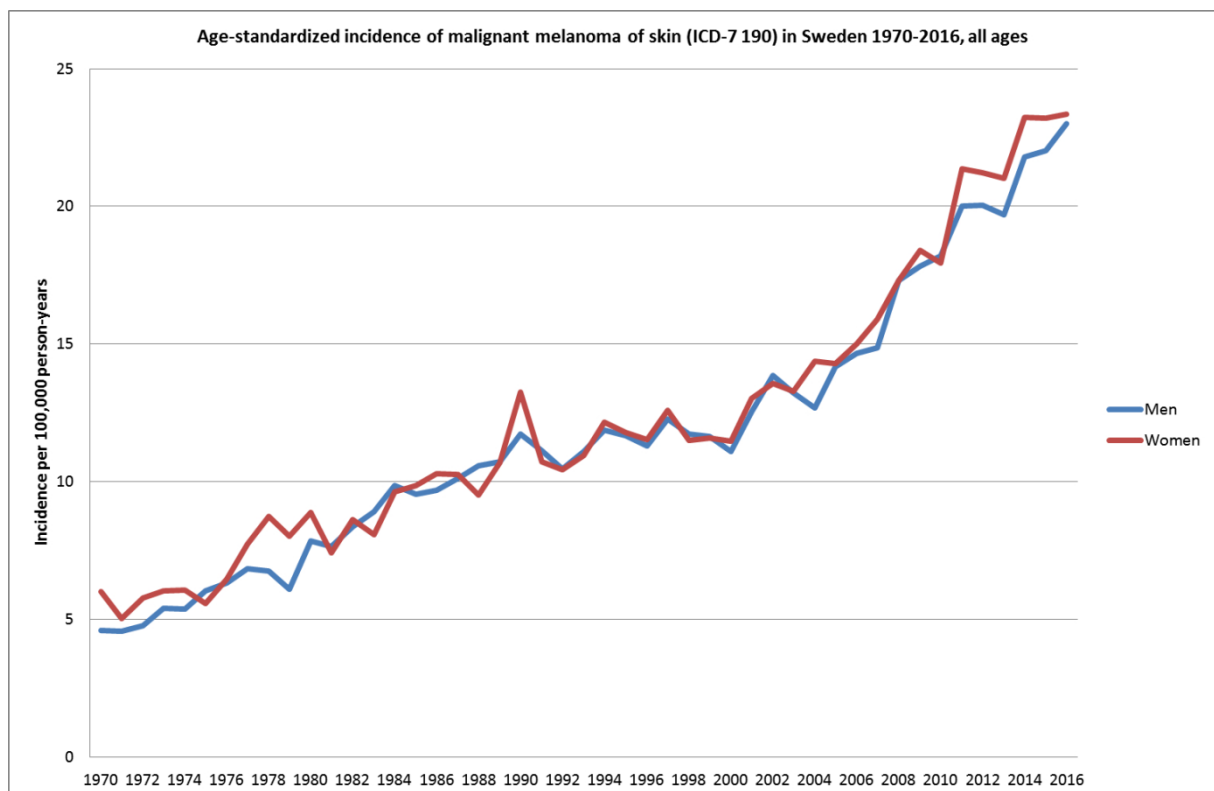


Figure 10. Age-standardized incidence of malignant melanoma (ICD-7 190) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

NTP study

Male rats exposed to GSM modulated cell phone RF radiation for 2 years (*NTP TR 595*) showed higher incidences of fibroma, fibrosarcoma, myxosarcoma, or malignant fibrous histiocytoma in the skin (subcutaneous tissue) in all exposed groups. The increased rates were not statistically significant. No statistically significant results were found in female rats.

The incidences of malignant fibrous histiocytoma were higher in 5 W/kg and 10 W/kg mice exposed to GSM modulated cell phone RF radiation for 2 years (*NTP TR 596*). The results were not statistically significant. The incidences of fibrosarcoma, sarcoma or malignant fibrous histiocytoma were higher in exposed mice compared with sham control, although not statistically significant, p trend = 0.093. No increased incidence was seen in female mice.

Evaluation

Based on human epidemiology studies and NTP animal studies there is equivocal evidence that RF radiation causes skin cancer in humans (may be related to exposure).

Conclusion

Based on case-control studies there is a consistent finding of increased risk for glioma and acoustic neuroma associated with use of mobile phones. Similar results are found for cordless phones in the Hardell group studies. These results are supported by the results in the NTP animal study (https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr595peerdraft.pdf, https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr596peerdraft.pdf). Malignant vestibular schwannoma is a similar tumor type as acoustic neuroma, also called vestibular schwannoma.

The findings are less consistent for meningioma although somewhat increased risk was seen in the meta-analysis of ipsilateral mobile phone use. A longer follow-up time is necessary for this type of slow growing tumor.

The results on glioma and acoustic neuroma are supported by results from other animal studies showing co-carcinogenic and tumor promoting effects from RF radiation (Tillman et al 2010, Lerchl et al 2015). The NTP study showed genotoxicity of RF radiation in rats and mice exposed to RF radiation (Smith-Roe et al 2017) and now presented in more detail. That result supports previous findings of DNA strand breaks in rat brain cells exposed to RF radiation (Lai, Singh 1997).

One mechanism in carcinogenesis could be oxidative stress with production of reactive oxygen species (ROS) as summarised by Yakymenko et al (2016). This could be an indirect mechanism for the increased brain and head tumor risk (Megha et al 2015) since ROS may give DNA damage.

By now carcinogenicity has been shown in human epidemiological studies replicated in animal studies. Laboratory studies on RF radiation have shown increased ROS production that can cause DNA strand brakes. We published in 2013 the conclusion that RF radiation should

be regarded as a human carcinogen Group 1 according to IARC definition, based on scientific evidence (Hardell, Carlberg 2013b) further supported in our up-dated article (Carlberg, Hardell 2017). That conclusion is reinforced by the current evaluation.

Overall evaluation of levels of evidence of carcinogenic activity

Glioma: Clear evidence

Meningioma: Equivocal evidence

Vestibular schwannoma (acoustic neuroma): Clear evidence

Pituitary tumor (adenoma): Equivocal evidence

Thyroid cancer: Some evidence

Malignant lymphoma: Equivocal evidence

Skin (cutaneous tissue): Equivocal evidence

Multi-site carcinogen: Some evidence

Based on the IARC preamble to the monographs, RF radiation should be classified as Group 1: The agent is *carcinogenic* to humans.

'This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.'

(<http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php>)

Respectfully submitted

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Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields (Monograph 102)[☆]

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ABSTRACT

Epidemiology studies (case-control, cohort, time trend and case studies) published since the International Agency for Research on Cancer (IARC) 2011 categorization of radiofrequency radiation (RFR) from mobile phones and other wireless devices as a possible human carcinogen (Group 2B) are reviewed and summarized. Glioma is an important human cancer found to be associated with RFR in 9 case-control studies conducted in Sweden and France, as well as in some other countries. Increasing glioma incidence trends have been reported in the UK and other countries. Non-malignant endpoints linked include acoustic neuroma (vestibular Schwannoma) and meningioma. Because they allow more detailed consideration of exposure, case-control studies can be superior to cohort studies or other methods in evaluating potential risks for brain cancer. When considered with recent animal experimental evidence, the recent epidemiological studies strengthen and support the conclusion that RFR should be categorized as carcinogenic to humans (IARC Group 1). Opportunistic epidemiological studies are proposed that can be carried out through cross-sectional analyses of high, medium, and low mobile phone users with respect to hearing, vision, memory, reaction time, and other indicators that can easily be assessed through standardized computer-based tests. As exposure data are not uniformly available, billing records should be used whenever available to corroborate reported exposures.

1. Introduction

With rapidly increasing applications for wireless devices targeting populations of all ages, exposures to the associated radiofrequency radiation (RFR) are increasing in number and diversity. Radiation sources include communications devices such as mobile (cell) or cordless phones, laptops and tablets, baby monitors, wearable devices and associated infrastructure (e.g. routers, antennae on towers, and distributed antennae systems (DAS) that can employ directional couplers or wireless amplifiers to enhance accessibility). Thus, the technology entails direct and growing personal exposures to an expanding array of wireless transmitting devices (WTDs).

In 2011, a Working Group of the World Health Organization's International Agency for Research on Cancer (IARC) classified RFR as a

possible human carcinogen (Group 2B) (IARC, 2013). In this paper we review the human epidemiology and some other relevant studies published since the IARC Working Group meeting.

1.1. Wireless phone types

The principal sources of exposure of humans to RFR are cell and cordless phones. The radiated power and technologies for cell phones have evolved over the years, as summarized in Table 1 (Hardell and Carlberg, 2015).

2. Case-control studies; glioma

Aydin et al. (2011) reported the results of CEFALO, a multicenter

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Table 1

Wireless phone types, year introduced and average radiated power.

Phone type	Year introduced	Average radiated power	Comment
Analogue ^a	1983	1 or 2 W	No longer in use
2 G, GSM	1991	10 s of mW	Adaptive power control
3 G, UMTS	2004	10 s of μ W	(APC)
4 G, LTE ^b	2010	< 10 s of μ W	
Cordless ^a	1992	250 mW	Base station radiates continuously

^a At maximum power; in-home base station is also a source.^b Too recent for epidemiological studies.**Table 2**

Risks for glioma from and mobile phone use from Aydin et al. (2011).

Exposure	Source	OR	95% CI	p-trend
Regular use ^a	Recall	1.36	0.92–2.02	
Time since first use:				
Never regular user	Recall	1.00		
0.5– ≤ 3.3 years	Recall	1.35	0.89–2.04	0.37
3.3–5.0 years	Recall	1.47	0.87–2.49	
> 5.0 years	Recall	1.26	0.70–2.28	
Time since first subscription:				
Never regular user	Operator	1.00		
≤ 1.8 years	Operator	0.78	0.43–1.40	0.001
1.8–2.8 years	Operator	1.71	0.85–3.44	
> 2.8 years	Operator	2.15	1.07–4.29	
Ipsilateral use				
Regular ipsilateral use	Recall	1.74	0.91–3.33	
< 936 cumulative number of calls	Recall	1.59	0.81–3.12	0.08
937–2638 cumulative number of calls	Recall	2.06	0.72–5.93	
> 2638 cumulative number of calls	Recall	2.91	1.09–7.76	
Contralateral use				
Regular contralateral use	Recall	2.07	0.95–4.52	
< 936 cumulative number of calls	Recall	1.74	0.78–3.90	0.06
937–2638 cumulative number of calls	Recall	5.37	1.54–18.72	
> 2638 cumulative number of calls	Recall	4.82	1.21–19.24	

^a At least once a week for 6 months or more.

case-control study conducted in Denmark, Sweden, Norway, and Switzerland that included children and adolescents aged 7–19 years (median age 13 years) diagnosed with a brain tumor between 2004 and 2008. In person interviews were conducted with 352 case patients (participation rate: 83%) and 646 control subjects (participation rate: 71%) and their parents. The authors concluded that there was no consistent evidence of increased risk. Self-reported use of mobile phones and billing records were the basis of the estimate of exposure. Overall, regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with never regular users (odds ratio (OR) 1.36; 95% CI 0.92–2.02) (Table 2). However, their data suggest that another interpretation might be offered. Analysis of a subset of cases (58% of all cases) based on operator-recorded information showed significant brain cancer risks for children with a significant trend of increase in risk with increasing years of use. Based on children's memory of both ipsilateral and contralateral use there were significant increased risk of brain cancer along with a marginal increase of risk with an increasing number of calls (Table 2).

Regular use was defined as making at least one call a week for 6 or more months.

Because both ipsilateral and contralateral self-reported use of phones in children show significant trends toward increasing brain cancer risk, the authors dismissed this finding. Three factors could account for this result. First, children's capacity to recall their phone use habits accurately may not be correct. Second, young children (25% were between 7 and 9 years; the median age of the study participants overall was 13 years) will absorb considerably more radiation further

Table 3

Glioma Risk relative to hours of phone use and Specific Absorption (J/kg) (Cardis et al., 2011).

Exposure	OR	95% CI
Hours of use		
61.0–199.9 h	0.74	0.55–0.99
735 + hours	1.72	1.07–2.77
Specific Absorption (SA)		
< 3 years in the past		
76.7–248 J/kg	0.63	0.41–0.96
987.3123.8 J/kg	0.56	0.32–0.99
3123.9 + J/kg	1.66	1.03–2.67
7 + Years in the past		
< 76.7 J/kg	1.11	0.61–2.02
76.7–284.1 J/kg	1.53	0.85–2.78
284.1–978.9 J/kg	1.50	0.81–2.78
978.9–3123.8 J/kg	1.69	0.91–3.13
3123.9 + J/kg	1.91	1.05–3.47

into their brains than adults (Fernandez-Rodriguez et al., 2015). Given that many of these cases began to use phones before age 5, their exposures would certainly have been extensive no matter what side of the head they reported having placed the phone. Therefore, the fact that the differences between the ORs for ipsilateral and contralateral use of cell phones and brain cancer were not significant while both ipsilateral and contralateral reported regular use showed a significant risk could signal that use of the phone on either side of the head by children involves proportionally more exposure than adults. The third potential explanation is recall bias.

Cardis et al. (2011) evaluated the absorbed radiation dose from cellphones and the risk of glioma and meningioma in five countries contributing to the Interphone study (Australia, Canada, France, Israel, New Zealand). Analyses included 553 glioma and 676 meningioma

cases and 1762 and 1911 controls, respectively. Employing radiological records, information on phone type, network properties, condition of use and tumor location, they estimated and analyzed absorbed radiation dose as total cumulative specific energy (TCSE), also known as Specific Absorption (SA) in Joules per kilogram of tissue. The authors state “~16% of brain volume received 50% of the total absorbed energy.” Table 3 summarizes the results for glioma. All Specific Absorption (SA) results (J/kg) indicate total energy absorbed by the brain tumor. The highest exposures during 735 + total hours of reported use or 3123.9 J/kg 3 or 7 years prior to diagnosis, resulted in statistically significant increases of risk, with evidence of increasing risk with increasing dose.

In the original pooled 13-country Interphone study report it was noted that “...non-participation bias may have led to a reduction in the ORs for regular use of 5–15%, which is less than the observed reductions below the null in the ORs in even regular mobile phone users for... glioma.” (19%, 95% CI 30–6; Table 2) (INTERPHONE Study Group, 2010). Morgan and Carlberg (2010) calculated that the reduced odds ratio bias was 25% with a binomial p-value = 0.0002.

Hardell et al. (2013b) reported on the risk from RFR of brain cancers diagnosed in Sweden between 2007 and 2009. Of the cases with a malignant brain tumor, 87% (n = 593) participated, and 85% (n = 1368) of controls in the whole study answered the questionnaire. Table 4 shows the risk of brain cancer for various phone types with a reference value (OR = 1.0) for no use of a mobile or cordless phone, or use for ≤ 1 years or ≤ 39 h of cumulative use. The odds ratios were higher in some of the short term follow up groups than the longer perhaps because few people have 25 years of extensive cell phone use, in part because they are not old enough.

Carlberg and Hardell (2012) analyzed the association of brain cancer with mobile phone use and heredity. The results were based on 1251 cases with malignant brain tumor (response rate 85%) and 2438 controls (response rate 84%). Heredity was defined in two ways: either

Table 4

Risk of brain cancer in Sweden, by years of use of wireless phones (Hardell et al., 2013b).

Phone type	Latency ^a	OR	95% CI
Analogue	1–5	–	–
	5–10	0.6	0.1–3.1
	10–15	1.4	0.7–3.0
	15–20	1.4	0.7–2.7
	20–25	2.1	1.1–4.0
	> 25	3.3	1.6–6.9
Digital (2G)	Total	1.8	1.04–3.3
	1–5	1.8	1.01–3.4
	5–10	1.6	0.97–2.2
	10–15	1.3	0.8–2.2
	15–20	2.1	1.2–3.6
	Total	1.6	0.996–2.7
Mobile phone, Total	1–5	1.8	1.0–3.4
	5–10	1.7	0.98–2.8
	10–15	1.3	0.8–2.2
	15–20	1.5	0.8–2.6
	20–25	1.9	1.1–3.5
	> 25	2.9	1.4–5.8
Cordless phone	Total	1.6	0.99–2.7
	1–5	2.0	1.1–3.4
	5–10	1.6	0.95–2.7
	10–15	1.6	0.9–2.8
	15–20	2.1	1.2–3.8
	20–25	1.5	0.5–4.6
	> 25	–	–
	Total	1.7	1.1–2.9

^a Time since first use (years).

having a first degree relative with any cancer except brain cancer; or having a first degree relative with brain cancer. They confirmed increased risk of brain cancer from mobile phone use and found that having a first degree relative with brain cancer (but no other cancers) increases the risk of brain cancer, but there was no interaction with mobile phone use.

Carlberg and Hardell (2013) also reported that persons diagnosed with a glioblastoma multiforme (GBM) exposed to RFR emanating from WTDs had a significantly shorter survival period than those without such exposures.

Coureau et al. (2014) reported on a French national study of mobile phone use and brain tumors (glioma and meningioma) between 2004 and 2006. Out of the subjects defined as eligible, 95% of cases and 61% of controls were contacted, and a total of 596 (73%) cases and 1192 (45%) controls were finally included in the study. Participation rate was 66% for glioma and 75% for meningioma cases. This resulted in a total of 253 gliomas, 194 meningiomas and 892 matched controls selected from the local electoral rolls being analyzed. The meningioma results can be found in the next section. This study defined heavy users as those with ≥ 896 h of use. The risk of glioma for heavy users was OR = 2.54, 95% CI = 1.19–5.41. There was a marginal increase in risk with increasing hours of use ($p_{\text{trend}} = 0.07$). A small number of urban users showed a significant 8-fold increased risk for brain tumors excluding temporal or frontal lobes (OR 8.2. 1.37–49.07). The authors commented: “Finally, we observed increased OR for urban use for gliomas, a result inconsistent with the hypothesis of a higher RF power output during calls in rural areas, documented by some Swedish study. However, our results are consistent with a recent international study showing no difference between rural and urban exposition in most countries except in Sweden, and a Hardell study when considering gliomas separately.” These and other findings are shown in Table 5.

Hardell and Carlberg (2015) conducted a pooled analysis of gliomas from 1997 to 2004 and 2007–2009 with > 25 years and for > 1486 h of use, by wireless phone types. In total, 1498 (89%) cases and 3530 (87%) controls were included in the analysis. Glioma risk by years or hours of use by phone types is shown in Table 8 and in Table 9. They reported increased risk with increasing latency since first use. For

Table 5

Risk of brain cancer for various measures of exposure in the CERENAT case-control study (Coureau et al., 2014).

Condition	OR	95% CI
Average calling time/hours/month		
Not regular user	1.00	
< 2	0.91	0.57–1.46
2–4	0.57	0.30–1.10
5–14	1.70	0.97–2.99
15 or more	4.21	1.84–8.86
Heavy User		
≥ 1 year	2.89	1.41–5.93
≥ 2 years	3.03	1.47–6.26
≥ 5 years	5.30	2.12–13.23
Temporal lobe	3.94	0.81–19.08
Other brain locations excluding temporal and frontal lobes	3.61	1.00–12.96
Urban use only	8.20	1.37–49.07
Urban and rural use	2.03	0.93–4.40
Analogue phone use	3.75	0.97–14.43
Digital phone use only	2.71	1.03–7.10

Table 6

Risk of glioma for years of use by phone type (Hardell and Carlberg, 2015) for 1498 cases.

Years of use	Phone type	OR	95% CI
> 1	Analogue	1.6	1.2–2.0
	2G, GSM	1.3	1.1–1.6
	3G, UMTS	2.0	1.0–4.4
> 1, temporal lobe	Analogue, 2 G, 3 G	1.3	1.1–1.6
		4.3	2.0–9.3
> 5–10	2G, GSM	1.7	1.3–2.2
	3G, UMTS	4.1	1.3–12
	Cordless	1.4	1.1–1.8
> 10–15	Analogue	1.4	1.04–1.9
	Cordless	1.4	1.1–1.9
> 15–20	Analogue	2.4	1.5–3.7
	2G, GSM	2.1	1.5–3.0
	Cordless	1.7	1.1–2.5
> 15–20 Astrocytoma I-II, ipsilateral	Cordless	3.2	0.99–10
> 20–25	Analogue	3.2	1.9–5.5
> 25	Analogue	4.8	2.5–9.1
> 25 temporal lobe	Wireless	4.2	1.9–9.1
> 1 Astrocytoma III-IV	Analogue + 2G	1.4	1.1–1.8
> 20		2.5	1.6–3.8
> 20, ipsilateral		3.3	1.9–5.7

Table 7

Risk of glioma by hours of use (Hardell and Carlberg, 2015).

Hours of Use	Phone Type	OR	95% CI
Per 100 h	Analogue	1.043	1.026–1.061
	2 G, GSM	1.014	1.009–1.018
	3 G, UMTS	1.047	1.002–1.093
	Cordless	1.014	1.008–1.019
1st Quartile: 1–122	2 G, GSM	1.3	1.05–1.5
2nd Quartile: 123–511	Analogue	1.8	1.3–2.5
	2 G, GSM	1.3	1.01–1.7
	Cordless	1.2	0.97–1.6
3rd Quartile: 512–1486	Analogue	1.8	1.2–2.8
	2 G, GSM	1.5	1.1–1.9
	3 G, UMTS	3.0	1.2–8
	Cordless	1.6	1.3–21
4th Quartile: > 1486 ^a	Analogue	4.8	2.8–8.2
	2 G, GSM	2.3	1.7–3.1
	Cordless	2.3	1.8–3.1
p-trend	Analogue	0.0001	
	2 G, GSM	0.0001	
	Cordless	< 0.0001	

^a ~25 min per day over 10 years.

example, the OR for tumors in the temporal lobe with latency of > 25 years was 4.2 (95% CI 1.9–9.1), while the OR for analogue phone use was 4.8 (95% CI 2.5–9.1). (Tables 6 and 7)

Manufacturers indicate that the 3G-UMTS phones' average radiated power (10s of μ W) is lower than 2G-GSM (10 s of mW). Nonetheless, the glioma risks for exposure to 3 G-UMTS are higher in this analysis. To explain this counter-intuitive finding, the authors cite three in vitro studies (Belyaev et al., 2009; Belyaev, 2010; Markova et al., 2010) that found UMTS inhibits significantly more DNA repair genes relative to GSM modulation.

Total absorbed radiative power is one important factor in determining risk (Hardell et al., 2005). But as Belyaev et al. (2009), Belyaev (2010) and Markova et al. (2010) have noted, modulation technology and signals for information content may be more important determinants of biological impact. Thus, the increased glioma risk reported with weaker 3-G-UMTS could reflect the fact that modulation is more critical than power alone.

Grell et al. (2016) examined the location of brain cancers diagnosed from 2000 to 2004 in the INTERPHONE study. The authors located brain cancers at various distances from the ear where the phone was held using neuro-radiologists to estimate peak areas of exposure in centers of gravity of the tumor within the brain. The main analysis included 792 regular mobile phone users diagnosed with a glioma between 2000 and 2004. Table 8 summarizes the significant results from the report's Table 3 (there are 7 additional tables reporting similar results) at the two closest ranges of out of four longer distances from the ear. The authors commented, "Our results concur with the observation of a statistically significant excess of gliomas on the self-reported side of mobile phone use." They showed significantly increased glioma risk with greater absorption, greater hours spent on phone and longer time since phone use began.

Momoli et al. (2017) undertook a re-analysis of the Canadian data from the 13-country case-control Interphone Study (2001–2004). They applied a probabilistic multiple-bias model to address possible biases simultaneously, using validation data from billing records and non-participant questionnaires as information on recall error and selective

participation. For glioma, when comparing those in the highest quartile of use (> 558 lifetime hours) to those who were not regular users, the odds ratio was 2.0 (95% confidence interval: 1.2, 3.4). After adjustment for selection and recall biases, the odds ratio was 2.2 (95% limits: 1.3, 4.1), thus allaying concerns that bias could explain the positive findings in the Interphone study.

Akhavan-Sigari et al. (2014) reported that patients with glioblastoma multiforme who had used cellphones \leq 3 h per day had better survival than those with cellphone use of \geq 3 h per day. The authors investigated p53 mutant gene expression in peripheral (within 2 cm of the area of MRI enhancement) and central (region of necrosis) zones within the tumor. They found that 41 out of 63 patients (65%) with the highest level of cell phone use (\geq 3 h per day) had higher mutant type p53 expression in the peripheral zone of the glioblastoma; the difference [compared to cellphone use of < 3 h per day] was statistically significant ($P = 0.034$). They noted that occupational exposure to other electromagnetic fields was excluded in all patients. This study shows that genetic changes, compatible with carcinogenic effects, result from higher exposure to RFR.

3. Case-control studies; meningioma

Little increased risk of meningioma was found in the five country Interphone analysis, except for the highest category of exposure in those with 7 or more years of use (Table 9).

Carlberg et al. (2013) reported on risk of meningioma from exposure to wireless phone radiation between the years 2007 and 2009, but found no overall association.

Table 10 summarizes the results for meningioma from the report on the French CERENAT case-control study (Coureau et al., 2014). There was only significant excess risk for "heavy users" (\geq 896 h of use).

Carlberg and Hardell (2015) performed a pooled analysis from 1997 to 2003 and 2007–2009 of the risk of meningioma from cell and cordless phone use. In total, 1625 meningioma cases and 3530 controls were analyzed. Overall no association with use of mobile or cordless phones was found. However, they reported an increased risk among heavy users of both mobile and cordless phones from various wireless phone types (wireless combines all phone types) (Table 11). The risk increased significantly per 100 h of use from four wireless phones categories.

4. Case-control studies of other cancers and other tumors

Case-control studies have also been performed on other cancers suspected as being associated with RFR exposure. Those examining thyroid and skin cancers are not considered here, as over-diagnosis of thyroid cancer and sun exposure, respectively, result in uncontrolled confounding. As limited studies have been reported thus far on leukemia risks tied with mobile phones, we do not consider these risks here.

In a population-based case-control study of children Li et al. (2012) included 939 leukemia and 394 brain neoplasm cases newly diagnosed between 2003 and 2007, aged 15 years or less. Controls were randomly

Table 8

Estimated Elevation in Brain Tumor Risk for Regular Mobile Phone Users with Information on Preferred Side of Use - by distance from the ear to the tumor in millimeters (Grell et al., 2016).

Distance from preferred ear to gravity center of tumor					
		Distance from Ear, 15–55 mm		Distance from Ear, > 55–75 mm	
Sex	Count ^a	OR ^b	95% CI	OR	95% CI
Female	284	1.85	1.41–4.04	1.85	1.36–2.96
Male	508	3.04	1.63–7.54	1.68	1.26–2.33
Age					
\leq 46	379	1.86	1.45–4.37	1.86	1.38–2.76
> 46	413	3.06	1.63–7.29	1.69	1.25–2.51
Grade					
1 or 2	331	2.59	1.15–6.61	1.82	1.25–2.75
2 or 4	417	2.16	1.05–5.01	1.64	1.34–2.39
Size (cm ³)					
\leq 18	461	1.96	1.51–3.66	1.96	1.48–2.97
> 18	331	4.09	1.90–12.0	1.51	1.17–2.25
Use, Years					
\leq 6	461	2.02	1.31–4.28	1.39	1.13–1.99
> 6	331	3.27	1.92–11.6	2.32	1.57–3.57
Use, Hours					
\leq 200	435	1.57	1.29–3.36	1.57	1.27–2.22
> 200	357	4.06	2.03–11.6	1.94	1.32–3.02
Use, Calls					
\leq 4000	420	1.55	1.25–3.42	1.44	1.19–2.02
> 4000	372	3.56	2.05–9.88	2.26	1.51–3.38

^a Total count from 4 distance ranges from the ear.

^b Risk of observing brain cancer within distance range.

Table 9

Meningioma risk by years of use and by Specific Absorption (SA) (Cardis et al., 2011).

Specific Absorption (SA)	OR	95% CI
7 + Years of use		
Never regular user	1.00	
< 76.7 J/kg	1.07	0.64–1.78
76.7–284.1 J/kg	0.74	0.33–1.67
284.1–978.9 J/kg	0.88	0.47–1.64
978.9–3123.9 J/kg	1.00	0.52–1.92
3123.9 + J/kg	2.01	1.03–3.93

Table 10

Risks for meningioma from the CERENAT study (Coureau et al., 2014).

Exposure	OR	95% CI
Cumulative duration of calls (hours)		
Not regular user	1.00	
< 43	1.12	0.61–2.04
43–112	0.85	0.45–1.61
113–338	0.52	0.25–1.07
339–895	0.52	0.18–1.45
≥ 896 total hours	2.57	1.02–6.44
Temporal lobe	7.89	0.48–130.14
Frontal lobe	4.82	0.78–29.63

Table 11

Risk of meningioma by hours of use for type of wireless phone (Carlberg and Hardell, 2015).

Phone Type	Hours of use	OR	95% CI
Analogue	Per 100	1.019	1.003–1.035
	1000	1.207	
	2000	1.457	
	3000	1.759	
Cellphone (2G, 3G)	Per 100	1.005	1.0001–1.010
	1000	1.051	
	2000	1.105	
	3000	1.161	
Cordless	Per 100	1.010	1.005–1.014
	1000	1.105	
	2000	1.220	
	3000	1.348	
Wireless	Per 100	1.006	1.003–1.009
	1000	1.062	
	2000	1.127	
	3000	1.197	
Analogue	> 1486	1.8	0.9–3.6
Cellphone (2G, 3G)	> 3358	1.5	1.0005–2.3
Cordless phone	> 1486	1.7	1.3–2.2
	> 3.358	2.0	1.4–2.8

selected, with a case/control ratio of 1:30 and matched on year of birth, from all non-neoplasm children insured in the same year when the index case was admitted. The Average Power Density (APD) was calculated for each township in Watt-Years per square kilometer (WYs/km²) 5 years prior to diagnoses. The median power density was 167.02 WYs/km². They reported that a higher than median averaged APD was significantly associated with an increased Adjusted Odds Ratio (AOR) for all neoplasms (1.13; 1.01–1.28), and for leukemia (1.23; 0.99–1.52), but not for all brain neoplasms (1.14, 0.83–1.55). They did not specifically analyze data on gliomas.

Hardell et al. (2013a) pooled acoustic neuroma results from case-control studies conducted in 1997–2003 and 2007–2009, including 316 participating cases and 3530 controls. Their main results by phone type are shown in Table 14. There is some evidence of a dose-response relationship is evident with mobile and cordless phones associated with ORs of 4.5 and 6.5 respectively for 20 or more years of use. There were similar results per cumulative hours of use (Table 12).

Additionally, the authors reported tumor volume increases from

Table 12

Risk of acoustic neuroma for years of wireless phone use (Hardell et al., 2013).

Years of use	All mobile phones		Cordless phones	
	OR	95% CI	OR	95% CI
> 1–5	1.3	0.9–1.8	1.5	1.1–2.1
> 5–10	2.3	1.6–3.3	1.6	1.1–2.5
> 10–15	2.1	1.1–3.5	1.4	0.8–2.6
> 15–20	2.1	1.02–4.2	0.5	0.1–2.1
> 20	4.5	2.1–9.5	6.5	1.7–26

Table 13

Findings for tumor volume from Moon et al. (2014).

	Tumor size (cm ³)	OR	95% CI
< 10 years	5.57	1.045	0.987–1.107
> 10 years	9.83		
Non-regular user	2.71	1.125	1.041–1.216
Regular user	8.10		

analogue cellphone use per 100 h of use (7.4%, 95% CI = 1.0–14.2%) and per year of use (10.4%, CI = 2.4–18.7%).

Moon et al. (2014), in a matched case-control study from Korea examining 119 cases of vestibular schwannoma and 238 controls attending for routine examinations in the same institution found no difference between cases and controls in the duration, time of use or cumulative use of mobile phones. However, in a case-case analysis they found that vestibular Schwannoma tumor volume was greater in those with higher use compared to lower use of mobile phones and in those with regular compared to non-regular use (Table 13).

Pettersson et al. (2014) conducted a population-based, nation-wide, case-control study in Sweden for acoustic neuroma (vestibular Schwannoma) diagnosed between 2002 and 2007. In total, 542 eligible acoustic neuroma cases and 1095 controls were identified, of whom 83% of the cases but only 65% of the controls participated. Detailed findings were presented for all mobile phones and types of mobile phones, as well as by laterality of the tumor in relation to mobile phone use. Table 14 presents the data for time since first regular use of mobile phones and regular use of cordless phones. The low proportion of controls participating could explain these findings, as mobile phone users would be more likely to participate than non-users.

5. Cohort studies

In an update of the Danish cohort study of fewer than half a million persons over more than a decade, Frei et al. (2011) reported that when analyses were restricted to individuals with the longest mobile phone use, ≥ 13 years of subscription, the incidence rate ratio was 1.03 (95% CI 0.83–1.27) in men and 0.91 (0.41–2.04) in women. Among those with subscriptions of ≥ 10 years, ratios were 1.04 (0.85–1.26) in men and 1.04 (0.56–1.95) in women for glioma and 0.90 (0.57–1.42) in men and 0.93 (0.46–1.87) in women for meningioma. There was no indication of dose-response relation either by years since first subscription for a mobile phone or by anatomical location of the tumor. However, corporate users, people who would have been the heaviest users, were included in the unexposed group, while those who began using phones after the first cohort was established were also placed in the category of non-exposed. Thus, misclassification of exposure could have been responsible for the lack of risk observed. In addition, the study

Table 14

Data on Acoustic Neuroma in Sweden (Pettersson et al., 2014).

Use	All cases		Histologically confirmed cases	
	OR	95% CI	OR	95% CI
Ever used mobile phones regularly ^a	1.18	0.88–1.59	0.99	0.65–1.52
Time since regular ^a use of mobile phones began				
< 5 years	1.04	0.72–1.52	0.94	0.56–1.57
5–9 years	1.40	0.98–2.00	1.11	0.66–1.86
10 or more years	1.11	0.76–1.61	0.94	0.55–1.62
Ever used cordless phones regularly ^a	1.41	1.07–1.86	1.24	0.83–1.86

^a Regular use is defined as having ever called or received a call at least once per week on average during 6 months or more.

lacked statistical power to detect a change in risk because of the small size of the population under surveillance and the relatively low rate of glioma.

In the UK Million Women cohort study the participants were asked only two questions at two points in time (1990 and 2005) about their cellphone use: “How often do you use a cellphone?”; “How long have you used it?” (Benson et al., 2013). These limited measures do not provide an accurate indicator of cellphone exposure. The authors reported no increase in glioma risk but an increased risk of a vestibular Schwannoma: the Relative Risk for ever use of a mobile phone was 1.44 (95% CI 0.91–2.28) and for 10 + years of use was 2.46 (1.07–5.64).

6. Brain tumor incidence, descriptive and trend analyses

Tos et al. (2004) examined Danish incidence rates of vestibular Schwannoma from 1996 to 2001. There is a slow and steady increase from 1976 to 1990, then from 1990 to 1995 a marginal increase followed by a significant increase with a mean incidence per 100,000 population of 1.74 in 1996–2001.

Lehrer et al. (2011) reported a significant correlation between number of cell phone subscriptions and brain tumors in nineteen US states ($r = 0.950$, $P < 0.001$) for years 2000–2004 using 2007 cell-phone subscription data. Latency for brain cancer is believed to extend from 7 to 40 years. The effect of cell phone subscriptions ($P = 0.017$) was independent of the effect of mean family income ($P = 0.894$), population ($P = 0.003$) and age (0.499). While phone subscriptions in 2007 are not directly indicative of use in prior decades, it may provide a surrogate indicator of relative use.

Baldi et al. (2011) reported age-adjusted incidence trends for CNS tumors from 2000 to 2007 in the Gironde CNS Tumor Registry, France (Table 15). The lack of significant trends in the APC for all categories except meningeal tumors could be a reflection that the time period studied was one of relatively early use of mobile phones.

Ding and Wang (2011) reported that brain and nervous system cancers had been increasing in Shanghai during the period 1983–2007, but for males age-adjusted data showed no significant increase, annual percent change in incidence (APC) 1.2, 95% CI 0.4–1.9, though it did for females (APC 2.8, 95% CI 2.1–3.4). The authors concluded, however, that the latter increase was unlikely to be related to increasing cell phone use. The authors did not examine glioma specifically, nor did they examine age-specific glioma trends in individuals ages 20–39 who have used phones heavily and regularly enough to have incurred a change in baseline rates. They also did consider that women generally use their phones for talking up to three times more than men, according to some global surveys by the Pew Foundation (pewglobal.org).

Dobes et al. (2011) reported increasing incidence in Australia from 2000 to 2008 for glioblastoma multiforme (GBM), especially in those age 65 or more, and increasing incidence of meningiomas in males but significant decreasing incidence of Schwannomas (Table 16).

Zada et al. (2012) examined data from three major U.S. cancer registries: Los Angeles County, California Cancer Registry, and the National Cancer Institute's Surveillance, Epidemiology and End Result for

Table 15

CNS tumor incidence rate changes in Gironde, France 2000–2007 (Baldi et al., 2011).

Category	APC ^a	95% CI
All CNS tumors	2.33	0.20–4.52
Men	0.65	– 2.69 to 4.09
Women	3.88	– 0.22 to 8.14
Urban residence	2.13	– 0.29 to 4.60
Rural residence	3.07	– 2.36 to 8.81
Neuroepithelial tumors	1.14	– 2.95 to 15.41
Meningeal tumors	5.40	1.15–9.83

^a Annual percent change in incidence rates.

Table 16

Trends in incidence of glioblastoma multiforme, meningioma and Schwannoma in Australia (Dobes et al., 2011).

Category	APC	95% CI
All GBMs	2.5	0.4–4.6
Males	2.6	– 0.1 to 5.4
Females	2.2	– 1.5 to 6.0
All, ≥ 65 years	3.0	0.5–5.6
Meningioma – Males	5.3	2.6–8.1
Meningioma – Females	0.6	– 3.6 to 5.0
Schwannomas –Males	– 1.0	– 7.9 to 6.3
Schwannomas –Females	– 5.3	– 9.4 to 0.5

12 U.S. states (SEER 12) from 1992. The APC for GBM (grade IV glioma) and Glioma was reported by brain region. Table 17 shows APC changes by cancer registry for GBM and for glioma located in three anatomical regions of the brain, showing significant increases compatible with increasing use of mobile phones.

Consistent with the study above, Cardis et al. (2011) reported that the combined percentage of the total radiation absorbed by the frontal lobe (19%), the temporal lobe (50%) and the cerebellum (18%) was 81% at 900 MHz and was 86% at 1800 MHz (frontal lobe 14%, temporal lobe 50%, cerebellum 13%).

Chapman et al. (2016a), using national cancer registration data, examined age and gender specific incidence rates for males and females diagnosed with brain cancer in Australia between 1982 and 2012, and mobile phone usage data from 1987 to 2012. They modeled expected age specific rates based on published reports of relative risks (RR) of 1.5 in ever-users of mobile phones from the Interphone study, and RR of 2.5 in a proportion of ‘heavy users’ (19% of all users), assuming a 10-year lag period between use and tumor incidence. Significant increases in brain cancer incidence were observed (in keeping with modeled rates) only in those aged ≥ 70 years. They suggested that the observed increases in brain cancer incidence in the older age group are unlikely to be related to mobile phone use.

The methods used by Chapman et al. (2016a), which involved several assumptions and conclusions were challenged (Bandara, 2016; Morgan et al., 2016; Wojcik, 2016) and defended (Chapman et al., 2016b). Bandara (2016), Morgan et al. (2016) and Wojcik (2016) noted that the data used by Chapman et al. (2016a) were based on estimates, due to an unavailability of data and mobile phone user was calculated using number of subscriptions, which the authors state uses invalid assumptions and is unreliable for accurately assessing mobile phone exposure. Overall, the Australian trend data are not definitive of an increased risk, but they are also not a clear indication of no risk in the most exposed age group, in light of the long latency of GBM.

de Vocht (2016) studied cancer trends and inferred the impact of cellphone use in England for selected brain tumor types. The author concluded that the annual incidence of malignant neoplasms of the temporal lobe has been increasing faster than expected during the period of 10 years post-1995, and that post-2005 an additional increase of 35% (95% CI 9–59%) was evident.

Sato et al. (2016) examined brain cancer incidence rates in Japan (Table 18). The authors considered whether use of a mobile phone for ≥ 1640 h (from the Interphone study (5,6)) correlates with the increases in brain cancer incidence found in young people between 1993 and 2010 in Japan and concluded that the increase cannot be explained by heavy mobile phone use, but did not provide an explanation as to what might be the cause of these significant and unexplained increases in brain cancer. Notably the rate of increase in 2002–2010 was more than three times that since 1993.

Kleijwegt et al. (2016) examined vestibular Schwannoma (VS) incidence rates from 2001 to 2012 in the Netherlands. The authors chose to focus on the Leiden region because they considered that the incidence of VS in the Netherlands may best be estimated on the basis of

Table 17

The Average Percent Change for Glioma by 3 anatomical brain regions from the Los Angeles, California, and SEER – 12 cancer registries (Zada et al., 2012).

Cancer	Brain Region	Los Angeles Cancer Registry		California Cancer Registry		SEER 12 Registry	
		APC	p	APC	p	APC	p
GBM	Frontal lobe	3.0	0.001	2.4	< 0.001	2.5	0.027
Glioma		1.7	0.012	1.4	0.004	1.6	< 0.001
GBM	Temporal lobe	2.3	0.010	2.3	0.026	1.3	0.027
Glioma		0.9	NS	0.07	NS	0.05	NS
GBM	Cerebellum	NA		11.9	< 0.001	0.06	NS
Glioma		0.04	NS	– 3.4	0.014	1.4	0.014

NA: Not available; NS: Not significant.

Table 18

Japanese brain cancer increases 1993–2010 in age groups 20–29 and 30–39 (Sato et al., 2016).

Age	Period	Sex	APC ^a	95% CI
20–29	1993–2010	M	3.9%	1.6–6.3%
	2002–2010	F	12.3%	3.3–22.1%
30–39	1993–2010	M	2.7%	1.3–22.1%
		F	3.0%	1.4–47%

^a APC Average percent change per year.

the incidence rates observed for the Leiden region. This region showed a fourfold increase from 2001 to 2012 from about 0.8 to about 3.3 per 100,000.

The Central Brain Tumor Registry of the United States (CBTRUS) has published annual reports from 2007 to 2016 with data from 2004 to 2013 (www.CBTRUS.org). The annual incidence rate of VS tumors (based on their published percentage of VS among all nerve sheath tumors) doubled from 0.88 to 1.73 per 100,000.

Gittleman et al. (2015) examined changes in incidence rates for malignant and non-malignant brain tumors (approximately two-thirds of all brain tumors) across all age groupings in the United States between 2000 and 2010 (Table 19). The authors concluded “The incidence of the most common cancers in adults decreased between 2000 and 2010, as did the incidence of MCNST [Malignant Central Nervous System Tumors]. However, the incidence of NMCNST [Non-Malignant Central Nervous System Tumors] increased significantly. In comparison, adolescents had increasing rates of MCNST and NMCNST, and children had increasing rates of ... MCNST.” We note that late ascertainment is a major problem in the 51 cancer registries in the U.S. It is likely that in later reports, there will be cases added in the recent 3-year bins, increasing the APC for the most recent periods.

Table 19

Trends in Brain Tumor Incidence in the United States (Gittleman et al., 2015).

Age Groups	Type ^a	Years	APC	95% CI
Children				
0–14	Ma	2000–2010	1.0	0.5–1.5
5–9	Ma	2000–2010	1.4	0.8–2.0
10–14	Ma	2000–2010	1.3	0.8–1.7
0–14	N-M	2004–2010	1.6	– 0.03 to – 3.6
10–14	N-M	2004–2010	3.9	0.4–7.5
Adolescents				
15–19	N-M	2004–2010	3.9	0.7–7.2
Adults				
≥ 20	Ma	2008–2010	– 3.1	– 6.1 to – 0.1
45–54	Ma	2000–2010	– 0.8	– 1.2 to – 0.4
55–64	Ma	2000–2004	1.1	0.1–2.1
		2004–2010	– 1.1	– 1.6 to – 0.7
20–44	N-M	2004–2010	3.5	0.9–6.1
45–54	N-M	2004–2010	2.2	0.2–4.2
≥ 75	N-M	2004–2010	3.6	0.8–4.9

^a Ma: Malignant; N-M: Non-Malignant.

Philips et al. (2018) analyzed UK Office of National Statistics data covering 81,135 ICD10 C71 brain tumors diagnosed in England (1995–2015) and calculated age standardized incidence rates (ASR) per 100k person-years. They reported a sustained and highly statistically significant ASR rise in glioblastoma multiforme (GBM) across all ages and a decline in earlier stage disease. The ASR for GBM more than doubled from 2.4 to 5.0, with annual case numbers rising from 983 to 2531. Overall, the rise was mostly hidden by a reduced incidence of lower grade tumors.

7. Case series

West et al. (2013) reported multiple primary breast cancers in young women who had regularly placed a cellphone in their bras (Table 20). Tumors were reported to have occurred subcutaneously directly under the antennas of the phones. Subsequently, a number of other such cases have come to light with unusually located breast tumors relative to reported cell phone storage in the bra.

Peleg (2012) discussed a cancer cluster among young workers at an Israeli Antenna Range Facility. It was believed that significant RFR exposures took place as a result of workplace conditions. Five of about 30 workers were diagnosed with cancer. This was regarded as significantly greater than the expectation. Peleg et al. (2018) extended this analysis to 47 patients with cancer previously exposed to whole-body prolonged RFR, mainly from communication equipment and radar. They found that the percentage frequency of haemo-lymphatic (HL) cancers in the case series was very high, at 40% with only 23% expected for the series age and gender profile, 95% confidence interval: 26–56%, $p < 0.01$; 19 out of the 47 patients had HL cancers.

Stein et al. (2011) studied 56 cancers among 49 military personnel (47 male, 7 females) exposed to intense prolonged RFR between 1992 and 2011. Based on exposure information reconstructed from reported histories, it was assumed that significant RFR exposures took place as a result of workplace conditions. The average duration of exposure was 13 years; the average age at diagnoses was 43. There appeared to be an excess of both haemolymphatic and testicular cancers.

8. Discussion

Because they allow more detailed consideration of exposure and more precision of diagnoses, case-control studies can be superior to prospective cohort studies, or other methods, in evaluating potential risks for cancers. Carrying out a credible, statistically valid cohort study with sufficient power to find a change in rate of a rare cancer such as glioma that occurs at between 7 and 10 per 100,000 in industrialized countries would require a costly detailed prospective study following cellphone users (and other RF exposures) of about 10 million persons over 10 years or more. Further, exposures will change over time and cannot easily be tracked in large cohorts and it is usually difficult to collect sufficient information on exposure, and especially exposure during follow-up. It may also be difficult to select an appropriate comparison cohort.

Table 20

Placement of cellphone in bras associated with multiple primary breast cancers (West et al., 2013).

Case	Age	Bra Placement	Diagnosis
1	21	Several hours per day	"...extensive ductal carcinoma in situ (DCIS) with multifocal micro invasion."
2	21	She had been placing her [cellphone] in her bra for \geq eight hours a day for 6 years	Four multifocal invasive cancer with extensive DCIS. Two of nine axillary lymph nodes were positive for metastatic disease.
3	33	Intermittently for 8 years. 2 years prior to Dx while jogging 3–4 times/week.	Six cancers with a 5 mm metastasis in one sentinel lymph node.
4	39	Four hours/day, 10 years	Four invasive ductal carcinomas ranging from 1 to 3 cm in size with 10 cm of DCIS.

However, estimates of exposure in case-control studies typically rely on either self-reports from patients recently operated on for brain cancer, or reports from surviving relatives about the case's cell phone patterns and habits, and thus potentially suffer from selection and recall bias, though the latter can be avoided if operator-generated data, collected equally from cases and controls, are available. To overcome the problems of self-report, Public Health organizations should mandate the collection of long-term cellphone use data that would be available to the user or researcher, with the user's permission.

Cross-sectional studies may point to issues that need evaluation, but do not permit a causal inference. Case series are useful to indicate a potential issue for action and better studies but these are not definitive and need to be followed by appropriately designed case-control or cohort studies.

Misclassification, the erroneous measurement of one or several categorical variables, is a major concern in many scientific fields. All epidemiological studies of cell phone radiation and brain cancer carry a risk of misclassification that will bias the risks towards the null. Even in rather simple scenarios, unless the misclassification probabilities are very small, major bias can arise in estimating the extent of association assessed in terms of the risk or odds ratio. Only in very special cases - for example, if misclassification takes place solely in one of two binary variables and is independent of the other variable, is misclassification non-differential, otherwise the estimates are biased towards a finding of no effect.

Nevertheless, recent case-control studies from Sweden and France corroborate findings of earlier studies in providing support for making a causal connection between cell phone use and brain cancer, as well as acoustic neuroma, also called Vestibular Schwannoma. [Hardell and Carlberg \(2013\)](#) concluded that the Bradford Hill criteria for causality have now been fulfilled. It is notable that three recent meta-analyses all confirm significant increased risk of glioma after 10 or more years of use of cell phones ([Bortkiewicz et al., 2017](#); [Prasad et al., 2017](#); [Yang et al., 2017](#)). The [Aydin et al. \(2011\)](#) data that relied on billing records along with children's recall of their uses of phones approaches and in some instances met conventional tests of statistical significance and indicated that four years or more of heavy cell phone radiation causes glioma in children. This finding is consistent with that of [Hardell and Carlberg \(2015\)](#) who showed that those who began using cell phones and/or cordless phones regularly as children had between 4 and 8-fold increased risk of glioma as adults.

Studies of time trends in cancer are of limited value in estimating the impact of cellphones. Such trends can simply suggest etiological hypotheses but cannot prove or disprove any single hypothesized factor, as was also true with tobacco use and lung cancer. Thus, time trends cannot be used to test hypotheses, but can be employed to generate them. In that regard several of the unexplained trends of GBM reported here indicate that there have been shifts in avoidable causal factors over time. As different causes can contribute to GBM at relatively greater proportions at different points of time, the interpretation of time trends remains highly problematic.

Since almost half of all brain cancers occur in persons age 60 and older, and the relatively recent increase in use by cell phones by those age 40 and under, the absence of an overall increase in rates is to be expected when the whole brain is considered; but when only the

temporal lobe, frontal lobe and cerebellum are considered a different picture arises. Some incidence trend studies suggest that rates of brain tumors are increasing in the younger population. In addition, some case series suggest concern, perhaps particularly about breast cancers occurring in young women who kept cell phones in their bras.

Although cohort data continue to provide no confirmation of increased brain cancer risks tied with cell phones, both cohort studies on which data have so far been reported had limited exposure data, while the Danish cohort study ([Frei et al., 2011](#)) placed corporate subscribers (likely heavy users of mobile phones) in the unexposed group. This misclassification of exposure will have biased the relative risks observed towards the null. Continuation of these existing Danish and British cohort studies would be unproductive because of the serious exposure misclassification and the related lack of statistical power to be able to detect significant associations. Further, the Mobi-kids study ([Sadetzki et al., 2014](#)) might also result in negative findings because it may not have been started at the correct time to correctly identify exposure and is focusing on chronic disease endpoints rather than relatively short-term impacts such as memory, reaction time, hearing and visual acuity, addiction and other endpoints in children.

Any new epidemiological studies of brain cancer to be carried out should include validated measures of exposure and/or biomarkers of possible impact of RFR on biological processes. However, if this need for validated exposure indicators implied the use of a monitor there could be a problem, because few are likely to consent to wear a monitor, unless a monitor could be incorporated as a part of the operating system of a smartphone. This has been proposed with the app Quanta, for which validation remains to be ascertained. In the meantime, studies that rely on surrogates of exposure such as billing records can still yield useful information.

Potential cancer sites and other outcomes for consideration in new studies include breast cancer because of the case reports of breast cancer in women carrying cell phones in their brassieres ([West et al., 2013](#)), haematolymphatic cancers, given the apparent excess of these cancers in a case series from the Israel army in young soldiers exposed to radar and communication transmitters in military settings ([Stein et al., 2011](#); [Peleg et al., 2018](#)) and as reported previously from the armies in Poland ([Szmigielski, 1996](#)) and Belgium ([Degraeve et al., 2009](#)). Other sites than brain and acoustic neuroma could potentially increase in incidence when untested whole-body exposure occurs, this may be the case with several evolving technologies. Thus, recently introduced and untested technologies include Wireless Power Transfer that involves sending recharging signals short distances between a central charging station and an untethered wireless device. In addition, other possible sources of exposures that have not been evaluated include areas close to cellular base station antennas, the yet-to-be introduced 5 G communication systems, and rapidly evolving occupational exposure and novel systems for Wi-Fi ([Peleg, 2009](#)).

Several studies have found increases in the incidence of brain cancer, especially glioblastoma multiforme (e.g. [Kleijwegt et al., 2016](#), [Sato et al., 2016](#), [Philips et al., in press](#)). However, additional data are needed to evaluate cancer risk from RFR in relation to national cancer trends, especially critical analysis to determine accurately if age-specific glioma incidence is rising in children and adolescents and in special occupational groups. In addition to this outcome trend data on

hematopoietic malignancies, testicular cancer and other cancers should also be considered. Such trends are ecologic, depend on good cancer registration and require data to exclude the role of changes in cancer registration and diagnostic practices. In evaluating these trends, it would be necessary to consider any data available concerning other environmental exposures such as MRI and CT scans as well as exposure to RFR.

To determine the overall public health importance of EMF, serious consideration should be given to epidemiological studies that have shorter latency non-cancer outcomes; examples are studies using motility in sperm along with sperm DNA fragmentation as end-points (Adams et al., 2014; Houston et al., 2016), and studies of Electrical Hypersensitivity (EHS) (Belpomme et al., 2015, 2016; McCarty et al., 2011; Genuis and Lipp, 2012), as well as studies of reaction time, hearing and visual acuity, memory, addiction, and sleep patterns. Recently experimental evidence has shown that RFR can affect the testicular proteome (Sepehrmanesh et al., 2017) and thus play a role in growing patterns of male infertility.

Susceptibility factors (e.g. age, genetic variability) and EHS have not yet been adequately evaluated in epidemiological studies of RFR. Age has generally been considered, but not germline or acquired genetic factors. There is a case for including detailed measures of RFR exposure in currently ongoing cohort studies in many countries designed to evaluate genetic susceptibility in disease causation and with suitable biologic specimens collected and stored. The role of RFR could be evaluated by carefully designed case-control studies nested within the cohort. There are indications particularly from the Ramazzini animal studies that other environmental exposures might make people more susceptible to a combination of exposures (Falcioni et al., 2018). This combinatorial issue been noted in studies of occupational exposure to chemicals, metals and electromagnetic fields (Navas-Acien et al., 2002). Separately, no effects were observed but when combined with EMF strong results were found. In the Ramazzini studies finding a synergistic interaction between RFR and ionizing radiation, RFR served as a promoter while in the NTP animal studies RFR served as a direct carcinogen and genotoxic agent (National Toxicology Program, a, b, 2018). In studies of case series of human cancers, it is important to take note of multiple primaries in proportion to the total number of cases observed as a possible indicator of unusual environmental risk or unusual environmental-susceptibility interactions (Stein et al., 2011).

Individual hypersensitivity to electric and radiofrequency fields (EHS) is a relatively newly reported phenomenon in the west, although cases of radiation sickness have been found in the former Soviet literature from the 1960s and 1970s. Case studies and individual reports together identify a population which would benefit from RFR exposure reduction (Davis et al., 2017). Because of serious methodological difficulties in operationalizing the concept and a lack of investment in research, definitive epidemiological studies of EHS have not yet been conducted.

In addition, it is important to identify sentinel outcomes potentially related to RFR exposure. Cancers other than brain to consider include breast, vestibular schwannoma/acoustic neuroma, parotid gland tumors, hematopoietic malignancies, testicular cancer, and even colorectal cancer, all tumors on sites of the body with close contact with RFR “hotspots”. However, non-cancer outcomes such as sperm damage, hearing loss and loss of visual acuity are likely to be more commonly linked to mobile phone use. Awareness of these non-cancer outcomes related to RFR exposure might be more likely to change policy, technology and behavior, which would have the effect of decreasing exposure. The major data gap is detail on actual personal exposure which could be obtained on specific occupational groups, as growing numbers of employers are requiring use of mobile phones. A critical priority is to close the major gap in the time trends in population wide impacts of screen time and RFR on children. There may also be issues with mixtures of exposures. All identified occupational groups with excess exposure to RFR should be fully studied.

9. Synthesis and conclusions

The Epidemiological studies reported since the 2011 IARC Working Group meeting are adequate to consider RFR as a *probable* human carcinogen (Group 2 A). However, they must be supplemented with the recently reported animal data as performed at the Ramazzini Institute and the US National Toxicology Program as well as by mechanistic studies. These experimental findings together with the epidemiology reviewed here are sufficient in our opinion, to upgrade the IARC categorization of RFR to Group 1, carcinogenic to humans.

It would be useful to know more about the association of additional tumor types such as parotid gland, testicular, breast, hematopoietic malignancies and multiple primaries with RFR. Case studies should continue to be conducted in the absence of a better exposure assessment system to increase awareness and understand the relationship between exposure to RFR and disease causation, as well as trial-error experiments and interventions.

In light of the evolving science concerning mobile phone and screen time exposures and the longer-term risk of cancer established by both epidemiological and toxicological studies, current evidence is strong enough to go from precaution concerning possible risk to prevention of known risks. Although the benefits of connectivity are extremely important, safety considerations demand reconciling use of information vs. risk of perceived rare outcomes. Thus, a concerted program of public and health professional education should be undertaken throughout society explaining current knowledge and devising policies to promote safer technology in partnership with designers of software and hardware. In addition, methods should be developed and validated to reduce exposures in schools, workplaces, hospitals and other workplaces. The precautionary principle should be applied now and suitable warning messages provided to adults and critically to children and their parents. Until technology has been devised that substantially lowers exposures, special efforts should be advanced to ensure that the exposures of children are limited to those deemed essential. Children should be encouraged to text to reduce their exposure to RFR, while every attempt should be made to reduce exposure to RFR in schools, as well as homes.

Research has so far been performed on technologies that have already been introduced, but is critically needed on new, untested technology prior to its use. Epidemiological studies necessarily confirm the impact of past exposures, while experimental studies provide indications of future risk. Thus, experimental evaluations and modeling are essential before distributing newer systems (e.g. 5G) for which no safety data have been obtained. The absence of systematic testing of such technologies should not be confused with proof of safety. Better modeling through anatomically based systems, such as the Virtual Family, should be encouraged.

In the meantime, the evidence amassed thus far from epidemiology strengthens the case for instituting the precautionary principle with respect to exposures to RFR, especially to young children and men and women that wish to reproduce. The lack of detailed studies at this point reflects a myopic attitude toward the technology that may well prove to be wishful and dangerous thinking. Where studies have been carried out on human sperm quantity and quality there are increasing indications of serious human health impacts. To ignore those findings and subject humans to unevaluated novel RFR frequencies places current and future generations at risk.

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Testing – Children; Exposure Limits: Absorption of wireless radiation in the child
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Absorption of wireless radiation in the child versus adult brain and eye from cell phone conversation or virtual reality

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ABSTRACT

Children's brains are more susceptible to hazardous exposures, and are thought to absorb higher doses of radiation from cell phones in some regions of the brain. Globally the numbers and applications of wireless devices are increasing rapidly, but since 1997 safety testing has relied on a large, homogenous, adult male head phantom to simulate exposures; the "Standard Anthropomorphic Mannequin" (SAM) is used to estimate only whether tissue temperature will be increased by more than 1 Celsius degree in the periphery. The present work employs anatomically based modeling currently used to set standards for surgical and medical devices, that incorporates heterogeneous characteristics of age and anatomy. Modeling of a cell phone held to the ear, or of virtual reality devices in front of the eyes, reveals that young eyes and brains absorb substantially higher local radiation doses than adults'. Age-specific simulations indicate the need to apply refined methods for regulatory compliance testing; and for public education regarding manufacturers' advice to keep phones off the body, and prudent use to limit exposures, particularly to protect the young.

1. Introduction

With many nations having more mobile phones than people, and the rapidly increasing use of wireless transmitting devices by infants, toddlers and young children, it is important to consider children's unique absorption of radiofrequency (RF), also called microwave (MW) non-ionizing radiation (Gandhi et al., 1996; de Salles et al., 2006; Wiart et al., 2008; Christ et al., 2010) and potential health impacts.

Standards for wireless devices have not changed since 1997, and are based on the assumption that the only adverse effect to be avoided is heat (Gandhi et al., 2012). Mobile phones are certified to be within RF radiation regulatory limits using robot-assisted determination of peak spatial Specific Absorption Rate (psSAR) – i.e. maximum dose rate – within a phantom of a large, adult male head and body, the Standard Anthropometric Mannequin (SAM). The plastic SAM head mold, filled with a homogeneous liquid to simulate dielectric characteristics of soft tissues at the frequency of the device being tested, is assumed to be valid for those with younger and smaller heads (U.S. Federal Communications Commission (FCC) Office of Engineering and Technology, 1997; IEEE International Committee on Electromagnetic Safety (SCC39), 2005), to test compliance with outdated standards set

for exposure to the entire head. This ignores human anatomy, and the fact that the brain and eyes are target tissues where such radiation can be especially biologically important. Studies have consistently indicated that children's brains absorb substantially higher peak doses than adults (Morris et al., 2015; Foster and Chou, 2016).

Anatomically-based, age-appropriate mathematical models of younger heads with thinner skulls and higher water content were used to examine specifics of psSAR averaging volume and dielectric constants within specific regions of the head. Specific regions include the eye and brain, to aid interpretation of international standards (Institute of Electrical and Electronics Engineers, 2013; Gosselin et al., 2014; International Commission on Non-Ionizing Radiation Protection, 1998; Peyman et al., 2009). Age-appropriate simulations are used to advance the understanding of the exposure of critical parts of the brain to RF radiation using models over a broad range of ages (from 3 to 34 years) (Fernandez-Rodriguez et al., 2015) from cell phones used against the ear, as well as in front of the face to view virtual reality (Google, n.d.).

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2. Materials and methodology

2.1. Cell phone model

A dual band (900 MHz and 1800 MHz) model was used (Garzon et al., 2013), with a common cell phone case $109 \times 60 \times 13.9$ mm and a Planar Inverted “F” Antenna (PIFA) in the top position. This antenna is widely used in modern phones. With the exception of virtual reality modeling, the phone was in the “touch” position (touching the cheek, with the antenna over the ear). Although manufacturers specify that wireless devices should be kept a minimum distance from the body in order to ensure meeting exposure standards, in this work the phone was modeled as it is commonly used, against the skin, with dimensions from phone to brain as indicated below. Virtual Reality (VR) modeling was carried out for a system similar to the Google Cardboard (Google, n.d.) in which the cell phone is positioned in front of the eyes. The distances between the antenna (inside the phone) and the eye lens are: 31.37 mm for Thel and 46.64 mm for Duke, based upon the dimensions of the anatomical models.

2.2. Head models

Head models of the 8 and 10 year old boys, developed by Porto Alegre/Environmental Health Trust (PAEHT) for this work, were obtained via segmentation of Computerized Tomography (CT) images of specific children after approval by the ethics committee of the Mae de Deus Hospital in the “Parecer n° 556/12 do Comitê de Ética em Pesquisa do Hospital Mãe de Deus CEP/HMD,” in Porto Alegre, Brazil. All other head models belong to the “Virtual Family” (VF) developed by the Swiss National Institute of Technology Research (IT’IS) in collaboration with the U.S. Food and Drug Administration. The VF, representing average dimensions and anatomy for the gender and age, have been detailed elsewhere (Gosselin et al., 2014). SAM, the homogenous head model employed by telecommunication testing worldwide is based on a male with a head weighing about 11 pounds, representing the 90th percentile of U.S. military recruits in 1989.

The models are: 3 year-old boy (Indy from VF; 13 mm distance antenna to brain (atb)), 5 year-old girl (Roberta from VF; 20 mm atb), 6 year-old boy (Thelonious from VF; 23 mm atb), 8 year-old girl (Eartha from VF; 29 mm atb), 8 year-old boy (David developed by PAEHT; 23 mm atb), 10 year-old boy (Diego developed by PAEHT; 24 mm atb), 11 year-old girl (Billie from VF; 26 mm atb), 14 year-old boy (Louis from VF; 19 mm atb), 26 year-old woman (Ella from VF; 29 mm atb), 34 year-old man (Duke from VF; 32 mm atb) and SAM (8 mm atb) (Institute of Electrical and Electronics Engineers, 2013). In the Diego, Duke, Louis and Thelonious simulated versions, the pinna has not been identified.

psSAR simulations were repeated in triplicate for a range of ages, grid sizes, and dielectric parameters, employing standard protocols as summarized below.

2.3. Dielectric parameters

Adult parameters obtained from the work of Gabriel (1996) are regularly used for this purpose in medical applications. Age specific parameters for children were estimated based on accepted methods by correlating age specific measurements in pigs (Peyman et al., 2009) with Gabriel data (Gabriel, 1996) and interpolating using the following equation:

$$P(a) = \left[\frac{P_{30} - P_{10}}{12 - 4} \times a + \left(P_{50} + \frac{P_{30} - P_{10}}{12 - 4} \times 12 \right) \right] \times \left(\frac{P_H}{P_{250}} \right)$$

where,

P is one of the dielectric parameters (permittivity or conductivity) of a given tissue;

a is the age (in years) for which the parameters are being adjusted (a must be in the range 4–12 years);

P_{250} , P_{50} and P_{10} are the parameter values measured in pigs (Peyman et al., 2009) weighing 250 kg, 50 kg and 10 kg corresponding to human ages of 18 (and adults), 12 and 4 years respectively;

P_H , is the value of the parameter published in Gabriel (1996), which is widely accepted as “adult human parameters.”

2.4. Simulations

Software – SEMCAD X 14.8. Hardware – aXware TESLA C1060@ Intel i5 – 3470 CPU 3.20 GHz, 32 GB RAM. Grid characteristics – voxel dimensions: from 0.002 to 0.07 wavelength (0.67–23.3 mm in surrounding space); grading and relaxation ratio: 1.2 minimum padding: 0.2 wavelength (6.67 cm of free space around the head); total model size: from 4 M to 54 M cells. Source characteristics – frequency: 900 MHz; power delivered: 250 mW; bandwidth: 200 MHz and harmonic (0 Hz); typical simulation length: 40 periods. Simulation time – from 30 min to 5 h depending on the grid adjustment (dimensions and orientation) and frequency bandwidth. Validation – Loss and radiated power > 240 mW (@ $P_{del} = 250$ mW). Uncertainties were estimated by varying simulation parameters (e.g. refining the mesh) and measuring the power budget. All psSAR values are in W/kg.

3. Results

When cell phones are held close to the head most of the energy (more than 80%) from the transmitting antenna is absorbed by the head. When the phone is used for virtual reality viewing, the head absorbs 50% of the energy.

3.1. Averaging volumes

Different averaging volumes are used in RF radiation regulatory limits, with North American standards referencing a cube of tissue weighing 1 g (U.S. Federal Communications Commission (FCC) Office of Engineering and Technology, 1997), while the International Commission on Non-Ionizing Radiation Protection (ICNIRP) relies on a 10 g volume (“Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). (International Commission on Non-Ionizing Radiation Protection”, 1998). psSAR in the whole head (ear and/or skull) as well as in the brain varies inversely with averaging volume (Fig. 1), as smaller volumes are on average closer to the antenna. Another consequence is that the SAM head psSAR values are higher than values calculated using anatomical models, by approximately 1.7-fold in 10 g of tissue and 1.4-fold in 1 g of tissue. Several factors contribute to this trend: the SAM head model has no skull so psSAR is measured in simulation fluid that mimics soft tissues (bone absorbs RF radiation less avidly than the brain); the SAM head has a non-absorbing space simulating a compressed 6 mm thick pinna, while the anatomical models have uncompressed pinnae ranging from 5 mm in Indy to approximately 2 cm in Duke, and these outer ears do absorb radiation; and the relatively large head model of SAM presents a flatter surface adjacent to the antenna, compared with the smaller, rounded heads of the anatomical models.

Consistent with previous reports (Kang and Gandhi, 2002), the averaging volume employed in the modeling is correlated inversely with the calculated maximum tissue dose or psSAR (Fig. 1). Averaging the SAR over 10 g of tissue with a 2 W/kg maximum SAR (consistent with the ICNIRP recommendation) permits over 3-fold greater radiation absorption in the skull (“head” per regulatory standards), compared with averaging over 1 g of tissue with a 1.6 W/kg maximum SAR (consistent with current FCC/FDA methods). Furthermore, averaging SAR over 0.1 g – one-tenth the smallest mass in current use – yields a tissue dose up to 6 times that calculated for the commonly used 10 g mass standard.

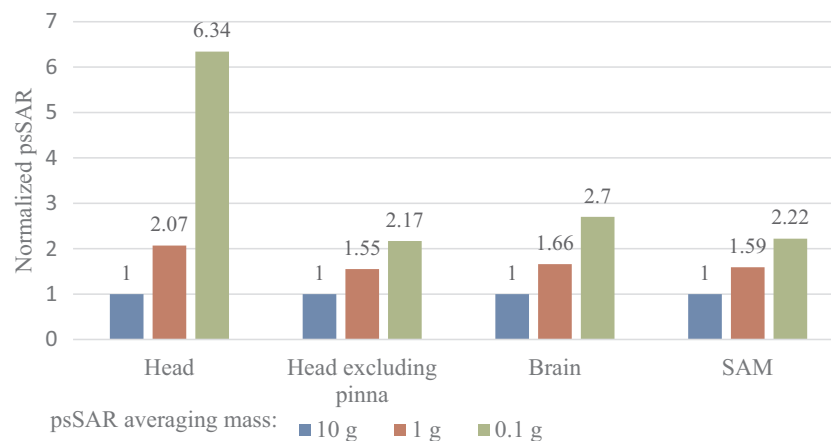


Fig. 1. psSAR averaged over cubic volumes containing 1 g and 0.1 g, relative to 10 g of continuous tissue. Values are normalized to the 10 g psSAR. Head including and excluding pinna, and brain psSAR values are averages of the psSAR obtained for 10 anatomical models. SAM is also presented.

The remainder of this report presents SAR data within 1 g cubes.

3.2. Developmental trends and tissue-specific doses

The psSAR for the skull, as predicted by these models, rises through childhood as the skull thickens, and then falls from youth to adulthood as the proportion of marrow in the bone decreases. The psSAR in the brain decreases with increasing age, with brain in the youngest models absorbing approximately 2-fold to 3-fold higher doses of RF radiation than older female and male models respectively.

Tissues that have been shown to absorb 80% of the radiation from a cell phone placed next to the head (Cardis et al., 2008) may be particularly sensitive and vulnerable to effects of RF radiation. These include the cerebellum, temporal and frontal lobes, and cheek (including parotid gland) and eyes. With the phone against the ear, the psSAR in the hippocampus and the cerebellum (Fig. 2) is greater in the younger models, with approximately 2-fold greater psSAR in the cerebellum, and approximately 30-fold greater psSAR in the hippocampus.

It is undisputed that the eyes are particularly vulnerable to RF radiation, as a result of little fluid circulation and thus poor cooling, plus high RF radiation absorption as a result of relatively high water content. The eyes in the youngest models absorb between 2-fold and almost 5-fold higher doses of RF radiation than those of the older models (Fig. 2). Older males' heavier features offer particular protection to the eyes when the phone is used for conversation.

Model geometry as well as dielectric constants change systematically with age, with greater head mass, and skull and skin thickness in adults compared with children. Fig. 3, psSAR in the grey matter as a function of distance from the antenna (approximating the pinna plus skull), depicts a clear trend of decreasing psSAR with increasing distance (as expected) and illustrates the trend amongst models. Substantial inter-individual variation in psSAR is seen in the more than two-fold difference between the David and Eartha models, both 8 years of age.

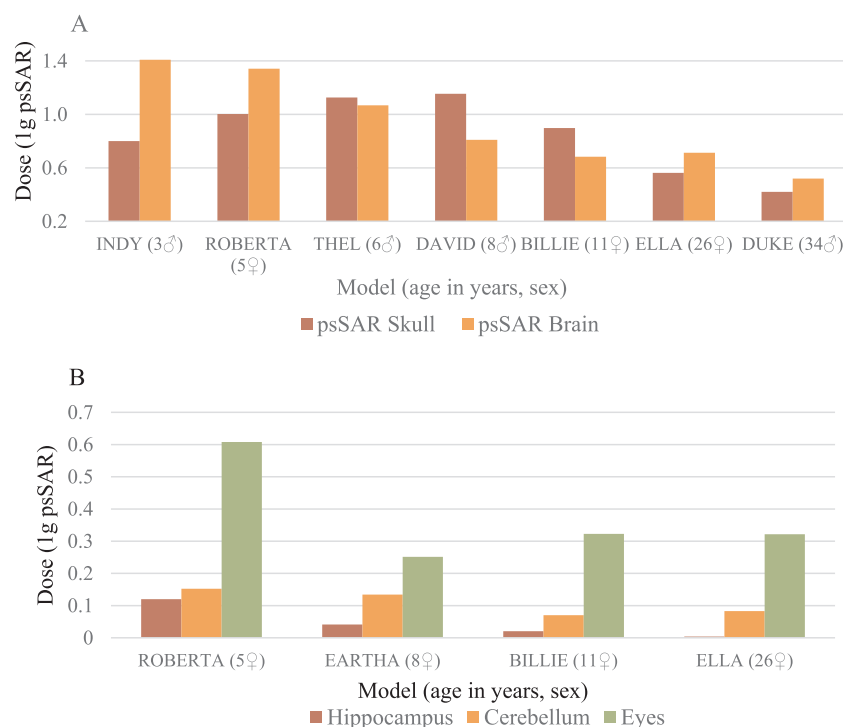


Fig. 2. psSAR in 1 g of specific tissues. A. the skull and brain and B. specific tissues in models with these features identified – hippocampus, cerebellum and eyes.

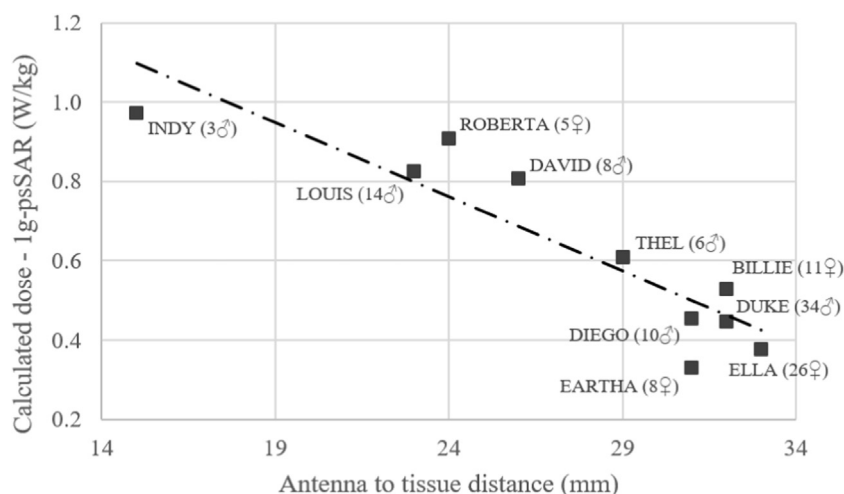


Fig. 3. Trend of psSAR in 1 g of grey matter, as a function of distance from the antenna to the brain, for phone in “talk” position.

3.3. Visualization of child versus adult doses

The previously quantified differences between doses of RF radiation (SAR) in critical components of the brain of the child and adult are clearly illustrated in Fig. 4, in child (Thelonious) and adult (Duke) head models, when the phone is used for talking, or for viewing virtual reality. The eyes and frontal lobe of the 6 year old model experiences a roughly 3-fold higher SAR than the adult's when a virtual reality cardboard holder containing a phone is placed directly in front of the eyes (Fig. 4B).

4. Discussion

In summary, compared with adult models, children experience two- to three-fold higher RF doses to: 1) localized areas of the brain when a cell phone is positioned next to the ear; and 2) the eyes and frontal lobe when a cell phone is used to view virtual reality. These findings raise serious questions about the current approach to certify cell phones; particularly the use of the SAM.

In 2012, the U.S. Government Accountability Office advised that the test system used to estimate human exposure should be modified to reflect changing uses and users of mobile phones (US Government Accountability Office, 2012). The analyses presented here further support the need for more pertinent modeling, particularly in light of the growing use of phones and other wireless transmitting devices by

infants, toddlers and young children, and new modes of use such as virtual reality. The current SAM Certification Process should be replaced, or at least complemented with computer simulation such as FDTD, as currently approved by the FDA and FCC. Certification should include child models, and should be based on a 1 g or lower averaging mass.

The influence of the averaging mass is important when comparing radiation standards for North America with an averaging mass of 1 g versus international standards based on 10 g of tissue, as psSAR values are lower within greater averaging masses. The differences in psSAR measured above are a mathematical consequence of the fact that the center of gravity of a larger tissue cube is further from the source. SAM is a homogenous model, but in order to discern risks for specific regions and small structures (e.g. parotid gland, or acoustic nerve that are suspected as being affected by RFR), it is necessary to model a physiologically relevant volume. Besides, 0.1 g of human tissue may contain 55 million cells (glial cells and neurons) (von Barthel et al., 2016; Garman, 2011; Herculano-Houzel and Kaas, 2011); moreover, the initiation of cancer is commonly thought to originate with the mutation of as few as one cell, for example as evidenced by clonal consistency in early stages of pediatric glioma (St. Jude Children's Research Hospital, 2012; Alcantara Llaguno and Parada, 2016).

In 2011, IARC classified RF/MW radiation as a possible human carcinogen (group 2B) (Baan et al., 2011), and subsequent epidemiological findings strengthen this finding (Hardell and Carlberg, 2015). In

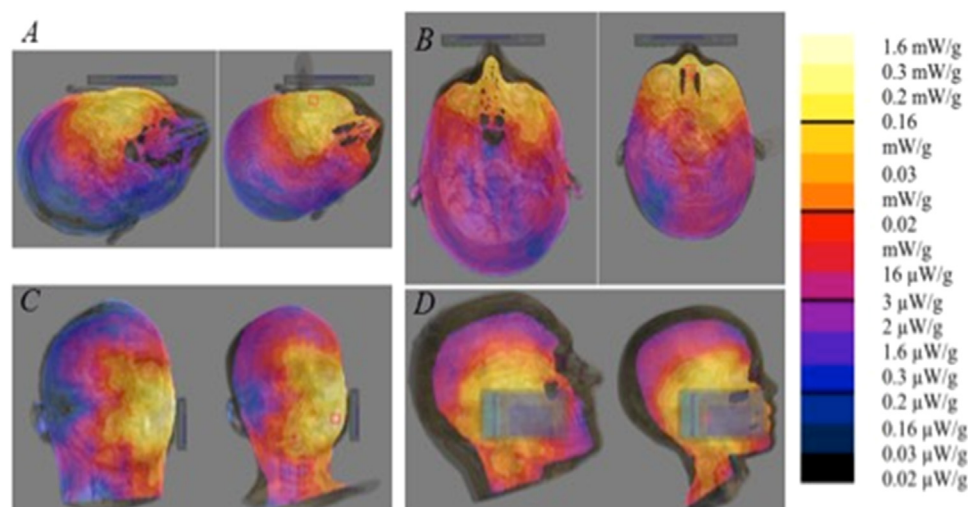


Fig. 4. SAR in cross-sectional views of child and adult male heads, with phone in talk and in virtual reality positions. A Axial slices (top view) of Thelonious (6 y) and Duke (34 y), with cell phone in cheek position, intersecting the eyes; B Axial slices (top view) of Thelonious (6 y) and Duke (34 y), with cell phone in virtual reality position, intersecting the eyes; C Quasi-coronal slices (frontal view) of Thelonious (6 y) and Duke (34 y) with cell phone in the cheek position, through the ear; D Parasagittal slices (side view) of Thelonious (6 y) and Duke (34 y), with cell phone in virtual reality position, intersecting the eye. The scale is 50 dB with 0 dB = 1.6 mW/g.

2016 the first results of U.S. National Toxicology Program animal studies reported that non-thermal levels of both GSM and CDMA wireless radiation – irregularly pulsed signals – significantly increased highly malignant rare cancers of the brain and heart (Wyde et al., 2016). Independent analysts find that these scientific advances merit IARC reclassification to 2A or even 1 (“known human carcinogen”).

Our modeling demonstrates clearly that localized psSAR varies significantly for critical components of the brain. Younger models absorb proportionally more radiation in the eyes and brain – grey matter, cerebellum and hippocampus—and the local dose rate varies inversely with age. This reflects the fact that the head is not homogeneous. Indeed, localized heating up to 5 Centigrade degrees has been detected as a result of mobile phone radiation studied *ex vivo* in cow brain using Nuclear Magnetic Resonance thermometry (Gultekin and Moeller, 2013).

Not only do children absorb higher peak doses in the brain than adults, their brain is growing rapidly, subject to different windows of vulnerability, and thus more susceptible to insult. In particular, glial cells are in an early developmental stage in the newborn brain and develop, grow, and reproduce extensively throughout the brain during childhood and early adulthood. It appears that RF radiation induces cancer in these cells (Wyde et al., 2016).

Myelin, the protective fatty sheath around neurons, is thin in the young brain and develops through the mid-twenties (Redmayne and Johansson, 2014). Lower myelin levels and consequent higher water levels are responsible for greater absorption of RF energy in young brains. Myelin also provides some protection of neurons from RF and other potential neurotoxins.

Timing, type, duration and variability of toxicant exposure levels all modulate toxicity. Indeed, exposures that take place during fetal development or early childhood may cause permanent brain injury, whereas the same doses may have little or no impact in adults (Heindel et al., 2015). Analogously, a number of chemicals are known to exert differentially greater toxicity to the young brain and body. As well, peak exposures are far more important than averages, and early exposures more damaging as they affect a child's trajectory through life. For example, sudden shifts in benzene exposure are known to be more damaging than would be expected from average continuous exposures (Agency for Toxic Substances and Disease Registry (ATSDR), 2007). Lead exposures that occur prior to age two have greater impacts on the adult brain and body than those that occur later in life.

Early RF radiation exposures have also demonstrated long term effects. Experimental prenatal (Bas et al., 2009) and adolescent rodent (Kerimoğlu et al., 2016) exposures to mobile phone radiation have been shown to impair the development of the dentate gyrus and pyramidal cells and to affect behavior (Aldad et al., 2012; Saikhedkar et al., 2014), similar to how early life stressors also impair subsequent neurogenesis of the hippocampus, and learning (Narayanan et al., 2015; Huang, 2014; Musaelyan et al., 2014; Deniz et al., 2017). As the hippocampus plays a critical role in the development of memory, impulse control and a number of other critical cognitive and motor functions, greater RF radiation doses to this part of the young brain merits serious attention in revising standards for emissions from cell phones.

Interest in physiologically relevant modeling will likely intensify as effects of RF radiation beyond heating gain relevance in standards setting. A sweeping review of scientific omissions and misrepresentations, as well as conflicts of interests, in a recent UK review of RF exposure guidance clearly makes the case for much more restrictive, better-informed science-based standards (Starkey, 2016).

5. Conclusions

Our findings support reexamination of methods to determine regulatory compliance for wireless devices, and highlight the importance of precautionary advice such as that of American Academy of Pediatrics (2016). The Academy recommends that younger children should not

use cell phones, and that prudent measures should be taken to eliminate exposure (e.g. using devices for amusement or education only when all wireless features are turned off – in “airplane mode”) or to minimize exposure (e.g. texting or using speakerphone), and that cell phones should not be kept next to the body. Use of wires/cables in schools and homes circumvents needless exposures of children to radiation from both devices and Wi-Fi routers. There is also an urgent need for research to evaluate the risks to the eye from use of cell phones in virtual reality applications.

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Contributions

C. Fernandez: Conceptualization, Methodology, Investigation, Validation, Formal Analysis, Writing – Review & Editing

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D.L. Davis: Conceptualization, Funding Acquisition, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

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BioInitiative Comments; Aug. 27, 2013

**FCC 13-39****Before the Federal Communications Commission****Washington, D.C. 20554**

In the Matter of

Reassessment of Federal Communications)	ET Docket No. 13-84
Commission Radiofrequency Exposure Limits and)	
Policies)	
)	
Proposed Changes in the Commission's Rules)	ET Docket No. 03-137
Regarding Human Exposure to Radiofrequency)	
Electromagnetic Fields)	

To: Office of the Secretary
Federal Communications Commission , Washington, DC 20554

As officially presented in the Federal Register/ Vol. 78, No. 107 / Tuesday, June 4, 2013 / Proposed Rules. Federal Communications Commission, 47 CFR Parts 1, 2, 15, 24, 25, 27, 73, 90, 95, 97, and 101 [ET Docket Nos. 03-137 and 13-84; FCC 13-39], Reassessment of Exposure to Radiofrequency Electromagnetic Fields Limits and Policies, Federal Communications Commission

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BioInitiative 2007 Report Conclusions

- 1) The 2007 BioInitiative Report conclusively established that low-intensity (non-thermal) bioeffects and adverse health effects of non-ionizing electromagnetic radiation (NIER) at levels significantly below existing public exposure standards.
- 2) The International Committee on Non-Ionizing Radiation Protection (ICNIRP) and the Institute for Electrical and Electronic Engineers/Federal Communications Commission (IEEE/FCC) public safety limits are inadequate and obsolete with respect to prolonged, low-intensity NIER exposures, based on an expert group's review of more than 2000 peer-reviewed and published scientific studies and reviews.
- 3) New, biologically-based public exposure standards are urgently needed to protect public health world-wide.
- 4) It is not in the public interest to wait.
- 5) The BioInitiative 2007 Report recommends a 0.1 microwatt per square centimeter limit for outdoor exposure for combined AM, FM, TV and wireless frequencies.

Background: The BioInitiative Report is an internationally acclaimed scientific and public health report on potential health risks of electromagnetic fields and radiofrequency/microwave radiation. In 2007, the BioInitiative Working Group, an international collaboration of prestigious scientists and public health experts from Columbia University and the University at Albany (New York), University of Washington (Seattle), the Karolinska Institute, Umea University and Orebro University Hospital (Sweden), the European Environmental Agency (Denmark) Medical University of Vienna (Austria) and Zhejiang University School of Medicine, (China) released a 650-page report citing more than 2000 studies that document health effects of EMFs from all sources. It is incorporated by reference in this filing.

The BioInitiative Report was produced for publication to the broadest possible audience, hence placed on the Web. Much of the BioInitiative Report content, including updated chapters and new chapters was published in a special two-volume issue of the journal *Pathophysiology* (August 2009, *Pathophysiology* 16: 2,3).

It documented that chronic exposure to electromagnetic fields (EMF) is associated in some scientific studies with increased health risks that vary from impaired learning, headaches, mental confusion, skin rashes, tinnitus and disorientation to a variety of cancers, and neurological diseases like amyotrophic lateral sclerosis (ALS) and Alzheimer's. Sources of concern may include but are not limited to power lines, cell and cordless phones, cell towers, WI-FI, WiMax and wireless internet.

Strong concern was voiced by scientists and public health and environmental policy experts, that the deployment of technologies that expose billions of people worldwide to new sources of EMF may pose a pervasive risk to public health. Such exposures did not exist before the age of industry and information. Prolonged exposure appears to disrupt biological processes that are fundamental



to plant, animal and human growth and health. Life on earth did not evolve may pose a pervasive risk to public health. Such exposures did not exist before the age of industry and information. Prolonged exposure appears to disrupt biological processes that are fundamental to plant, animal and human growth and health. Life on earth did not evolve with biological protections or adaptive biological responses to these EMF exposures. A rapidly accumulating body of scientific evidence of harm to health and well-being constitute warnings that adverse health effects can occur with prolonged exposures to very low-intensity EMF at biologically active frequencies or frequency combinations.

BioInitiative 2012 Report Conclusions

- 1) The 2012 BioInitiative Report was prepared by 29 international experts studying more than 1800 new peer-reviewed scientific studies published since 2007 and concluded again that exposure to EMF and radiofrequency radiation (RFR) produces biological effects and adverse health effects at levels significantly below existing public exposure standards; and substantially below levels identified in 2007.
- 2) The scientific evidence for health harm in 2012 is stronger and more consistent than in 2007; and the levels of exposure at which biological effects and adverse health impacts are reported to occur are far lower than in 2007.
- 3) ICNIRP and IEEE/FCC public safety limits remain unchanged and are still inadequate and obsolete with respect to prolonged, low-intensity NIER exposures. Worse, FCC Dockets 13-84, 03-137 and 13-39 propose to significantly relax rather than tighten exposure standards, in stark contrast to what the scientific evidence suggests is needed to protect public health from RFR.
- 4) Specific absorption rate (SAR) as a measure of compliance with new biologically-based exposure limits should be abandoned. Setting public safety limits based on heating is an unsuitable starting point for developing new standards that properly address chronic exposures to very low-intensity RFR. SAR should not be applied to new biologically-based public exposure standards since by definition SAR is a measure of tissue heating, and the biological effects of NIER are by definition, not due to a heating mechanism. It makes no sense to continue misapplying existing thermal concepts of biological harm, time-averaging and metrics for thermal heating as a basis for detecting and preventing harm from new wireless technologies in the face of strong evidence of harm without measureable heating.
- 5) New, biologically-based public exposure standards should be developed under the direction of experts in the biological effects and adverse health effects of chronic exposures to electromagnetic fields, drawing upon the substantial international body of scientific and public health literature, and not be limited to individuals in electrical and electronic engineering.
- 6) The agency to develop new biologically-based public exposure standards should be chosen to avoid the conflicts present now where the FCC acts both as the auctioneer to promote sale and use of radiofrequency radiation spectrum and works to actively enable the telecommunications



and electronics industries to develop and market new technologies through FCC compliance testing (Grants of Authorization). At the same time the FCC is charged with adopting effective

public health limits (for which it admits it has no health expertise) and for enforcing compliance with FCC public safety limits (for which it has a dismal and ineffective track record).

7) Immediate precautionary actions are urgently needed. New safety standards will take time to be developed and implemented. Societies in the interim need to begin making changes to reduce exposures now from wireless technologies (communications, data transmission, transportation, surveillance, environmental and medical monitoring, medical implants, etc.) in the interim.

8) It is not in the public interest to wait. The continued rollout of wireless technologies and devices puts global public health at risk from unrestricted wireless commerce unless new and far lower exposure limits and strong precautionary warnings for their use are implemented. Many millions of people, including the most vulnerable populations (the fetus, young children, the ill, the elderly and those with extreme sensitivity to exposures) who are affected by second-hand wireless radiation exposures must have better protection.

9) The cost of doing nothing is unacceptable. Substantial evidence for health risks from chronic exposure to wireless technologies cannot be dismissed in 2012, and if we do nothing, it will simply worsen rates of chronic diseases, disability and premature mortality.

10) The BioInitiative 2012 Report reports biological effects at exposure levels significantly below the 2007 recommended goal of 0.1 uW/cm². Since 2007, five new studies of base-station level RFR at intensities ranging from less than 0.001 uW/cm² to 0.05 uW/cm² report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. If these results are confirmed to be due to RFR exposure exposure standards may need to be set at even lower levels in the future, as new and better studies are completed.

Background: The BioInitiative 2012 Report concludes that the evidence for health risks from electromagnetic fields (EMFs) generated by wireless technologies have substantially increased since 2007. A review of over 1800 new scientific studies indicates current guidelines are inadequate to protect the public from chronic exposure to very low-intensity (non-thermal) electromagnetic fields and radiofrequency radiation (EMF and RFR). It is incorporated by reference in this filing.

The 2012 BioInitiative Report was prepared by 29 authors from ten countries, ten holding medical degrees (MDs), 21 PhDs, and three MsC, MA or MPHs. Among the authors are three former Presidents of the Bioelectromagnetics Society and five full members of BEMS. One distinguished author is the Chair of the Russian National Committee on Non-Ionizing Radiation. Another is a Senior Advisor to the European Environmental Agency. Full titles and affiliations of authors is in Section 25 of the BioInitiative Report at www.bioinitiative.org



In twenty-four technical chapters, the BioInitiative Working Group authors discuss the content and implications of about 1800 new studies since 2007. Overall, these new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9); carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on the fetus, neonate and offspring (Section 18 and 19); effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18); and findings in autism spectrum disorders consistent with EMF/RFR exposure effects. Global precautionary actions that have been taken in countries around the world, and recommended by medical and research experts are documented in Section 22. Use of the Precautionary Principal and it's relevance are presented in Section 23. Key scientific evidence and public health policy recommendations are in Section 24.

See Appendix A for specific conclusions and findings of the BioInitiative 2012 Report, and see the Report at www.bioinitiative.org

Recommendations to the FCC

The FCC review of health and safety standards for radiofrequency radiation as presented (Federal Register/ Vol. 78, No. 107 / Tuesday, June 4, 2013 / Proposed Rules. Federal Communications Commission, 47 CFR Parts 1, 2, 15, 24, 25, 27, 73, 90, 95, 97, and 101 [ET Docket Nos. 03–137 and 13–84; FCC 13–39], Reassessment of Exposure to Radiofrequency Electromagnetic Fields Limits and Policies, Federal Communications Commission) does not begin to properly address the current scientific evidence that conclusively demonstrates biological effects and some adverse health effect of EMF and RFR exposures at low-intensity (non-thermal) exposure levels. The BioInitiative Reports (2007 and 2012) should define the discussion range for new chronic exposure limits; and not be drawn from re-examination of existing thermal standards.

In fact, these proposed rules and regulations relax rather than tighten exposure levels in the face of overwhelming scientific evidence that an entirely new paradigm for developing safety standards is warranted, and in fact, overdue. For example, declaring the pinna of the ear (the earlobe) to be an extremity, so as to allow a huge increase in allowable SAR exposure ⁽⁵⁾ at the head (affecting the brain including the auditory and other cranial nerves, the eye and salivary glands in the cheek) is reckless and unsupported by any legitimate expert review of the available evidence. ^(1,2,3) The FCC has not considered the special biology of the developing fetus, the young child, people of small stature, people with medical implants for serious chronic diseases and chronic pain in these proposed rule changes. These changes avoid making exposure-relevant reductions keyed to scientific benchmarks established in hundreds of in peer-reviewed, published studies reporting low-intensity (non-thermal) effects of chronic (prolonged) exposures now common in public life.



The new FCC public exposure limits must take into account the variable conductivity and permittivity of tissues of various ages and developmental stages and aging of humans, and the exquisite sensitivity of the human reproductive cells.

1) SUPPORT DEVELOPMENT OF NEW, BIOLOGICALLY-BASED PUBLIC SAFETY LIMITS BY A QUALIFIED AGENCY OR PROFESSIONAL ORGANIZATION:

The FCC'S thermal-based public safety MPEs and the SAR approach are useful to prevent tissue heating and damage; but not useful to protect the public against chronic exposures (as opposed to acute exposures) biologically active non-thermal, low-intensity NIER.

2) RECOGNIZE THE WHO IARC CLASSIFICATION OF RFR:

The WHO IARC classified RF radiation as a Group 2B Possible Human Carcinogen; it joins the IARC classification of ELF-EMF (Extremely Low Frequency Electromagnetic Fields) as a Group 2B Possible Human Carcinogen, which the FCC has also ignored. The evidence for carcinogenicity for RFR was primarily from cell phone/brain tumor studies but IARC applies this classification to all RFR exposures.

3) ADOPT SPECIFIC LANGUAGE ENDORSING THE PRECAUTIONARY PRINCIPLE:

The Commission should address and incorporate appropriate precautionary, public-health based measures to take into account the recent World Health Organization International Agency for Research on Cancer (IARC) classification of RFR as a Possible Human Carcinogen before subjecting widespread national populations to a preventable toxic exposure.

4) DEFINE BIOLOGICAL EFFECT AS HARMFUL INTERFERENCE WITH BIOLOGICAL ORGANISMS

A definition of biological effects should key to such effects that can reasonably be presumed to result in adverse health effects from exposure to RFR including but not limited to DNA damage; immune, blood-brain barrier, and calcium channel disruption; disturbed circadian rhythms; hormone dysregulation; degraded cognition and sleep; disrupted autonomic regulation; desynchronization of neural activity and other biological consequences of acute or chronic exposure to low-intensity NIER as documented in the BioInitiative 2007 and 2012 Reports.

5) RECLASSIFICATION OF THE PINNA SHOULD BE DEFERRED:

A reclassification of the pinna should be delayed by the FCC in all open dockets pertaining to completion of the FCC'S review of RFR health effects and proposed FCC compliance testing rule changes. New studies show adverse effects without relaxing this limit. ^(1,2,3,4) Lin ⁽⁵⁾ gives an answer to the FCC'S question asking on page 79 "*We request comment on the significance, if any, of the differences between these standards. For example, we request comment on whether using an averaging mass of 10 grams over a contiguous layer of tissue would yield a significantly different SAR value than that averaged over a 1-gram cube and whether that difference would be consistently higher or lower, particularly with enough consistency to be able to establish a definable relationship between the measurement methods*". See footnote to reference (5)



6) NEPA ASSESSMENT FOR FINAL RULES – APPENDIX A AND B

The Commission should require a NEPA assessment for Final Rules (App. A) and Proposed Rules (App. B). Proposed Rules in Appendix B, in particular, have the potential to adversely affect human health and environmental resources.

7) COMPLIANCE TESTING REQUIREMENTS

a) **Medical and Metal Implants:** Metal detectors in the 9 kHz range are not covered by current FCC rules and should be addressed with respect to the public with disabilities (medical and metal implants). People with deep brain stimulators for Parkinson's disease are unable to pass through metal detectors because evidence exists that such exposures can shut down the electrodes in these devices, and such exposures are now preventing people with deep brain stimulators from normal activities (shopping, air travel, hospitals and health care facilities, attendance at public meetings and events, etc).

b) **Distance Exemptions:** More realistic provisions must be developed regarding distancing from RFR transmitters (wireless devices, wireless access points and routers, baby monitors, wireless utility meters, etc) for infants and children who cannot reasonably be expected to observe FCC rules for 20 cm or 40 cm separation. The basis for exemptions from routine evaluations (Appendix C – fixed, mobile or portable RF sources) assumes conservative derivations or worst-case predictions leading to “*minimal likelihood for the exposure limits for the general public to be exceeded*” based on faulty logic about what can be expected with regard to the general public knowing or being able to avoid breaching an arbitrary 20 cm or 40 cm distances.

c) **Compliance Testing:** Realistic assumptions about operation of wireless utility meter devices ('smart meters') should be mandatory in FCC testing and issuance of Grants of Authorization. FCC testing labs ignore the obvious two-antenna or three-antenna design of wireless utility meters, yet issue 'Conditions' for compliance that specify “*this compliance test is issued with the condition that the antenna may not operate in conjunction with other antennas*”. The FCC cannot reasonably issue Grants of Authorization based on lab testing that ignores typical construction of the device, and how in common practice it is installed and operated.

d) **Cumulative Effects:** Cumulative effects of RFR exposures from multiple wireless devices and environmental exposures are not sufficiently addressed, measured or tested under current or proposed FCC rules. The 2008 NAS Report on Research Needs for Wireless Device summarizes deficiencies for wireless effects on children, adolescents and pregnant women; wireless personal computers and base station antennas; multiple element base station antennas under highest radiated power conditions; hand-held cell phone compliance testing; and better dosimetric absorbed power calculations using realistic anatomic models for both men, women and children of different height and ages. Realistic assessments of cumulative RFR exposures need to be addressed, taking into account the high variability in environmental situations; and safety buffers below 'effects levels' need to be built into new FCC public safety limits.

e) **100% Duty Cycle:** FCC OET 65 should make clear that a 100% duty cycle will continue to be required in calculations of power density 'where the public cannot be excluded'.



f) **Time-Averaging vs Pulsed RFR:** New public exposure limits for pulsed RFR are needed, rather than specifying compliance limits based on time-averaged fields. Many new wireless devices and exposures create pulsed RFR for users; such exposures are linked to biological disruption effects and adverse health impacts. Time-averaging is biologically inappropriate where such measurements effectively camouflage exposures by mathematical dilution. Positive assertions of safety of pulsed RFR exposures that are characterized only by time-averaging have been shown to be unsupportable.

8. **Basis for Biologically-based Public Exposure Limits:** Recommendations for new, biologically-based public exposure standards should not be derived from existing FCC/IEEE C95.1 thermal standards, which have other useful purposes but which are obsolete with respect to low-intensity, chronic exposure to new wireless technologies.

Respectfully submitted:

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The 2007 and 2012 BioInitiative Reports at www.bioinitiative.org are incorporated by reference.

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*"First and foremost, for the first time in its history, the new IEEE standard instituted an exclusion for the pinnae or the external ears by relaxation of the above-mentioned basic SAR restriction from 2 W/kg to 4 W/kg. This choice segregates tissues in the pinnae apart from all other tissues of the human head. Of equal significance is the basic restriction for localized exposure at 2 W/kg in terms of SAR averaged over any 10 g of tissue. The SAR value has been increased from 1.6 W/kg averaged over any 1 g of tissue to 2 W/kg over any 10 g of tissue. Aside from the numerical difference between the SARs, the volume of tissue mass used to define the SARs in the new standard was increased from 1 g to 10 g. **The increase in tissue mass can have a profound influence on the actual quantity of RF energy allowed to be deposited in tissue by the new exposure standard.** It has been well established that the distribution of absorbed microwave energy is nonuniform, and it varies greatly from point to point inside a body. **An averaging volume that is as large as 10 g would tend to artificially flatten out the SAR distribution, whether it is computed or measured.** And the smoothing tends to substantially reduce the resulting SAR value. **Thus, a 10-g SAR at 2 W/kg could be equivalent to 1-g SARs of 5 W/kg or higher. Simply put, the absorbed energy averaged over a defined tissue mass of 10 g is inherently low compared to a 1-g SAR.**" (emphasis added)*

BioInitiative; 2012 Conclusions

BIOINITIATIVE 2012 - CONCLUSIONS Table 1-1

Overall, these 1800 or so new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9), carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on offspring behavior (Section 18, 19 and 20); and effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18). This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

BIOEFFECTS ARE CLEARLY ESTABLISHED

Bioeffects are clearly established and occur at very low levels of exposure to electromagnetic fields and radiofrequency radiation. Bioeffects can occur in the first few minutes at levels associated with cell and cordless phone use. Bioeffects can also occur from just minutes of exposure to mobile phone masts (cell towers), WI-FI, and wireless utility 'smart' meters that produce whole-body exposure. Chronic base station level exposures can result in illness.

BIOEFFECTS WITH CHRONIC EXPOSURES CAN REASONABLY BE PRESUMED TO RESULT IN ADVERSE HEALTH EFFECTS

Many of these bioeffects can reasonably be presumed to result in adverse health effects if the exposures are prolonged or chronic. This is because they interfere with normal body processes (disrupt homeostasis), prevent the body from healing damaged DNA, produce immune system imbalances, metabolic disruption and lower resilience to disease across multiple pathways. Essential body processes can eventually be disabled by incessant external stresses (from system-wide electrophysiological interference) and lead to pervasive impairment of metabolic and reproductive functions.

LOW EXPOSURE LEVELS ARE ASSOCIATED WITH BIOEFFECTS AND ADVERSE HEALTH EFFECTS AT CELL TOWER RFR EXPOSURE LEVELS

At least five new cell tower studies are reporting bioeffects in the range of 0.003 to 0.05 $\mu\text{W}/\text{cm}^2$ at lower levels than reported in 2007 (0.05 to 0.1 uW/cm^2 was the range below which, in 2007, effects were not observed). Researchers report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. Public safety standards are 1,000 – 10,000 or more times higher than levels now commonly reported in mobile phone base station studies to cause bioeffects.

EVIDENCE FOR FERTILITY AND REPRODUCTION EFFECTS: HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities in the low microwatt and nanowatt/cm² range (0.00034 – 0.07 uW/cm²). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage.

Studies of human sperm show genetic (DNA) damage from cell phones on standby mode and wireless laptop use. Impaired sperm quality, motility and viability occur at exposures of 0.00034 uW/cm² to 0.07 uW/cm² with a resultant reduction in human male fertility. Sperm cannot repair DNA damage.

Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Eroglu et al., 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. 2012 report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared (μ W/cm²).

EVIDENCE THAT CHILDREN ARE MORE VULNERABLE

There is good evidence to suggest that many toxic exposures to the fetus and very young child have especially detrimental consequences depending on when they occur during critical phases of growth and development (time windows of critical development), where such exposures may lay the seeds of health harm that develops even decades later. Existing FCC and ICNIRP public safety limits seem to be not sufficiently protective of public health, in particular for the young (embryo, fetus, neonate, very young child).

The Presidential Cancer Panel (2010) found that children '*are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.*'

The American Academy of Pediatrics, in a letter to Congressman Dennis Kucinich dated 12 December 2012 states “*Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child’s brain compared to an adult’s brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure they are safeguarded through their lifetimes.*”

FETAL AND NEONATAL EFFECTS OF EMF

Fetal (*in-utero*) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school.

Fetal Development Studies: Effects on the developing fetus from *in-utero* exposure to cell phone radiation have been observed in both human and animal studies since 2006. Divan et al (2008) found that children born of mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al., 2008).

Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted.

Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy).

Exposure to whole-body RFR from base stations and WI-FI, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant mother, and greater susceptibility to leukemia and asthma in the child where there have been maternal exposures to ELF-EMF.

A precautionary approach may provide the frame for decision-making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

(Bellieni and Pinto, 2012 – Section 19)

EMF/RFR AS A PLAUSIBLE BIOLOGICAL MECHANISM FOR AUTISM (ASD)

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments,
 - Special education classrooms should observe 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
 - All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
 - School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
 - Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
 - There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later, and
 - Wired classrooms should reasonably be provided to all students who opt-out of wireless environments.
- (Herbert and Sage, 2012 – Section 20)

Many disrupted physiological processes and impaired behaviors in people with ASDs closely resemble those related to biological and health effects of EMF/RFR exposure. Biomarkers and indicators of disease and their clinical symptoms have striking similarities. Broadly speaking, these types of phenomena can fall into one or more of several classes: a) alteration of genes or gene expression, b) induction of change in brain or organismic development, c) alteration of phenomena modulating systemic and brain function on an ongoing basis throughout the life course (which can include systemic pathophysiology as well as brain-based changes), and d) evidence of functional alteration in domains such as behavior, social interaction and attention known to be challenged in ASD.

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

Reducing life-long health risks begins in the earliest stages of embryonic and fetal development, is accelerated for the infant and very young child compared to adults, and is not complete in young people (as far as brain and nervous system maturation) until the early 20's. Windows of critical development mean that risk factors once laid down in the cells, or in epigenetic changes in the genome may have grave and life-long consequences for health or illness for every individual.

All relevant environmental conditions, including EMF and RFR, which can degrade the human genome, and impair normal health and development of species including homo sapiens, should be given weight in defining and implementing prudent, precautionary actions to protect public health.

Allostatic load in autism and autistic decompensation - we may be at a tipping point that can be pushed back by removing unnecessary stressors like EMF/RFR and building resilience.

The consequence of ignoring clear evidence of large-scale health risks to global populations, when the risk factors are largely avoidable or preventable is too high a risk to take. With the epidemic of autism (ASD) putting the welfare of children, and their families in peril at a rate of one family in 88, the rate still increasing annually, we cannot afford to ignore this body of evidence. The public needs to know that these risks exist, that transition to wireless should not be presumed safe, and that it is very much worth the effort to minimize exposures that still provide the benefits of technology in learning, but without the threat of health risk and development impairments to learning and behavior in the classroom.

(Herbert and Sage, 2010 – Section 20)

THE BLOOD-BRAIN BARRIER IS AT RISK

The BBB is a protective barrier that prevents the flow of toxins into sensitive brain tissue. Increased permeability of the BBB caused by cell phone RFR may result in neuronal damage. Many research studies show that very low intensity exposures to RFR can affect the blood-brain barrier (BBB) (mostly animal studies). Summing up the research, it is more probable than unlikely that non-thermal EMF from cell phones and base stations do have effects upon biology. A single 2-hr exposure to cell phone radiation can result in increased leakage of the BBB, and 50 days after exposure, neuronal damage can be seen, and at the later time point also albumin leakage is demonstrated. The levels of RFR needed to affect the BBB have been shown to be as low as 0.001 W/kg, or less than holding a mobile phone at arm's length. The US FCC standard is 1.6 W/kg; the ICNIRP standard is 2 W/kg of energy (SAR) into brain tissue from cell/cordless phone use. Thus, BBB effects occur at about 1000 times lower RFR exposure levels than the US and ICNIRP limits allow.

(Salford, 2012 - Section 10)

If the blood-brain barrier is vulnerable to serious and on-going damage from wireless exposures, then we should perhaps also be looking at the blood-ocular barrier (that protects the eyes), the blood-placenta barrier (that protects the developing fetus) and the blood-gut barrier (that protects proper digestion and nutrition), and the blood-testes barrier (that protects developing sperm) to see if they too can be damaged by RFR.

EPIDEMIOLOGICAL STUDIES CONSISTENTLY SHOW ELEVATIONS IN RISK OF BRAIN CANCERS

Brain Tumors: There is a consistent pattern of increased risk of glioma and acoustic neuroma associated with use of mobile phones and cordless phones.

“Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings. (Hardell, 2012 – Section 11)

“There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts. There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results. Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen.

Based on our own research and review of other evidence the existing FCC/IEE and ICNIRP public safety limits and reference levels are not adequate to protect public health. New public health standards and limits are needed.

EVIDENCE FOR GENETIC EFFECTS

Eighty six (86) new papers on genotoxic effects of RFR published between 2007 and mid-2012 are profiled. Of these, 54 (63%) showed effects and 32 (37%) showed no effects.

Forty three (43) new ELF-EMF papers and two static magnetic field papers that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 35 (81%) show effects and 8 (19%) show no effect.

EVIDENCE FOR NEUROLOGICAL EFFECTS

One hundred fifty five (155) new papers that report on neurological effects of RFR published between 2007 and mid-2012 are profiled. Of these, 98 (63%) showed effects and 57 (37%) showed no effects.

Sixty nine (69) new ELF-EMF papers (including two static field papers) that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 64 (93%) show effects and 5 (7%) show no effect.

EVIDENCE FOR CHILDHOOD CANCERS (LEUKEMIA)

With overall 42 epidemiological studies published to date power frequency EMFs are among the most comprehensively studied environmental factors. Except ionizing radiation no other environmental factor has been as firmly established to increase the risk of childhood leukemia.

Sufficient evidence from epidemiological studies of an increased risk from exposure to EMF (power frequency magnetic fields) that cannot be attributed to chance, bias or confounding. Therefore, according to the rules of IARC such exposures can be classified as a **Group 1 carcinogen (Known Carcinogen)**.

There is no other risk factor identified so far for which such unlikely conditions have been put forward to postpone or deny the necessity to take steps towards exposure reduction. As one step in the direction of precaution, measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG. This value is arbitrary at present and only supported by the fact that in many studies this level has been chosen as a reference.

Base-station level RFR at levels ranging from less than 0.001 uW/cm² to 0.05 uW/cm². In 5 new studies since 2007, researchers report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults.

MELATONIN, BREAST CANCER AND ALZHEIMER'S DISEASE

MELATONIN AND BREAST CANCER

Conclusion: Eleven (11) of the 13 published epidemiologic residential and occupational studies are considered to provide (positive) evidence that high ELF MF exposure can result in decreased melatonin production. The two negative studies had important deficiencies that may certainly have biased the results. There is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production

Conclusion: New research indicates that ELF MF exposure, in vitro, can significantly decrease melatonin activity through effects on MT1, an important melatonin receptor.

ALZHEIMER'S DISEASE

There is strong epidemiologic evidence that exposure to ELF MF is a risk factor for AD. There are now twelve (12) studies of ELF MF exposure and AD or dementia which . Nine (9) of these studies are considered positive and three (3) are considered negative. The three negative studies have serious deficiencies in ELF MF exposure classification that results in subjects with rather low exposure being considered as having significant exposure. There are insufficient studies to formulate an opinion as to whether radiofrequency MF exposure is a risk or protective factor for AD.

There is now evidence that (i) high levels of peripheral amyloid beta are a risk factor for AD and (ii) medium to high ELF MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high ELF MF exposure to brain cells likely also increases these cells' production of amyloid beta.

There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

(Davanipour and Sobel, 2012 – Section 13)

STRESS PROTEINS AND DNA AS A FRACTAL ANTENNA FOR RFR

DNA acts as a 'fractal antenna' for EMF and RFR.

The coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies.

The structure makes DNA particularly vulnerable to EMF damage.

The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false)

Many EMF frequencies in the environment can and do cause DNA changes.

The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

EMF stimulates stress proteins (indicating an assault on the cell).

EMF efficiently harms cells at a billion times lower levels than conventional heating.

Safety standards based on heating are irrelevant to protect against EMF-levels of exposure. There is an urgent need to revise EMF exposure standards. Research has shown thresholds are very low (safety standards must be reduced to limit biological responses). Biologically-based EMF safety standards could be developed from the research on the stress response.

**EVIDENCE FOR DISRUPTION OF THE MODULATING SIGNAL
HUMAN STEM CELL DNA DOES NOT ADAPT OR REPAIR**

Human stem cells do not adapt to chronic exposures to non-thermal microwave (cannot repair damaged DNA), and damage to DNA in genes in other cells generally do not repair as efficiently.

Non-thermal effects of microwaves depend on variety of biological and physical parameters that should be taken into account in setting the safety standards. Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful alone for the evaluation of health risks from non-thermal microwave of mobile communication. Other parameters of exposure, such as frequency, modulation, duration, dose should be taken into account.

Lower intensities are not always less harmful; they may be more harmful.

Intensity windows exist, where bioeffects are much more powerful.

A linear, dose-response relationship test is probably invalid for testing of RFR and EMF (as is done in chemicals testing for toxicity).

Resonant frequencies may result in biological effects at very low intensities comparable to base station (cell tower) and other microwave sources used in mobile communications.

These exposures can cause health risk. The current safety standards are insufficient to protect from non-thermal microwave effects.

The data about the effects of microwave at super-low intensities and significant role of duration of exposure in these effects along with the data showing that adverse effects of non-thermal microwave from GSM/UMTS mobile phones depend on carrier frequency and type of the microwave signal suggest that microwave from base-stations/masts, wireless routers, WI-FI and other wireless devices and exposures in common use today can also produce adverse effects at prolonged durations of exposure.

Most of the real signals that are in use in mobile communication have not been tested so far. Very little research has been done with real signals and for durations and intermittences of exposure that are relevant to chronic exposures from mobile communication. In some studies, so-called “mobile communication-like” signals were investigated that in fact were different from the real exposures in such important aspects as intensity, carrier frequency, modulation, polarization, duration and intermittence.

New standards should be developed based on knowledge of mechanisms of non-thermal effects. Importantly, because the signals of mobile communication are completely replaced by other signals faster than once per 10 years, duration comparable with latent period, epidemiologic studies cannot provide basement for cancer risk assessment from upcoming new signals.

In many cases, because of ELF modulation and additional ELF fields created by the microwave sources, for example by mobile phones, it is difficult to distinguish the effects of exposures to ELF and microwave. Therefore, these combined exposures and their possible cancer risks should be considered in combination.

As far as different types of microwave signals (carrier frequency, modulation, polarization, far and near field, intermittence, coherence, *etc.*) may produce different effects, cancer risks should ideally be estimated for each microwave signal separately.

The Precautionary Principle should be implemented while new standards are in progress.

It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the non-thermal microwave exposures.

N. EFFECTS OF WEAK-FIELD INTERACTIONS ON NON-LINEAR BIOLOGICAL OSCILLATORS AND SYNCHRONIZED NEURAL ACTIVITY

A unifying hypothesis for a plausible biological mechanism to account for very weak field EMF bioeffects other than cancer may lie with weak field interactions of pulsed RFR and ELF-modulated RFR as disrupters of synchronized neural activity. Electrical rhythms in our brains can be influenced by external signals. This is consistent with established weak field effects on coupled biological oscillators in living tissues. Biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels (Buzsaki, 2006; Strogatz, 2003). The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously. Synchronous biological oscillations in cells (pacemaker cells) can be disrupted by artificial, exogenous environmental signals, resulting in desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles (Strogatz, 1987). The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles (Strogatz, 2001, 2003). *“Rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance”* (Buzsaki, 2006).

“Organisms are biochemically dynamic. They are continuously subjected to time-varying conditions in the form of both extrinsic driving from the environment and intrinsic rhythms generated by specialized cellular clocks within the organism itself. Relevant examples of the latter are the cardiac pacemaker located at the sinoatrial node in mammalian hearts (1) and the circadian clock residing at the suprachiasmatic nuclei in mammalian brains (2). These rhythm generators are composed of thousands of clock cells that are intrinsically diverse but nevertheless manage to function in a coherent oscillatory state. This is the case, for instance, of the circadian oscillations exhibited by the suprachiasmatic nuclei, the period of which is known to be determined by the mean period of the individual neurons making up the circadian clock (3–7). The mechanisms by which this collective behavior arises remain to be understood.” (Strogatz, 2001; Strogatz, 2003)

Synchronous biological oscillations in cells (pacemaker cells) can be disrupted by artificial, exogenous environmental signals, resulting in desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles. The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles.

EMF AND RFR MAKE CHEMICAL TOXINS MORE HARMFUL

EMF acts on the body like other environmental toxicants do (heavy metals, organic chemicals and pesticides). Both toxic chemicals and EMF may generate free radicals, produce stress proteins and cause indirect damage to DNA. Where there is combined exposure the damages may add or even synergistically interact, and result in worse damage to genes.

EMF IS SUCCESSFULLY USED IN HEALING AND DISEASE TREATMENTS

“The potential application of the up-regulation of the HSP70 gene by both ELF-EMF and nanosecond PEMF in clinical practice would include trauma, surgery, peripheral nerve damage, orthopedic fracture, and vascular graft support, among others. Regardless of pulse design, EMF technology has been shown to be effective in bone healing [5], wound repair [11] and neural regeneration [31,36,48,49,51,63,64,65,66]. In terms of clinical application, EMF-induction of elevated levels of hsp70 protein also confers protection against hypoxia [61] and aid myocardial function and survival [20,22]. Given these results, we are particularly interested in the translational significance of effect vs. efficacy which is not usually reported by designers or investigators of EMF devices. More precise description of EM pulse and sine wave parameters, including the specific EM output sector, will provide consistency and “scientific basis” in reporting findings.”

“The degree of electromagnetic field-effects on biological systems is known to be dependent on a number of criteria in the waveform pattern of the exposure system used; these include frequency, duration, wave shape, and relative orientation of the fields [6,29,32,33,39,40]. In some cases pulsed fields have demonstrated increased efficacy over static designs [19,21] in both medical and experimental settings.”

(Madkan et al, 2009)

ELF-EMF AND RFR ARE CLASSIFIED AS POSSIBLE CANCER-CAUSING AGENTS – WHY ARE GOVERNMENTS NOT ACTING?

The World Health Organization International Agency for Research on Cancer has classified wireless radiofrequency as a Possible Human Carcinogen (May, 2011)*. The designation applies to low-intensity RFR in general, covering all RFR-emitting devices and exposure sources (cell and cordless phones, WI-FI, wireless laptops, wireless hotspots, electronic baby monitors, wireless classroom access points, wireless antenna facilities, etc). The IARC Panel could have chosen to classify RFR as a Group 4 – Not A Carcinogen if the evidence was clear that RFR is not a cancer-causing agent. It could also have found a Group 3 designation was a good interim choice (Insufficient Evidence). IARC did neither.

NEW SAFETY LIMITS MUST BE ESTABLISHED - HEALTH AGENCIES SHOULD ACT NOW

Existing public safety limits (FCC and ICNIRP public safety limits) do not sufficiently protect public health against chronic exposure from very low-intensity exposures. If no mid-course corrections are made to existing and outdated safety limits, such delay will magnify the public health impacts with even more applications of wireless-enabled technologies exposing even greater populations around the world in daily life.

SCIENTIFIC BENCHMARKS FOR HARM PLUS SAFETY MARGIN = NEW SAFETY LIMITS THAT ARE VALID

Health agencies and regulatory agencies that set public safety standards for ELF-EMF and RFR should act now to adopt new, biologically-relevant safety limits that key to the lowest scientific benchmarks for harm coming from the recent studies, plus a lower safety margin. Existing public safety limits are too high by several orders of magnitude, if prevention of bioeffects and minimization or elimination of resulting adverse human health effects. Most safety standards are a thousand times or more too high to protect healthy populations, and even less effective in protecting sensitive subpopulations.

SENSITIVE POPULATIONS MUST BE PROTECTED

Safety standards for sensitive populations will more likely need to be set at lower levels than for healthy adult populations. Sensitive populations include the developing fetus, the infant, children, the elderly, those with pre-existing chronic diseases, and those with developed electrical sensitivity (EHS).

PROTECTING NEW LIFE - INFANTS AND CHILDREN

Strong precautionary action and clear public health warnings are warranted immediately to help prevent a global epidemic of brain tumors resulting from the use of wireless devices (mobile phones and cordless phones). Common sense measures to limit both ELF-EMF and RFR in the fetus and newborn infant (sensitive populations) are needed, especially with respect to avoidable exposures like baby monitors in the crib and baby isolettes (incubators) in hospitals that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RFR are easily instituted.

Wireless laptops and other wireless devices should be strongly discouraged in schools for children of all ages.

STANDARD OF EVIDENCE FOR JUDGING THE SCIENCE

The standard of evidence for judging the scientific evidence should be based on good public health principles rather than demanding scientific certainty before actions are taken.

WIRELESS WARNINGS FOR ALL

The continued rollout of wireless technologies and devices puts global public health at risk from unrestricted wireless commerce unless new, and far lower exposure limits and strong precautionary warnings for their use are implemented.

EMF AND RFR ARE PREVENTABLE TOXIC EXPOSURES

We have the knowledge and means to save global populations from multi-generational adverse health consequences by reducing both ELF and RFR exposures. Proactive and immediate measures to reduce unnecessary EMF exposures will lower disease burden and rates of premature death.

DEFINING A NEW ‘EFFECT LEVEL’ FOR RFR

On a precautionary public health basis, a reduction from the BioInitiative 2007 recommendation of 0.1 uW/cm² (or one-tenth of a microwatt per square centimeter) for cumulative outdoor RFR down to something three orders of magnitude lower (in the low nanowatt per square centimeter range) is justified.

A scientific benchmark of 0.003 uW/cm² or three nanowatts per centimeter squared for ‘lowest observed effect level’ for RFR is based on mobile phone base station-level studies. Applying a ten-fold reduction to compensate for the lack of long-term exposure (to provide a safety buffer for chronic exposure, if needed) or for children as a sensitive subpopulation yields a 300 to 600 picowatts per square centimeter precautionary action level. This equates to a 0.3 nanowatts to 0.6 nanowatts per square centimeter as a reasonable, precautionary action level for chronic exposure to pulsed RFR.

These levels may need to change in the future, as new and better studies are completed. We leave room for future studies that may lower or raise today’s observed ‘effects levels’ and should be prepared to accept new information as a guide for new precautionary actions.

BioInitiative; Section 24: Key Scientific Evidence
and Public Health Policy Recommendations; 2012



SECTION 24

Key Scientific Evidence and Public Health Policy Recommendations

(2012 Supplement)

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I. INTRODUCTION

In public health and environmental policy-making, asking the right questions is a highly evolved art form. It is necessary to periodically look for ‘*not-so-early-now warnings*’ from new science and medical information. At some point it becomes ‘*old news*’ in the real-world process of commercializing new technologies* and is ignored. Precious time is lost if the ‘*evidence curve*’ does not come quickly enough to ‘*change the rollout curve*’ and result in early enough interventions. EMF may be a highly preventable source of disease but not without early enough translation of the science into action. The time for arguing whether EMF health effects exist is over. We know they exist and that they result in human disease.

Asking the right questions and looking for proportionate responses necessarily involves make mid-course corrections guided by new evidence. This is particularly true when the consequences of doing nothing are too great to ignore – because they will affect billions of people in societies around the world. “*While there are many unanswered questions, the cost of doing nothing will result in an increasing number of people, many of them young, developing cancer.*” (Carpenter, 2010).

What questions should be asked now, to move forward on the body of evidence? How much evidence do we need to act? Do we have enough? What standard of evidence should be used to judge (purely scientific vs precautionary public health). What is a relevant biological ‘dose’? How long does a biological effect last? Are we accounting for differences among individuals or different types of cells?

Which of the studies are truly measuring chronic exposures (is a one-month or a one-year study really revealing chronic effects; if mid-length studies show no effect, does this tell us anything useful)? Why is it still considered reasonable to base safety standards on time-averaged radiofrequency exposures when the technologies today use pulsed RFR?

*Electronics, the internet, cellular telecommunications, wireless medical technologies, and wireless sensors for energy conservation, electric utilities management, transportation, education, banking and national security.

For example, the collective behavior of neurons is established through synchrony.

“Individual neurons have a time window of tens of milliseconds range for single neurons, but oscillatory coalitions of neurons can expand the effect window of synchronization from hundreds of milliseconds to many seconds” (Buzaki, 2006). This means the time span a bioeffect can last long enough to overlap with the next environmental provocation (pulsed RFR in this case) so that repetitive exposures may induce an unending cascade of neurological firing that eventually disrupts normal homeostasis and causes chronically abnormal function in cooperative assemblies of cells like neurons. RFR is bioactive and already classified as a Possible Human Carcinogen but the relevant RFR bursts are camouflaged and their relevant metrics are diluted away by time averaging. Why is it reasonable to use safety standards that were developed to guard against induced currents in tissue (ELF-EMF) or that heat or burn tissue (RFR)?

Briefly stated, here is what we knew in 2007.

- Bioeffects and adverse health effects of chronic exposure to low-intensity (non-thermal) non-ionizing radiation are established.
- Existing FCC and ICNIRP public safety limits are not sufficiently protective of public health.
- The World Health Organization has classified ELF-EMF as a Group 2B Possible Human Carcinogen (2001).
- New, biologically-based public exposure standards are critically needed.
- It is not in the public interest to wait.

Here is what we know in 2012. There is more evidence, over a broader range of studies. The levels of biological responses are extraordinarily low (down to the nanowatt and picowatt power density level).

New studies address fertility and reproduction, fetal and neonatal effects, cognitive and behavioral problems in children and neurological damage. There are more mobile phone base station studies with longer testing periods, much more information on genetic damage and confirmation of increased risk of brain cancers from not one or two

studies, but from many studies and many authors including the World Health Organization's massive 13-country INTERPHONE STUDY (Interphone Study Group, 2010).

There are many studies reporting effects of cell phone radiation (even on standby-mode), wireless laptop exposure, cell phone use by mothers resulting in altered fetal brain development in the offspring, and more evidence that the blood-brain barrier and memory are at risk from cell phone use. There is evidence from human and animal studies that key areas of the brain are negatively affected by RFR at legal levels.

There is better understanding of the important physical and biological factors that make ELF-EMF and RFR potent disruptors of living tissues and basic metabolic processes. More and more, EMF devices are being used for medical treatments in cancer, bone and wound healing and re-tuning the nervous system. Increased depth of evidence in many threads is presented in this report by well-regarded scientists and researchers from around the world. The number of good studies has grown. The exposure levels causing effects are documented to be much lower than in the past. The epidemiological evidence is now showing risks for a variety of adverse health outcomes. All this should be taken seriously by governments, and translated quickly into more protective safety standards, and in the interim, into strong preventative actions, warnings and substitution of safer technologies and redesigned devices.

Bioeffects are clearly established and occur at very low levels of exposure to electromagnetic fields and radiofrequency radiation. Bioeffects can occur in the first few minutes at levels associated with cell and cordless phone use. Bioeffects can also occur from just minutes of exposure to mobile phone masts (cell towers), WI-FI, and wireless utility 'smart' meters that produce whole-body exposure. Chronic base station level exposures can result in illness.

Many of these bioeffects can reasonably be expected to result in adverse health effects if the exposures are prolonged or chronic. This is because they interfere with normal body processes (disrupt homeostasis), prevent the body from healing damaged DNA, produce immune system imbalances, metabolic disruption and lower resistance to disease across multiple pathways. Essential body processes can eventually be disabled by incessant external stresses (from system-wide electrophysiological interference) and lead to pervasive impairment of metabolic and reproductive functions.

What does the WHO IARC Classification of ELF-EMF and RFR as Group 2B Possible Human Carcinogens Mean?

The World Health Organization International Agency for Cancer Research (IARC) designated ELF-EMF as a Group 2B (Possible) Carcinogen in 2001. This is the kind of exposure from power lines, battery switching in cell phone devices, laptop computers and appliances. The World Health Organization specifically reaffirmed its finding that EMF is classifiable as a Group 2B Possible Human Carcinogen in 2006 in their Health Criteria Monograph #238 (WHO, 2007).

World Health Organization International Agency for Research on Cancer (IARC) Cancer Classifications

Group 1	Known Carcinogen
Group 2A	Probable Carcinogen
Group 2B	Possible Human Carcinogen
Group 3	Insufficient Information
Group 4	Not a Carcinogen

In 2011, IARC determined that scientific evidence is sufficient now to classify radiofrequency radiation as a Group 2B Possible Human Carcinogen (Baan et al, 2011). This is the kind of exposure coming from cell and cordless phones, cell towers, WI-FI, wireless laptops, electronic baby monitors and wireless ‘smart’ utility meters.

So, what does this mean? According to the classification categories, it is again clear IARC did NOT find so little clear and consistent evidence that it should support a finding of “Not A Carcinogen”. That would be the valid test that RFR is safe, as best public health experts can judge the evidence. Nor did IARC find that the evidence sufficient so as to make a stronger classification (Probably or Known Carcinogen). Rather, IARC found the evidence supports classification as a “Possible” cancer-causing

agent. That is not a weak or reckless judgment made with few facts. It should be a strong warning to governments to reconsider their safety standards, particularly in light of the billions of people at potential health risk from new wireless technologies. Studies of cell and cordless phones and of wireless whole-body RFR exposures consistently show human health impacts that have become ‘epidemiologically visible’ (Sections 11 and 21).

ELF-EMF AND RFR ARE CLASSIFIED AS POSSIBLE CANCER-CAUSING AGENTS – WHY ARE GOVERNMENTS NOT ACTING?

The World Health Organization International Agency for Research on Cancer has classified wireless radiofrequency as a Possible Human Carcinogen (May, 2011). The designation applies to low-intensity RFR in general, covering all RFR-emitting devices and exposure sources (cell and cordless phones, WI-FI, wireless laptops, wireless hotspots, electronic baby monitors, wireless classroom access points, wireless antenna facilities, etc). The IARC Panel could have chosen to classify RFR as a Group 4 – Not A Carcinogen if the evidence was clear that RFR is not a cancer-causing agent. It could also have found a Group 3 designation was a good interim choice (Insufficient Evidence). IARC did neither.

II. KEY SCIENTIFIC EVIDENCE (2006- 2012)

Many thousand scientific studies over four decades have provided warnings of serious biological effects and potential health harm from EMF and RFR. About 1800 new, scientific papers published in the last five years report more bioeffects and adverse health effects of EMF and RFR, and are presented in great detail in the BioInitiative Report 2012.

These studies since 2006 give critical support to the argument that current safety standards are grossly inadequate. They cannot be protecting public health if they do not prevent harm to a variety of types of human cells, human sperm and the developing fetus *in-utero*. These are all effects reported today due to cell phone radiation exposures that are both legal and common in daily home, business and school environments. These effects are shown to occur at very low-intensity permissible levels that have become ‘typical’ for pregnant women, the fetus, the infant, the child, and for adults. Such effects are occurring at hundreds to thousands of times lower intensity exposure levels than the current FCC public safety limits allow. These exposure levels are common in the

environment, but worst in close proximity to wireless devices like cell and cordless phones, 'smart' wireless utility meters, wireless routers, wireless classroom access points and laptops, to baby surveillance devices, and in the first few hundred meters of cell towers. WI-FI levels of RFR and cell phones-on-standby mode are sufficient to cause effects that, if chronic, may be damaging to the health of cellular DNA, reproductive germ cells (sperm) and the male reproductive organs.

Overall, these new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9), carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on offspring behavior (Section 18, 19 and 20); and effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18). This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

Many of these bioeffects are associated with disruption of normal biological functioning in the genes, and in the physiology of the nervous and cardiac systems of the body (brain, blood-brain barrier, heart, vascular system). Sleep disruption (insomnia) is a hallmark bioeffect of RFR. Hypersensitivity disorders like allergies and asthma are reported from exposure to environmental chemicals and to EMF. A pregnant woman's exposure to EMF has been linked to increased asthma and behavioral problems in the human child after *in-utero* exposure. Pregnant mice exposed to cell phone radiation give birth to baby mice with attention disorders, hyperactivity and impaired memory function, similar to effects seen in human babies as reported by Divan et al (2008).

A. Stress, Stress Proteins and DNA as a Fractal Antenna: The word stress invokes different concepts for people, but needs to be understood as a physiological response. BioInitiative author Martin Blank has described how both ELF-EMF and RFR produce stress proteins at very low exposure levels, and why this is only adaptive in the short-

term. Chronic exposures that trigger stress responses (stress proteins) regardless of their environmental cause are mal-adaptive if they go on too long. Any agent (EMF, ionizing radiation, chemicals, heavy metals, etc) that continuously generates stress proteins is not adaptive, and is harmful, if it is a constant provocation.

The work of Martin Blank and Reba Goodman of Columbia University has established that stress proteins are produced by ELF-EMF and RFR at levels far below current safety standards allow. Further, they think DNA is actually a very good fractal RF-antenna which is very sensitive to low doses of EMF, and may induce the cellular processes that result in chronic 'unrelenting' stress. That daily environmental levels of ELF-EMF and RFR can and do throw the human body into stress protein response mode (out of homeostasis) is a fundamental and continuous insult. Chronic exposures can then result in chronic ill-health.

B. Fetal Effects and Fetal Development Studies: Effects on the developing fetus from *in-utero* exposure to cell phone radiation have been observed in both human and animal studies since 2006. Divan et al (2008) found that children born of mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. The July 2008 issue of Epidemiology reports that children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al., 2008).

Aldad et al (2012) showed that cell phone radiation significantly altered fetal brain development and produced ADHD-like behavior in the offspring of pregnant mice. Exposed mice had a dose-dependent impaired glutamatergic synaptic transmission onto Layer V pyramidal neurons of the prefrontal cortex. The authors conclude the behavioral changes were the result of altered neuronal developmental programming *in utero*. Offspring mice were hyperactive and had impaired memory function and behavior problems, much like the human children in Divan et al (2008).

A new study from Greece reports altered development of the cranial bones of the mouse fetus from low intensity (0.6 to 0.9 W/kg) *in-utero* 900 MHz cell phone radiation (Fragopoulou et al, 2009). They report “*our results clearly show that even modest exposure (e.g., 6-min daily for 21 days) is sufficient to interfere with the normal mouse developmental process.*”

Other new studies by Fragopoulou et al report that brain astrocyte development followed by proteomic studies is adversely affected by DECT (cordless phone radiation) and mobile phone radiation (Fragopoulou et al, 2012); and that whole body exposure with GSM 900MHz affects spatial memory in mice (Fragopoulou et al, 2010).

FETAL BRAIN DEVELOPMENT MAY BE ALTERED

There is increasing evidence that fetal (*in-utero*) and early childhood exposures to cell phone radiation and wireless technologies in general is a risk factor for hyperactivity, learning disorders and behavioral problems in school.

Neonatal physician Carlo Bellieni of Italy found that heart rate variability is adversely affected in infants hospitalized in isolettes or incubators where ELF-EMF levels are in the 0.8 to 0.9 μ T range (8 to 9 mG) (Bellieni, 2008). Infants suffer adverse changes in heart rate variability, similar to adults. He also reported that newborns cared for in the high ELF-EMF environments of isolettes have disrupted melatonin levels (Bellieni et al, 2012a).

C. Studies of Sperm: Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Eroglu et al., 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line

(Dasdag et al, 1999; Yan et al, 2007; Otitolaju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. 2012 report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared ($\mu\text{W}/\text{cm}^2$).

Agarwal et al (2009) evaluated the effect of cell phone radiation during talk mode on human sperm samples. The authors found *“radiofrequency electromagnetic waves emitted from cell phones may lead to oxidative stress in human semen. We speculate that keeping the cell phone in a trouser pocket in talk mode may negatively affect spermatozoa and impair male fertility.”*

Aitken et al (2005) studied the effect of 900 MHz cell phone radiation on mice (7 days, 12-hr per day at 0.09 W/kg). The authors found statistically significant damage to the mitochondrial genome of epididymal spermatozoa ($p < 0.05$).

Avendano et al, 2012 provided evidence that a 4-hr exposure to WI-FI at exceeding low levels ($0.5\text{-}1.0 \mu\text{W}/\text{cm}^2$) near a laptop computer caused decreased sperm viability and DNA fragmentation in human sperm samples. Avendado says *“(T)o our knowledge, this is the first study to evaluate the direct impact of a laptop use on human spermatozoa. Ex vivo exposure of human spermatozoa to a wireless internet-connected laptop decreased motility and induced DNA fragmentation by a nonthermal effect. We speculate that keeping a laptop connected wirelessly to the internet on the lap near the testes may result in decreased male fertility.”*

De Iuliis et al (2009) reported that *“RF-EMR in both the power density and frequency range of mobile phones enhances mitochondrial reactive oxygen species generation by human spermatozoa, decreasing the motility and vitality of these cells*

while stimulating DNA base adduct formation, and ultimately DNA fragmentation.” They warned their findings *“have clear implications for the safety of extensive mobile phone use by males of reproductive age, potentially affecting both their fertility and the health and wellbeing of their offspring”* based on damage from a 6-hr exposure to 1800 MHz cell phone radiation in human sperm cells. This 6-hr exposure caused reduced sperm motility and viability and caused a significant increase in reactive oxygen species (free radicals that are associated with oxidative damage to DNA), and the effects were worse with more exposure (a significant dose-response was observed). Atasoy (2012) also questioned the safety of 2400 MHz exposure to those of reproductive age. This study reports that WI-FI internet access devices can damage DNA and reduce DNA repair when the exposures are very low (exposure level of 0.091 W/kg) and chronic; damage can occur even at levels that comply with 802.11 g WI-FI public safety limits.

Behari et al (2006) reported that chronic exposure of rats to cell phone radiation caused double-strand DNA breaks in sperm cells (35 days, 2-hr per day). This study also showed that the mobile radiation exposure at 900 MHz (at 0.9 W/kg) and at 2.45 GHz (at 0.1 W/kg) caused a statistically significant decrease in sperm count and the weight of testes.

Otitolaju et al, 2010 graphically describe sperm head abnormalities in mice exposed for six months to base-station level RF/MW at 70 to 100 nanowatts/cm² (0.07 – 0.1 µW/cm²). Only 2% of controls but a stunning 39% to 46% of exposed mice had damaged sperm.

“The major abnormalities observed were knobbed hook, pin-head and banana-shaped sperm head. The occurrence of sperm head abnormalities was also found to be dose dependent. The implications of the observed increased occurrence of sperm head abnormalities on the reproductive health of humans living in close proximity to GSM base stations were discussed.”

These studies taken together should provide a strong warning that ‘normal’ use of a cell phone presents risks that warrant strong preventative actions to protect the integrity of the human genome from de novo mutations and loss of fertility across entire male populations of cell phone users. Further, even the much lower exposure levels associated with mobile phone base station (cell tower) RFR levels are deleterious over time.

HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities (0.00034 – 0.07 $\mu\text{W}/\text{cm}^2$). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage.

D. Human Stem Cell Studies: Markova et al (2010) reported that 915 MHz microwave exposure significantly affects human stem cells. They found that very low-intensity microwave radiation from mobile phones can inhibit DNA repair processes in human stem cells. By placing a mobile phone at one meter distance from human stem cells in petri dishes (SAR = 0.037 W/Kg), they found a significant reduction in 53BP1 foci.

These foci are a measure of DNA repair in cells with double strand DNA damage. The damage was greater to stem cells (derived from adipose tissue in humans) than in fibroblasts. Stem cells did not repair over time - and the damage was done within one hour of microwave exposure. Fibroblasts were similarly affected (inhibited 53BP1 foci) but repaired over time. The effects are carrier-frequency dependent. The effects occurred with GSM exposure at 915 MHz, but not at 905 MHz. The failure of DNA repair also occurred at the mobile phone UTMS carrier frequency of 1947 MHz. Analysis of the 53BP1 foci is a sensitive technique to measure double-strand DNA breaks in both unexposed cells and in cells exposed to cytotoxic agents. In the authors' words, *"this represents a direct mechanistic link to epidemiological data showing an association of MW exposure with increased cancer risk."* The data obtained from human stem cells is of *"utmost relevance for assessment of possible health risks of MW exposure from mobile phones."* Most, if not all adult tissues and organs including blood, skin and brain contain stem cells. Therefore, *"stem cells like blood cells and fibroblasts are always subjected to exposure from mobile phones."* With respect to children, because *"almost all organs and tissues possess stem cells and stem cells are more active in children, the possible relationship of chronic MW exposure and various types of tumors and leukemia especially in children should be investigated."*

Czyz et al (2004) reported that GSM cell phone exposure affected gene expression levels in embryonic stem cells (p53-deficient); and significantly increased heat shock protein HSP 70 production.

HUMAN STEM CELL DNA DOES NOT ADAPT OR REPAIR

Human adipose tissue stem cells lack the ability to repair DNA damage caused by chronic exposure to non-thermal microwaves. Damage to DNA in some other cells may be incompletely repaired.

E. Mobile Phone Base Station (Cell Tower) Studies

Human Studies: Hutter et al (2006) reported that short-term exposure to GSM cell phone radiation resulted in complaints of headache, neurological problems, sleep and concentration problems in adults with 0.01 - 0.05 $\mu\text{W}/\text{cm}^2$ exposure levels. Kundi and Hutter (2009) reviewed human effects in fourteen (14) mobile phone base station studies and reported *“(F)rom available evidence it is impossible to delineate a threshold below which no effect occurs, however, given the fact that studies reporting low exposure were invariably negative it is suggested that power densities around 0.5–1 mW/m² [0.05 – 0.1 $\mu\text{W}/\text{cm}^2$] must be exceeded in order to observe an effect.”*

Buchner and Eger (2012) conducted an eighteen (18) month study to assess changes in stress hormones in 60 persons exposed before and after a mobile phone base station went into operation in the Rimbach village in Germany. The study showed that chronic exposure to base station RF (whole-body) at 0.006 - 0.01 $\mu\text{W}/\text{cm}^2$ in humans had significant impacts on stress hormones over time. In the beginning months, adrenaline levels first increased in a dose-dependent fashion according to exposure level ($p < 0.002$) and then decreased below normal levels ($p < 0.005$). Both the average as well as the median adrenaline values increased after the activation of the transmitter and decreased again after one year with exposure levels $>0.006 \mu\text{W}/\text{cm}^2$. Chronically ill subjects and children showed especially strong responses; except for some "outliers," no effect was observed in healthy adults (Buchner and Eger, 2012). For dopamine, inverse effects to

those for adrenaline and noradrenaline were observed. The median dopamine levels decreased from 199 to 115 $\mu\text{g/g}$ creatinine between January and July 2004. The fact that the dopamine levels of the study subjects decreased during this period is highly significant ($p < 0.0002$). Thereafter, the median increased again: In January 2005, it was at 131 $\mu\text{g/g}$ creatinine, in July of 2005. This increase is also significant between July 2004 and July 2005 ($p < 0.05$).

Buchner (2012) indicates that the RFR transmitter induced changes in stress hormones that follow the classic stress syndrome of adaptation, then exhaustion established by Hans Seyle in the 1950's. *"After the stages of alarm and resistance, the last stage of exhaustion sets in. The parameters investigated in the Rimbach study follow this pattern"*.

A long-term 6-yr study assessed the role of exposure to radio frequency radiation (RFR) emitted either from mobiles or base stations and its relations with human's hormone profiles. The study revealed significant RFR effects on pituitary–adrenal axis, resulting in reduction of ACTH, cortisol, thyroid hormones, prolactin in young females, and testosterone levels in males (Eskander et al, 2012). But no direct measurements of RFR power density levels were made, only categories of distance from transmitter.

Oberfeld et al (2004) reported that populations exposed to base stations transmitting cell phone frequencies had more fatigue, depressive tendency, sleeping disorders, concentration difficulties, and cardio-vascular problems reported with exposure to GSM 900/1800 MHz cell phone signal.

Navarro et al (2003) reported that exposure levels of 0.01 - 0.11 $\mu\text{W}/\text{cm}^2$ resulted in fatigue, headaches, sleeping problems in populations around mobile phone base stations.

Thomas et al (2008) reported an increase in adult complaints of headaches and concentration difficulties with short-term cell phone use at 0.005 to 0.04 $\mu\text{W}/\text{cm}^2$ exposure levels.

Heinrich et al (2010) reported that children and adolescents (8-17 years old) with short-term exposure to base-station level RFR experienced headache, irritation, and concentration difficulties in school. RFR levels were 0.003 - 0.02 $\mu\text{W}/\text{cm}^2$.

Thomas et al (2010) reported that RFR levels of 0.003 - 0.02 $\mu\text{W}/\text{cm}^2$ resulted in conduct and behavioral problems in children and adolescents (8-17 years old) exposed to short-term cell phone radiation in school.

Mohler et al (2010) reported that adults exposed to 0.005 $\mu\text{W}/\text{cm}^2$ cell phone radiation (base-station exposure levels) had sleep disturbances with chronic exposure, but this effect was not significantly increased across the entire population.

Human Studies at Base Station Exposure Levels (Cell Towers)

At least five new cell tower studies with base-station level RFR at levels ranging from 0.003 $\mu\text{W}/\text{cm}^2$ to 0.05 $\mu\text{W}/\text{cm}^2$ published since 2007 report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. This is highly consistent with studies done prior to 2007, but the 'effect levels' are significantly lower (dropping from the microwatt to the nanowatt range per square centimeter).

Public safety standards are 1,000 – 10,000 or more times higher than levels now commonly reported in mobile phone base station studies to cause bioeffects.

Sperm studies are showing DNA damage, impaired sperm quality, motility and viability from cell phones on standby mode and wireless laptop use at exposures of 0.00034 $\mu\text{W}/\text{cm}^2$ to 0.07 $\mu\text{W}/\text{cm}^2$. Several studies report sperm damage effects at 'standby model' cell phone emission levels, which are in the low nanowatt to picowatt per square centimeter range.

F. Electrohypersensitivity (EHS) Studies: McCarty et al, 2011 studied electrohypersensitivity in a patient (a female physician). The patient was unable to detect the presence or absence of EMF exposure, largely ruling out the possibility of bias. In multiple trials with the fields either on or not on, the subject experienced and reported temporal pain, feeling of unease, skipped heartbeats, muscle twitches and/or strong headache when the pulsed field (100 ms, duration at 10 Hz) was on, but no or mild symptoms when it was off. Symptoms from continuous fields were less severe than with pulsed fields. The differences between field on and sham exposure were significant at the $p < 0.05$ level. The authors conclude that electromagnetic hypersensitivity is a neurological syndrome, and statistically reliable somatic reactions could be provoked in this patient by exposure to 60-Hz electric fields at 300 volts per meter (V/m). They conclude *"EMF hypersensitivity can occur as a bona fide environmentally inducible*

neurological syndrome.” In their response to a letter to the editor of the journal, the authors say: “(W)e followed an empirical approach and demonstrated a cause-and-effect relationship ($p < 0.05$) under conditions that permitted us to infer the existence of electromagnetic hypersensitivity (EHS), a novel neurological syndrome.” (Marino et al, 2012)

Further, the authors explain the significance of detecting EHS effects by non-linear methods.

“The important issue at this point is not whether EMF can produce symptoms (we empirically demonstrated that it can) but rather why this effect historically has been difficult to detect. It occurred to us that EHS has remained elusive because of the way it was studied. The experiments designed to detect EHS had been based on the assumption that if it existed, it was a linear phenomenon, whereas EHS is actually a nonlinear phenomenon.” “Our study was designed to detect whether EHS was a linear or nonlinear phenomenon, and we were successful in showing a link between acute EMF exposure and somatic responses ($p < 0.05$). This finding – taken together with the unfailingly negative results of the linear studies – is good evidence that EHS is a nonlinear phenomenon, as we suspected.”

With the exception of the McCarty study there have not been clear demonstrations in controlled circumstances showing that persons reporting to be electrophysensitive can distinguish whether or not RFR is being applied. There are, however, multiple reports of symptoms experienced by individuals exposed to EMFs in uncontrolled circumstances.

A. Johansson et al (2010) studied symptoms, personality traits and stress in people with mobile phone-related symptoms and electromagnetic hypersensitivity. They reported there is support for a difference between people with symptoms related to specific EMF sources and people with general EHS. The symptoms are anxiety, depression, somatization, exhaustion and stress. The EHS group reported more neurasthenic symptoms.

Two publications on electrophysensitivity by O. Johansson (2007, 2009) provide an extensive overview of the relevant literature on electrophysensitivity. Both publications document symptoms and conditions giving rise to increased sensitivity to

ELF-EMF and RFR. The need for new, biologically-based public exposure standards is recommended in both publications, in order to address electrohypersensitivity.

Landgrebe et al (2007) reported that their study of electrosensitive patients showed participants had a reduced intracortical facilitation as compared to two control groups. The EHS group of patients showed altered central nervous system function. In a follow-up study, the authors reported that EHS patients but not controls “*demonstrated significant cognitive and neurobiological alterations pointing to a higher genuine individual vulnerability of electromagnetic hypersensitive patients.*” (Landgrebe et al, 2008).

The team of Sandstrom, Hansson Mild and Lyskov produced numerous papers between 1994 and 2003 involving people who are electrosensitive (Lyskov et al, 1995; Lyskov et al, 1998; Sandstrom et al, 1994; Sandstrom et al, 1995; Sandstrom et al, 1997; Sandstrom et al, 2003). Sandstrom et al (2003) presented evidence that heart rate variability is impaired in people with electrical hypersensitivity and showed a dysbalance of the autonomic nervous system. “*EHS patients had a disturbed pattern of circadian rhythms of HRF and showed a relatively ‘flat’ representation of hourly-recorded spectral power of the HF component of HRV*”. This research team also found that “*EHS patients have a dysbalance of the autonomic nervous system (ANS) regulation with a trend to hyper-sympathotonia, as measured by heart rate (HR) and electrodermal activity, and a hyperreactivity to different external physical factors, as measured by brain evoked potentials and sympathetic skin responses to visual and audio stimulation.*” (Lyskov et al, 2001 a,b; Sandstrom et al, 1997). The reports referenced above provide evidence that persons who report being electrosensitive differ from others in having some abnormalities in the autonomic nervous system, reflected in measures such as heart rate variability. At present it remains unclear whether EHS is actually caused by RF/EMF exposure, or rather is a self-identifying syndrome of excessive responsiveness to a variety of stimuli. But given the relatively high percentage of persons reported to be electrosensitive (5% of the general population of Switzerland according to Schreier et al., 2006), with some being severely disabled as a consequence, it is critical that there be

more study of this syndrome.

Tuengler and von Klitzing et al (2012) reported EHS people that were tested showed significant changes in regulation of the autonomic nervous system, including changes in capillary blood flow (microcirculation), heart rate variability, and electric skin potentials. The continuous detection of capillary blood flow is an important tool in analyzing the capacity of the autonomic nervous system. In EHS patients, von Klitzing finds that intestinal motility may also be disregulated and show no activity at all for some time after exposure.

G. Effects on the Blood-brain Barrier (BBB): The Lund University (Sweden) team of Leif Salford, Bertil Persson and Henrietta Nittby has done pioneering work on effects of very low level RFR on the human brain's protective lining – the barrier that protects the brain from large molecules and toxins that are in the blood.

THE BLOOD-BRAIN BARRIER IS AT RISK

The BBB is a protective barrier that prevents the flow of toxins into sensitive brain tissue. Increased permeability of the BBB caused by cell phone RFR may result in neuronal damage. Many research studies show that very low intensity exposures to RFR can affect the blood-brain barrier (BBB) (mostly animal studies). Summing up the research, it is more probable than unlikely that non-thermal EMF from cell phones and base stations do have effects upon biology. A single 2-hr exposure to cell phone radiation can result in increased leakage of the BBB, and 50 days after exposure, neuronal damage can be seen, and at the later time point also albumin leakage is demonstrated. The levels of RFR needed to affect the BBB have been shown to be as low as 0.001 W/kg, or less than holding a mobile phone at arm's length. The US FCC standard is 1.6 W/kg; the ICNIRP standard is 2 W/kg of energy (SAR) into brain tissue from cell/cordless phone use. Thus, BBB effects occur at about 1000 times lower RFR exposure levels than the US and ICNIRP limits allow. (Salford, 2012)

The consequence to modern life is that cell and cordless phone use may cause a pathological leakage of the BBB with very short use periods, and the damage may be long-lasting. Harmful substances may enter the brain. If the damage is ongoing (if cell and cordless phone use continues to occur over months and years), the potential for harmful effects increases. There is already 'epidemiologically visible' evidence of

increased brain cancer risk in humans (Section 11).

Volkow et al (2011a, b) reported increased glucose metabolism in the brain with cell phone use in humans. This important investigation of 47 human subjects used a randomized crossover design and labeled fluorodeoxyglucose to measure the metabolisms of the brain when the cell phone was activated but muted for 50 minutes as compared to not being activated. *“Our study showed that cell phone activation was associated with metabolic increases in brain regions closest to the antenna and that the increases showed a negative linear correlation with distance from the antenna. While the effect was small, the negative correlation of the effect with distance was statistically significant ($R = -0.91$; $P < .001$).* This study is particularly important in that it demonstrates definitively that an active cell phone, placed on the ear as one would normally be used, alters brain metabolic activity, but only in the region close to the cell phone.

H. Brain Cancer Studies: The Orebro University (Sweden) team led by Lennart Hardell, MD, an oncologist and medical researcher, has produced an extraordinary body of work on environmental toxins of several kinds, including the effects of radiofrequency/microwave radiation and cancer. Their 2012 work concludes:

“Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings.

In summary:

- *There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts.*
- *There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly*

based on results from case-control studies from the Hardell group and Interphone Final Study results.

- *Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen.*
- *Based on our own research and review of other evidence the existing FCC/IEEE and ICNIRP public safety limits and reference levels are not adequate to protect public health.*
- *New public health standards and limits are needed.* (Hardell et al, 2012)

I. Genetic Damage (Genotoxicity Studies): There are at least several hundred published papers that report EMF affects cellular oxidative processes (oxidative damage). Increased free radical activity and changes in enzymes involved in cellular oxidative processes are the most consistent effects observed in cells and animals after EMF exposure. Aging may make an individual more susceptible to the detrimental effects of ELF EMF from oxidative damage, since anti-oxidants may decline with age. Clearly, the preponderance of genetic studies report DNA damage and failure to repair DNA damage.

Eighty six (86) new papers on genotoxic effects of RFR published between 2007 and mid-2012 are profiled. Of these, 54 (63%) showed effects and 32 (37%) showed no effects (Lai, 2012)

Forty three (43) new ELF-EMF papers and two static magnetic field papers that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 35 (81%) show effects and 8 (19%) show no effect (Lai, 2012).

J. Nervous System Damage: Factors that act directly or indirectly on the nervous system can cause morphological, chemical, or electrical changes in the nervous system that can lead to neurological effects. Both RF and ELF EMF affect neurological functions and behavior in animals and humans.

One hundred fifty five (155) new papers that report on neurological effects of RFR published between 2007 and mid-2012 are profiled. Of these, 98 (63%) showed effects and 57 (37%) showed no effects.

Sixty nine (69) new ELF-EMF papers (including two static field papers) that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 64 (93%) show effects and 5 (7%) show no effect. (Lai, 2012)

L. Children are More Vulnerable: Many studies demonstrate that children are more sensitive to environmental toxins of various kinds (Barouki et al, 2012; Preston, 2004; WHO, 2002; Gee, 2009; Sly and Carpenter, 2012).

The Presidential Cancer Panel (2010) found that children *'are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.'*

The American Academy of Pediatrics, in a letter to Congressman Dennis Kucinich dated 12 December 2012 states *"Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure they are safeguarded through their lifetimes."*

II. ISSUES AND ANSWERS IN THE EMF DEBATE

Much of the emphasis in the 2007 Bioinitiative Report focused on cancer, which is still the best documented disease of concern from exposure to EMF/RF. The evidence that exposure to EMF/RF increases the risk of cancer has only gotten significantly stronger since then, and we have a better, albeit still incomplete, understanding of the mechanisms involved. However, in terms of threshold exposures that result in human disease, new research on male reproduction and neurobehavioral alterations provide evidence for harm at even lower exposure levels. RFR has been shown in this Report to act as an external synchronizer of neural activity, capable of disrupting sleep, circadian rhythms, diurnal hormone fluctuations, brain wave activity and heart rate variability by exposure to artificial electromagnetic signals (as opposed to natural evolutionary frequencies) and to do so at exceedingly low intensities.

Much of the debate over the body of EMF science ignores simple questions that would help to discriminate among studies with apparently conflicting results. Section 15 by Dr. Belyaev is helpful in identifying key factors which must be known and controlled for in experiments (biological variables and physical parameters include bandwidth, frequency, modulation, polarization, intermittence and coherence time of exposure, static

magnetic field, electromagnetic stray fields, sex, age, individual traits, and cell density during exposure). Dr. Andrew Marino emphasizes that detection of EMF/RFR effects require investigation of non-linear phenomena, a critical difference that if ignored, may miss important biological effects (Marino, 2012).

A unifying hypothesis for a plausible biological mechanism to account for very weak field EMF bioeffects other than cancer may lie with weak field interactions of pulsed RFR and ELF-modulated RFR as disrupters of synchronized neural activity. Electrical rhythms in our brains can be influenced by external signals. This is consistent with established weak field effects on coupled biological oscillators in living tissues. Biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels (Buzsaki, 2006; Strogatz, 2003). The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously according to the mathematics described for Josephson junctions (Brian Josephson, the 1993 Nobel prize winner for this concept). This concept has been professionally presented in journal articles and also popularized in print by Prof. Steven Strogatz, a mathematician at Cornell University who has written about 'sync' as a fundamental organizing principle for biological systems (Strogatz, 2001; 2003).

“Organisms are biochemically dynamic. They are continuously subjected to time-varying conditions in the form of both extrinsic driving from the environment and intrinsic rhythms generated by specialized cellular clocks within the organism itself. Relevant examples of the latter are the cardiac pacemaker located at the sinoatrial node in mammalian hearts and the circadian clock residing at the suprachiasmatic nuclei in mammalian brains. These rhythm generators are composed of thousands of clock cells that are intrinsically diverse but nevertheless manage to function in a coherent oscillatory state. This is the case, for instance, of the circadian oscillations exhibited by the suprachiasmatic nuclei, the period of which is known to be determined by the mean period of the individual neurons making up the circadian clock. The mechanisms by which this collective behavior arises remain to be understood.” (Strogatz, 2003)

Synchronous biological oscillations in cells (pacemaker cells) can be disrupted by artificial, exogenous environmental signals, resulting in desynchronization of neural

activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles (Strogatz, 1987). The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles. Buzsaki (2006) says *“rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance. Rhythms are a robust phenomenon.”*

The heart's natural pacemaker center is the sinoatrial node, a cluster of about 10,000 cells that generate electrical rhythm that commands the rest of the heart to beat. Diseases related to disruption of that synchronization include epilepsy, chronic insomnia, and cardiac arrhythmias (Strogatz, 2003). Some EMF diseases are those where desynchronization of neural activity results in physiological changes that, if chronic, result in chronically disrupted homeostasis, and eventually ill-health and chronic diseases. Such a future burdens health care systems in an irreversible way.

The late Dr. Ross Adey in his last publication in Bioelectromagnetic Medicine (P. Roche and M. Markov, eds. 2004) concluded:

“There are major unanswered questions about possible health risks that may arise from exposures to various man-made electromagnetic fields where these human exposures are intermittent, recurrent, and may extend over a significant portion of the lifetime of the individual.”

“Epidemiological studies have evaluated ELF and radiofrequency fields as possible risk factors for human health, with historical evidence relating rising risks of such factors as progressive rural electrification, and more recently, to methods of electrical power distribution and utilization in commercial buildings. Appropriate models describing these bioeffects are based in nonequilibrium thermodynamics, with nonlinear electrodynamics as an integral feature. Heating models, based in equilibrium thermodynamics, fail to explain an impressive new frontier of much greater significance. Though incompletely understood, tissue free radical interactions with magnetic fields may extend to zero field levels.”

Our society appears determined to make everything wireless, and the consequence is to increase cumulative exposure to RFR. Many homes and almost every Starbucks or McDonalds has WiFi. Smart phones, tablets, video iPods and other wireless devices are even given to children as playthings. The result is a significant increase in cumulative RFR exposure of the whole population, but particularly of those who have and use wireless devices for prolonged periods of time. No national or international standard of RFR exposure considers cumulative effects, all being developed to avoid local tissue heating from acute exposures.

The issues around exposure of children to RFR is of critical importance. There is overwhelming evidence that children are more vulnerable than adults to many different exposures (Sly and Carpenter, 2012), including RFR, and that the diseases of greatest concern are cancer and effects on neurodevelopment. Yet parents place RFR baby monitors in cribs, provide very young children with wireless toys, and give cell phones to young children, usually without any knowledge of the potential dangers. A growing concern is the movement to make all student computer laboratories in schools wireless. A wired computer laboratory will not increase RFR exposure, and will provide safe access to the internet.

An urgent example for the need to address the lack of adequate public protection from inadequate safety standards for pulsed RFR exposures is the rapid, global rollout of wireless utility meters ('smart' meters for electricity, gas and water meters). Current safety standard calculations that rely on time-averaging of RFR almost entirely dilute out the power density of RFR levels that are delivered in millisecond bursts, but occur at intervals of every second, or multiple times per second when in use within a wireless mesh network. Said differently, the RFR power density levels are usually legal. While there have been no long term studies of adverse effects of smart meters on human health (primarily because they are so new), there are increasing reports from electrosensitive individuals of harm. Added together, these RFR pulses that now appear to be a highly bioactive agent but are essentially erased or made energetically invisible by time-averaging the pulses as current FCC safety rules mandate.

The wireless meters transmit RF signals like a mini-cell tower antennas in the cell phone radiation frequencies. Currently, they are being deployed in the US and are on the drawing boards around the world including many European countries. The 'smart meter' infrastructure represents the largest single commercial saturation of living space with pulsed RFR yet rolled out by industry. This program places a wireless device (like a mini-mobile phone base station) on the wall, replacing the electromechanical (spinning dial) meter. They will be installed on every home and classroom (every building with an electric meter). Utilities from California to Maine have installed tens of millions already, despite health concerns of experts who already are seeing thousands of health complaints. The wireless meters produce spikes of pulsed radiofrequency radiation on a continuous basis (24/7), and in typical operation, will saturate living space at levels that can be much higher than already reported to cause bioeffects and adverse health effects for some people. These meters, depending on where they are placed relative to occupied space in the home or classroom, can produce RFR exposure levels similar to that within the first 100 feet to 600 feet of a mobile phone base station (cell tower). In the not-so-distant future the plan is to have a wireless device implanted in every household appliance, which will communicate with the smart meter whenever electricity is being used. This will likely make the kitchen a major source of exposure to RFR.

The cumulative RFR burden within any community is largely unknown. Both involuntary sources (like cell towers, smart meters and second-hand radiation from the use of wireless devices by others) plus voluntary exposures from ones' personal use of cell and cordless phones, wireless routers, electronic baby surveillance monitors, wireless security systems, wireless hearing aids, and wireless medical devices like implanted insulin pumps all add up. No one is tallying up the combined exposure levels. Billions of new RFR transmitters from a global smart meter rollout will significantly add to the existing RFR body-burden of pulsed RFR for millions of people. The health concerns are the same as with all other sources of EMF/RF. Cancer is the most serious adverse effect, but alteration of male reproduction and central nervous system effects may results from even lower levels of exposure. The work by Strogatz (2001, 2003) and Bezsaki (2006) on weak-field effects on non-linear biological oscillators (brain waves and synchronization of neural activities that regulate body processes) is directly relevant to an

understanding of the profound biological disruptions and health symptoms that continued exposures of pulsed RFR may produce.

The Commons of the Air

Turning to questions of social equity and the individuals' choice not to be exposed to harmful levels of environmental toxins, there has been little inclusion of the public in discussions of wireless radiofrequency exposure. Wireless technologies have become infused in daily habits of billions of people; often choices for wired equivalents are lacking (or those that exist are disappearing). Involuntary exposure to EMF and RFR is becoming more the norm, even where it runs counter to individual choice (second-hand radiation, like second-hand smoke is difficult to avoid).

“Wireless technologies drive electromagnetic energy through our air, into and through virtually all indoor and outdoor living environments. The protective air cushion around our planet holds breathable air, buffers us from space radiation, and supports and sustains life in tandem with the natural electromagnetic signature of the earth itself. We are changing this ‘commons of the air’ in major ways. Wireless signals from broadcast and communications technologies are crowding out and overpowering the natural background. The ‘commons of the air’ is being altered in unprecedented ways that have enormous consequences for life on earth.”(Sage, 2010).

The rush to ‘buy the airwaves’ and to market them for commercial purposes is loading ‘*the commons of the air*’ with unsustainable levels of exposure (Sage, 2010). Commercial markets for wireless spectrum successfully lobby government regulators to allocate even more spectrum, once the existing frequencies are allocated. Sage (2010) asks:

“Who owns the ‘commons of the air’? Who should be allowed to pollute it? What are the limits? On what basis should carrying capacity be defined? Who defines the limits? Do these limits conserve the resource for the future? Do they protect public health and welfare, and the health and well-being of other living things on earth? Who bears the burden of proof of safety or of harm? How should the ‘new commons’ be managed for the greater good? Do we know enough to act responsibly? Who decides? When should limits be placed on utilization?”

With no regard to cumulative harm, this commercial rush to buy up wireless spectrum territorial rights has vast implications for public health and well-being. Environmental protections afforded to other natural resources under the National Environmental Policy Act have been ignored. The cumulative impacts and irretrievable commitments on humans, wildlife, and natural resources have never been assessed.

“Societies must now define carrying capacity for chronic electromagnetic and wireless exposures. Taking into account the large individual variability to withstand it, new limits must conserve and sustain the ‘commons of the air’ so that is sustainable for all—and this includes sensitive populations, the young, the elderly, and those with existing sensitivity. Some countries of the world already have surpassed sustainable wireless exposure levels as demonstrated by significant percentages that have already become electrosensitive.” (Sage, 2010)

Homeostasis and Human Health Rights

Chronic exposure to low-intensity RFR and to ELF-modulated RFR at today’s environmental levels in many cities will exceed thresholds for increased risk of many diseases and causes of death (Sage and Huttunen, 2012). RFR exposures in daily life alter homeostasis in human beings. These exposures can alter and damage genes, trigger epigenetic changes to gene expression and cause de novo mutations that prevent genetic recovery and healing mechanisms. These exposures may interfere with normal cardiac and brain function; alter circadian rhythms that regulate sleep, healing, and hormone balance ; impair short-term memory, concentration, learning and behavior; provoke aberrant immune, allergic and inflammatory responses in tissues; alter brain metabolism; increase risks for reproductive failure (damage sperm and increase miscarriage risk); and cause cells to produce stress proteins. Exposures now common in home and school environments are likely to be physiologically addictive and the effects are particularly serious in the young (Sage and Huttunen, 2012). This declaration of human health rights below (Sage and Huttunen, 2012) is based on specific reference to health impacts of EMF and RFR that are reasonably well established to occur (Sage and Carpenter, 2009).

Human Health Rights Declaration
Fundamental Human Health Rights (Sage and Huttunen, 2012)

The right to homeostasis in our own bodies.

The right to normal central nervous system function.

The right to natural environmental cues that synchronize our circadian rhythms.

The right to sleep.

The right to heal.

The right to hear.

The right to reproduce.

The right to learn and retain memories.

The right to an intact genome.

If even one of these rights is compromised – placed at risk from involuntary wireless exposures in daily life, it is a breach of human health rights. When many of these human health rights are compromised without the consent of the individual, then the deployment of wireless technologies should be halted and existing exposures reduced or eliminated, in accord with the scientific and public health findings on chronic exposure to low-intensity radiofrequency radiation, and other forms of potentially harmful electromagnetic fields (Sage and Huttunen, 2012)

V. CONCLUSIONS FOR PRUDENT PUBLIC HEALTH PLANNING

Methodology and Approach for Precautionary Action Limits

In 2007, the BioInitiative Report chapter on Key Scientific Evidence and Public Health Policy Implications, proposed a specific, interim radiofrequency radiation target level of $0.1 \mu\text{W}/\text{cm}^2$ for cumulative, outdoor RFR exposure (for AM, FM, TV and wireless). It was based on best-available scientific studies to that date. There were few studies prior to 2006 that reported effects at less than 0.1 to $1 \mu\text{W}/\text{cm}^2$ chronic RFR exposures.

In 2009, the journal Pathophysiology produced many peer-reviewed articles in a special two-volume edition on EMF (both ELF-EMF and RFR) essentially publishing the contents of the BioInitiative Report and updating some information. One of these 2009 Pathophysiology papers presented a review of mobile phone base station studies (Kundi and Hutter, 2009). It concluded that the overall studies did not detect effects (headache,

fatigue, tinnitus, concentration difficulties, sleep disruption, etc) at levels of RFR exposure below 0.05 to 0.1 $\mu\text{W}/\text{cm}^2$.

New base station-level RFR studies are available in 2012 that can be analyzed to determine if new (and lower) RFR recommendations are warranted. The approach in this chapter relies on "lowest levels at which effects are not seen" akin to the "no observed effect level (NOEL)" used for chemical exposures, as a sufficient basis to establish scientific benchmarks for harm (or alternately, the lowest observed effects level of exposure). It is the province of the science and public health evaluation we do here to report the evidence regardless of what political or strategic complications it may create. An objective presentation of what the studies reveal for 'effects levels' is our goal; not to pre-judge or dilute the evidence because it may present strategic or political hurdles to achieve consensus on policy and regulatory changes. What this report does not intend to do is take into account "how could we do this" or "what would it mean". The purpose is to lay out the science, and make some defensible reductions for factors that studies cannot or do not yet test for, and compensate with deductions for them (safety margins). As interim targets for precautionary action, they will serve as guides for decision-makers who will take up the issues of health, the quality of the future gene pool, social equity and cost.

There is no one study alone that meets impeccable standards for exposure assessment or totally eliminates all possibility for bias, but the constellation of studies together gives adequate support to delineate a 'lowest observed effects level', that in turn, with added safety margins, can serve as a guideline for precautionary action.

A reduction from the BioInitiative 2007 recommendation of 0.1 $\mu\text{W}/\text{cm}^2$ (or one-tenth of a microwatt per square centimeter which is the same as 100 nanowatts/ cm^2) for cumulative outdoor RFR down to something three orders of magnitude lower (in the low nanowatt per square centimeter range) is justified on a public health basis. We use the new scientific evidence documented in this Report to identify 'effect levels' and then apply one or more reduction factors to provide a safety margin. We do note however, even a precautionary action level of several tenths of a nanowatt per square centimeter (or

several hundred picowatts per square centimeter) would still allow for cell phone transmissions (that can operate down to about 0.00003 V/m).

Even so, these levels may need to go lower in the future, as new and better studies are completed. This is what the authors said in 2007 (Carpenter and Sage, 2007, BioInitiative Report) and it remains true today in 2012. We leave room for future studies that may lower today's observed 'effects levels' and should be prepared to accept new information as a guide for new precautionary actions.

Establishing A Scientific Benchmark for 'Lowest Observed Effect Levels'

Studies that provide information at 'new levels of observed effect' have been identified. These serve as scientific benchmarks for possible risk to health and well-being. Next, we identify reduction factors to compensate for sensitive subpopulations and apply them to the scientific benchmarks (lowest observed effect levels).

A ten-fold reduction factor is warranted (or higher) for studies that report effects from only shortp-term (i.e., acute) rather than chronic (i.e., long-term) exposures. Longer duration of exposure can cause bioeffects at lower exposures where these effects are NOT seen with shorter (acute) exposures (Belyaev, 1997; Belyaev, 2012). Chronic exposures with longer durations of weeks, months or years is what most populations face with respect to wireless classrooms, wireless offices and locations near base stations.

A second ten-fold reduction (or higher) is justified as a buffer for sensitive populations including children, the elderly and other adult groups that may be ill, already sensitized, in remission or suffer from ailments made worse by physiological stress and insomnia.

Studies which contribute together can reasonably contribute to delineating a new RFR lower effects level are primarily mobile phone (cell phone) base station studies of healthy human populations and studies of sperm damage in men who use and/or wear their wireless devices on or around the belt or pants pocket.

Power Density Studies (Mobile Phone Base Stations and Sperm/Fertility Studies)

A scientific benchmark of 0.003 uW/cm² or three nanowatts per centimeter squared for 'lowest observed effect level' for RFR is based on mobile phone base station-level studies. The Thomas et al (2008) study shows effects at a LOEL of 0.005 uW/cm² on adults exposed to short-term cell phone radiation only (it is not a chronic exposure study). Other studies that are relevant are Thomas et al (2010) with a LOEL of 0.003 uW/cm² and Heinrich et al, (2010) with a LOEL of 0.003 uW/cm². Both studied mixed child/adolescent populations of students, but have short-term test periods (are not chronic exposure studies) and have LOELs of 0.003 uW/cm². Buchner et al (2012) shows a 0.006 uW/cm² 'effect level' and tests adult populations, but achieves 'chronic' exposure testing criterion (over 18 months). Applying a ten-fold reduction to compensate for the lack of long-term exposure (to provide a safety buffer for chronic exposure) or for children as a sensitive subpopulation yields a 300 to 600 picowatts per square centimeter precautionary action level. This is also equal to a 0.3 nanowatts to 0.6 nanowatts per square centimeter as a reasonable, precautionary action level.

Of the studies that deal with children and base-station level RFR exposures, none studied children exclusively, so the results may dilute out any apparent effects accruing to the younger test subjects. Thomas et al (2010) is a short-term exposure study of children and adolescents 8 to 17 years in age. Heinrich et al (2010) is a further study of the same population of 8 to 17 year olds over the short-term. A 100-fold reduction could be defended as reasonably conservative in this instance.

Behari et al (2006) provides the one sperm study expressed in power density units with a LOEL of 0.00034 uW/cm². It is a chronic exposure study. The majority of sperm studies with good exposure information are expressed in SARs (W/kg). These range from LOELs of 0.014 (Kumar et al, 2012) to 0.091 W/kg (Atasoy et al, 2012) to 0.43 W/kg (Salama et al, 2008) to 0.795 W/kg (Panagopoulous et al, 2012) to 0.9 W/kg (Kesari et al, 2012). All the other sperm damage or ovarian damage studies have SARs

of greater than 1.0 W/kg (7 more studies). All are short-term studies. There are more sperm damage studies but without any measurements or other specific exposure information. These are studies that place sperm, or mice, or give prenatal exposures to animals close to sources of cell phone radiation. Such studies give weight to the argument that low-intensity RFR exposures can cause damage, but do not help in delineating LOELs because they have no specific exposure numbers, just distances.

Most of the sperm studies and base station studies which have exposures expressed power density (microwatts per square centimeter) have 'effect' levels in the nanowatt range (0.34 nanowatt/cm² to 100 nanowatt/cm²)*. They include Behari and Kesari, 2006; Buchner and Eger, 2012; Oberfeld et al, 2004; Thomas et al, 2008, 2010; Heinrich et al, 2010; Navarro et al, 2003; and Otitoloju et al 2010. Avendano et al (2012) report that WI-FI exposure from a 4-hr laptop exposure decreased sperm viability and caused DNA fragmentation in human sperm samples (exposure in petri dishes) at 0.5 to 1.0 uW/cm². The Kundi-Hutter 2009 Pathophysiology Journal review paper of base station studies through 2006 reports an overall NOEL below 0.05 to 0.1 uW/cm². Overall, the new 2007-2012 power density studies are reporting 'lowest effects levels' two or three orders of magnitude lower than in 2006, down from the microwatt/cm² range to the nanowatt/cm² range.

SAR Studies (Sperm Studies and Ovarian Damage with Cell Phone Radiation Exposures)

Studies on male fertility (adverse effects on sperm, on the testes size and morphology, etc) coming from cell phone-in-the-pocket-on-stand-by-mode and wireless laptop studies provide us with a flood of new data showing very low-intensity effects to guide precautionary actions and to educate the public about potential risks to health, fertility and reproduction.

*The RF Color Charts in this Report are a guide to reported biological effects and those RFR levels reported to cause them.

Sperm and fertility studies with ‘effects levels’ in the 9 microwatt/kg to 80 milliwatt/kg range are Kumar et al, 2012 (male infertility) and Aitken et al, 2005 (sperm DNA damage). Sperm studies with ‘effect levels’ in the 90 to 900 milliwatt/kg range are De Iuliis et al, 2009 (human sperm cell damage), Salama et al, 2008 (decrease in sperm mobility and concentration), Panagopoulous et al, 2012 (ovarian damage) and Kesari et al, 2012 (sperm damage). Studies from 1 W/kg to 1.8 W/kg that report sperm or reproductive damage are Gul et al, 2009 (toxic effect on ovaries), Agarwal et al, 2008 (sperm damage), Agarwal et al, 2009 (sperm damage) and Yan et al, 2007 (deformed sperm cells, disabled for swimming).

The WI-FI laptop study by Atasoy et al (2012) reports that exposures to laptops estimated at 0.091 W/kg increase DNA damage and reduce DNA repair in damaged sperm, and *“raise questions about safety of radiofrequency exposure from WI-FI internet access dices for growing organisms of reproductive age, with a potential effect on fertility and integrity of germ lines.”*

Altered fetal development in mice exposed to RFR at SARs of 0.3 to 60 milliwatt/kg is reported to result in consequent adverse effects on learning and behavior (Aldad et al, 2012). Fragopoulou et al (2009) reported changes at 600 to 900 milliwatts/kg in mouse embryos.

General Approach to Delineating a Precautionary Action Level

As a methodology, is not necessary or wise to use an averaging approach among studies. The technique itself is too vulnerable to weighting problems by the older studies that did not test for effects at the lowest range of exposures to RFR (or did not have the power to assess effects). Averaging also is insensitive to giving proper visibility to important NEW results at the very low-intensity (nanowatt, picowatt and femtowatt/cm² range). Even when they are averaged together, these studies contribute vanishingly small influence when averaged together with studies of much higher power density to determine a scientific benchmark for harm.

One limitation of the sperm studies using base station-level RFR exposures is that good estimates of exposure are available if sperm are tested outside the body (in petri dishes), but that does not reflect the more realistic situation of sperm exposed in humans themselves (using or carrying a mobile phone near the testes) where exposure estimates are more difficult to determine. So, it is useful and informative to observe the combined results of both in-vivo and ex-vivo studies as a guide. For base station studies on human populations, the quality of exposure assessments is variable, and in some cases inadequate. Further, very few base station studies are conducted so that test subjects do not know if/when they are subjected to elevated RFR (blinded studies), so that some bias may influence results. People often report more ill effects because they are aware of the exposure (from a nearby base station, for example). These variations in quality across the studies, however, do not offset their usefulness in the aggregate for delineating what the lowest observable effect exposures are, and helping to guide decision-making for public health and precautionary actions.

A further concern is that time-averaging of RFR to give a single numeric recommendation for a precautionary action guideline does not address the critical difference between peak power levels (RFR spikes that occur intermittently) and measurements that hide how high peak power spikes are by dilution. Since biological responses can last over seconds of time, or have even longer effects on proteins and enzymes, while the RFR pulses may be in microseconds or milliseconds in duration, it is entirely possible that what causes bioeffects is the high, intermittent RFR spikes that the body perceives and responds to as one continuous, high-power assault. For example, the DECT phone peak power is about 100 times larger than what RFR is measured with time-averaging. A person near a cell tower that produces an RFR measurement of 0.1 microwatts/cm² is probably getting RFR power density spikes of eight times higher, if you could measure the spikes individually. None of the studies profiled in this section deal with peak power pulses and biological response times that are longer than the 'intermission' between RFR spikes. Thus, precautionary action levels should err on the side of being conservative.

The planning of base stations, and other site evaluations needs to have a scientific benchmark below which effects have not (not yet) been characterized, published or vetted. Then, a reasonable safety buffer should be added - remembering that the design life of such facilities may be 30-50 years long. This is standard procedure for environmental planning constraints.

Health Agencies Should Act Now

Health agencies and regulatory agencies that set public safety standards for ELF-EMF and RFR should act now to adopt new, biologically-relevant safety limits that key to the lowest scientific benchmarks for harm coming from the recent studies, plus a lower safety margin. Existing public safety limits are too high by several orders of magnitude, if prevention of bioeffects and resulting adverse health effects are to be minimized or eliminated. Most safety standards are a thousand times or more too high for healthy populations, and even less effective in protecting sensitive subpopulations.

New, biologically-based public exposure standards are critically needed now and should key to scientific benchmarks for harm, plus a safety margin below that level.

Standard of Evidence for Judging the Science

The standard of evidence for judging the scientific evidence should be based on good public health principles rather than demanding scientific certainty before actions are taken.

Sensitive Populations Require Special Protections

Safety standards for sensitive populations will need to be set at lower levels than for healthy adult populations to protect the developing fetus, the infant and young child, school-age children, the elderly, those with pre-existing chronic diseases, and those with developed electrical sensitivity (EHS). Men of child-bearing age should not wear

wireless devices on their body in order to protect the integrity of sperm DNA. Sperm should be considered a 'sensitive population'. Scientific benchmarks for lowest effect levels should be identified, and applied with additional safety margin reductions to safeguard populations against excessively high exposure to chronic ELF-EMF and RFR.

Protect Children Against Chronic Exposure to Wireless Devices

Strong precautionary action and clear public health warnings are universally warranted for use of cordless and cell phones to help prevent a global epidemic of brain tumors. This is especially important for children, adolescents and young adults, while new safety standards are established and implemented. Children should not use wireless devices except in the case of emergencies, or be exposed on an involuntary and chronic basis to wireless in their living, sleeping or learning environments.

Common Sense Precautionary Measures are Warranted Now

Common sense measures to limit both ELF-EMF and RFR in the fetus and newborn infant are needed, especially with respect to avoidable exposures like baby monitors in the crib and baby isolettes (incubators) in hospitals that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RFR are easily instituted.

Wireless laptops and other wireless devices should be strongly discouraged in schools for children of all ages, and wireless systems already installed should be replaced with wired (cable) alternatives. While without question it is important for children to have access to the internet, wired computer laboratories will have no elevated exposure to RFR. What might be lost in flexibility of moving rooms arounds will be more than gained by reducing exposure to RFR if wired connections, rather than wireless, are used. Pregnant women should be strongly cautioned not to use wireless devices during pregnancy. If a school already has wireless facilities, classrooms without wireless should be made available to students, teachers and staff during the transition if sensitivities to

EMF are reported by the individual. Special education classroom teaching environments should offer wired teaching environments (not wireless), nor should they be exposed to off-site wireless radiofrequency radiation from other sources that elevate interior levels for children.

Special Protections for the Integrity of the Genome and Reproduction

Reducing life-long health risks should begin in the earliest stages of embryonic and fetal development. Development pace is accelerated for the infant and very young child compared to adults, and is not complete in young people (as far as brain and nervous system maturation) until the early 20's. Windows of critical development mean that risk factors once laid down in the cells, or in epigenetic changes in the genome may have grave and life-long consequences for health or illness for every individual, and furthermore these genetic and epigenetic changes may be passed to the next generation. All relevant environmental conditions, including biologically active exposures to EMF and RFR that can degrade the human genome, and impair normal health and development of all species including humans - should be given weight in defining and implementing strong precautionary actions now to protect public health. The consequence of ignoring clear evidence of large-scale health risks to global populations, when the risk factors are largely avoidable or preventable is too high a risk to take.

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BioInitiative; Section 1: Summary for the Public (2014 Supplement)



SECTION 1

Summary for the Public (2014 Supplement)

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I. SUMMARY FOR THE PUBLIC

A. Introduction

The BioInitiative Working Group concluded in 2007 that existing public safety limits were inadequate to protect public health, and agreed that new, biologically-based public safety limits were needed five years ago. The BioInitiative Report was prepared by more than a dozen world-recognized experts in science and public health policy; and outside reviewers also contributed valuable content and perspective.

From a public health standpoint, experts reasoned that it was not in the public interest to wait. In 2007, the evidence at hand coupled with the enormous populations placed at possible risk was argued as sufficient to warrant strong precautionary measures for RFR, and lowered safety limits for ELF-EMF. The ELF recommendations were biologically-based and reflected the ELF levels consistently associated with increased risk of childhood cancer, and further incorporated a safety factor that is proportionate to others used in similar circumstances. The public health cost of doing nothing was judged to be unacceptable in 2007.

What has changed in 2012? In twenty-four technical chapters, the contributing authors discuss the content and implications of about 1800 new studies. Overall, these new studies report abnormal gene transcription (Section 5); genotoxicity and single- and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers, particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9); carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on the fetus, neonate and offspring (Section 18 and 19); effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18); and findings in autism spectrum disorders consistent with EMF/RFR exposure. This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

There is reinforced scientific evidence of risk from chronic exposure to low-intensity electromagnetic fields and to wireless technologies (radiofrequency radiation including microwave radiation). The levels at which effects are reported to occur is lower by hundreds of times in comparison to 2007. The range of possible health effects that are adverse with chronic exposures has broadened. There has been a big increase in the number of studies looking at the effects of cell phones (on the belt, or in the pocket of men radiating only on standby mode) and from wireless laptops on impacts to sperm quality and motility; and sperm death (fertility and reproduction). In other new studies of the fetus, infant and young child, and child-in-school – there are a dozen or more new studies of importance. There is more evidence that such exposures damage DNA, interfere with DNA repair, evidence of toxicity to the human genome (genes), more worrisome effects on the nervous system (neurology) and more and better studies on the effects of mobile phone base stations (wireless antenna facilities or cell towers) that report lower RFR levels over time can result in adverse health impacts.

Importantly, some very large studies were completed on brain tumor risk from cell phone use. The 13-country World Health Organization Interphone Final study (2010) produced evidence (although highly debated

among fractious members of the research committee) that cell phone use at 10 years or longer, with approximately 1,640 hours of cumulative use of a cell and/or cordless phone approximately doubles glioma risk in adults. Gliomas are aggressive, malignant tumors where the average life-span following diagnosis is about 400 days. That brain tumors should be revealed in epidemiological studies at ONLY 10 or more years is significant; x-ray and other ionizing radiation exposures that can also cause brain tumors take nearly 15-20 years to appear making radiofrequency/microwave radiation from cell phones a very effective cancer-causing agent. Studies by Lennart Hardell and his research team at Orebro University in Sweden later showed that children who start using a mobile phone in early years have more than a 5-fold (more than a 500%) risk for developing a glioma by the time they are in the 20-29 year age group. This has significant ramifications for public health intervention.

In short order, in 2011 the World Health Organization International Agency on Cancer Research (IARC) classified radiofrequency radiation as a Group 2B Possible Human Carcinogen, joining the IARC classification of ELF-EMF that occurred in 2001. The evidence for carcinogenicity for RFR was primarily from cell phone/brain tumor studies but by IARC rules, applies to all RFR exposures (it applies to the exposure, not just to devices like cell phones or cordless phones that emit RFR).

B. Why We Care?

The stakes are very high. Exposure to electromagnetic fields (both extremely low-frequency ELF-EMF from power frequency sources like power lines and appliances; and radiofrequency radiation or RFR) has been linked to a variety of adverse health outcomes that may have significant public health consequences. The most serious health endpoints that have been reported to be associated with extremely low frequency (ELF) and/or radiofrequency radiation (RFR) include childhood and adult leukemia, childhood and adult brain tumors, and increased risk of the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS). In addition, there are reports of increased risk of breast cancer in both men and women, genotoxic effects (DNA damage, chromatin condensation, micronucleation, impaired repair of DNA damage in human stem cells), pathological leakage of the blood-brain barrier, altered immune function including increased allergic and inflammatory responses, miscarriage and some cardiovascular effects. Insomnia (sleep disruption) is reported in studies of people living in very low-intensity RF environments with WI-FI and cell tower-level exposures. Short-term effects on cognition, memory and learning, behavior, reaction time, attention and concentration, and altered brainwave activity (altered EEG) are also reported in the scientific literature. Biophysical mechanisms that may account for such effects can be found in various articles and reviews (Sage, 2012).

Traditional scientific consensus and scientific method is but one contributor to deciding when to take public health action; rather, it is one of several voices that are important in determining when new actions are warranted to protect public health. Certainly it is important, but not the exclusive purview of scientists alone to determine for all of society when changes are in the public health interest and welfare of children.

C. Do We Know Enough to Take Action

Human beings are bioelectrical systems. Our hearts and brains are regulated by internal bioelectrical signals. Environmental exposures to artificial EMFs can interact with fundamental biological processes in the human body. In some cases, this may cause discomfort, or sleep disruption, or loss of well-being (impaired mental functioning and impaired metabolism) or sometimes, maybe it is a dread disease like cancer or Alzheimer's disease. It may be interfering with one's ability to become pregnant, or to carry a child to full term, or result in brain development changes that are bad for the child. It may be these exposures play a role in causing long-term impairments to normal growth and development of children, tipping the scales away from becoming productive adults. The use of common wireless devices like wireless laptops and mobile phones requires urgent action simply because the exposures are everywhere in daily life; we need to define whether and when these exposures can damage health, or the children of the future who will be born to parents now immersed in wireless exposures.

Since World War II, the background level of EMF from electrical sources has risen exponentially, most recently by the soaring popularity of wireless technologies such as cell phones (six billion in 2011-12, up from two billion in 2006), cordless phones, WI-FI, WiMAX and LTE networks. Some countries are moving from telephone landlines (wired) to wireless phones exclusively, forcing wireless exposures on uninformed populations around the world. These wireless exposures at the same time are now classified by the world's highest authority on cancer assessment, the World Health Organization International Agency for Research on Cancer to be a possible risk to health. Several decades of international scientific research confirm that EMFs are biologically active in animals and in humans. Now, the balance has clearly shifted to one of 'presumption of possible adverse effects' from chronic exposure. It is difficult to conclude otherwise, when the bioeffects that are clearly now occurring lead to such conditions as pathological leakage of the blood-brain barrier (allowing toxins into the brain tissues); oxidative damage to DNA and the human genome, preventing normal DNA repair in human stem cells; interfering with healthy sperm production; producing poor quality sperm or low numbers of healthy sperm, altering fetal brain development that may be fundamentally tied to epidemic rates of autism and problems in school children with memory, attention, concentration, and behavior; and leading to sleep disruptions that undercut health and healing in numerous ways.

In today's world, everyone is exposed to two types of EMFs: (1) extremely low frequency electromagnetic fields (ELF) from electrical and electronic appliances and power lines and (2) radiofrequency radiation (RFR) from wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers. In this report we will use the term EMFs when referring to all electromagnetic fields in general; and the terms ELF or RFR when referring to the specific type of exposure. They are both types of non-ionizing radiation, which means that they do not have sufficient energy to break off electrons from their orbits around atoms and ionize (charge) the atoms, as do x-rays, CT scans, and other forms of ionizing radiation. A glossary and definitions are provided in this report to assist you. Some handy definitions you will probably need when reading about ELF and RF in this summary section (the language for measuring it) are shown in Section 26 – Glossary.

II. SUMMARY OF THE SCIENCE

A. Evidence for Damage to Sperm and Reproduction

Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (See Section 18 for references including Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Eroglu et al, 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) reported rats exposed to stand-by level RFR (phones on but not transmitting calls) had a decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared ($\mu\text{W}/\text{cm}^2$). See Section 18 for references.

HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities ($0.00034 - 0.07 \mu\text{W}/\text{cm}^2$). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage. (Behari and Rajamani, Section 18) young child are more vulnerable than older persons are to chemicals and ionizing radiation. The US Environmental Protection Agency (EPA) proposes a 10-fold risk adjustment for the first 2 years of life exposure to carcinogens, and a 3-fold adjustment for years 3 to 5. These adjustments do not deal with fetal risk, and the possibility of extending this protection to the fetus should be examined, because of fetus' rapid organ development.

The Presidential Cancer Panel (2010) found that children "are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation." The American Academy of Pediatrics, in a letter to Congressman Dennis Kucinich dated 12 December 2012 states: "Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure they are safeguarded through their lifetimes."

The issue around exposure of children to RFR is of critical importance. There is overwhelming evidence that children are more vulnerable than adults to many different exposures (Sly and Carpenter, 2012), including RFR, and that the diseases of greatest concern are cancer and effects on neurodevelopment. Yet parents place RFR-emitting baby monitors in cribs, provide very young children with wireless toys, and give cell phones to young children, usually without any knowledge of the potential dangers. A growing concern is the movement to make all student computer laboratories in schools wireless. A wired computer laboratory will not increase RFR exposure, and will provide safe access to the Internet (Section, Sage and Carpenter, BioInitiative 2012 Report).

C. Evidence for Fetal and Neonatal Effects

Effects on the developing fetus from in-utero exposure to cell phone radiation have been observed in both human and animal studies since 2006. Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy). Sources include exposure to whole-body RFR from base stations and Wi-Fi, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant mother, and greater susceptibility to leukemia and asthma in the child where there have been maternal exposures to ELF-EMF. Divan et al (2008) found that children born to mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al, 2008). Aldad et al (2012) showed that cell phone radiation significantly altered fetal brain development and produced ADHD-like behavior in the offspring of pregnant mice. Exposed mice had a dose-dependent impaired glutamatergic synaptic transmission onto Layer V pyramidal neurons of the prefrontal cortex. The authors conclude the behavioral changes were the result of altered neuronal developmental programming in utero. Offspring mice were hyperactive and had impaired memory function and behavior problems, much like the human children in Divan et al (2008). See Sections 19 and 20 for references. Fragopoulou et al (2012) reports that brain astrocyte development followed by proteomic studies is adversely affected by DECT (cordless phone radiation) and mobile phone radiation.

Fetal (in-utero) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school. Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted.

A precautionary approach may provide the frame for decision-making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

(Bellieni and Pinto, 2012 – Section 19)

D. Evidence for Effects on Autism (Autism Spectrum Conditions)

Physicians and health care practitioners should raise the visibility of EMF/RFR as a plausible environmental factor in ASC clinical evaluations and treatment protocols. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence for a link to ASCs.

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

Many disrupted physiological processes and impaired behaviors in people with ASCs closely resemble those related to biological and health effects of EMF/RFR exposure. Biomarkers and indicators of disease and their clinical symptoms have striking similarities. At the cellular and molecular level many studies of people with ASCs have identified oxidative stress and evidence of free-radical damage, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Lipid peroxidation of cell membranes, disruption of calcium metabolism, altered brain wave activity and consequent sleep, behavior and immune dysfunction, pathological leakage of critical barriers between gut and blood or blood and brain may also occur. Mitochondria may function poorly, and immune system disturbances of various kinds are common. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common than in the population at large. Sleep disruption and high levels of stress are close to universal. All of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure.

- • Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments.
 - • Special education classrooms should observe 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
 - • All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
 - • School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
 - • Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
 - • There is sufficient scientific evidence to warrant the selection of wired Internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later.
 - • Wired classrooms should reasonably be provided to all students who opt-out of wireless environments.
- (Herbert and Sage, 2012 – Section 20)

The public needs to know that these risks exist, that transition to wireless should not be presumed safe, and that it is very much worth the effort to minimize exposures that still provide the benefits of technology in learning, but without the threat of health risk and development impairments to learning and behavior in the classroom.

Broader recommendations also apply, related to reducing the physiological vulnerability to exposures, reduce allostatic load and build physiological resiliency through high quality nutrition, reducing exposure to toxicants and infectious agents, and reducing stress, all of which can be implemented safely based upon presently available knowledge.

E. Evidence for Electrohypersensitivity

The contentious question of whether electrohypersensitivity exists as a medical condition and what kinds of testing might reveal biomarkers for diagnosis and treatment has been furthered by several new studies presented in Section 24 – Key Scientific Evidence and Public Health Policy Recommendations. What is evident is that a growing number of people world-wide have serious and debilitating symptoms that key to various types of EMF and RFR exposure. Of this there is little doubt. The continued massive rollout of wireless technologies, in particular the wireless ‘smart’ utility meter, has triggered thousands of complaints of ill-health and disabling symptoms when the installation of these meters is in close proximity to family home living spaces.

McCarty et al (2011) studied electrohypersensitivity in a patient (a female physician). The patient was unable to detect the presence or absence of EMF exposure, largely ruling out the possibility of bias. In multiple trials with the fields either on or not on, the subject experienced and reported temporal pain, feeling of unease, skipped heartbeats, muscle twitches and/or strong headache when the pulsed field (100 ms, duration at 10 Hz) was on, but no or mild symptoms when it was off. Symptoms from continuous fields were less severe than with pulsed fields. The differences between field on and sham exposure were significant at the $p < 0.05$ level. The authors conclude that electromagnetic hypersensitivity is a neurological syndrome, and statistically reliable somatic reactions can be provoked in this patient by exposure to 60-Hz electric fields at 300 volts per meter (V/m). Marino et al (2012) responded to comments on his study with McCarty saying:

“EMF hypersensitivity can occur as a bona fide environmentally inducible neurological syndrome. We followed an empirical approach and demonstrated a cause-and-effect relationship ($p < 0.05$) under conditions that permitted us to infer the existence of electromagnetic hypersensitivity (EHS), a novel neurological syndrome.”

The team of Sandstrom, Hansson Mild and Lyskov produced numerous papers between 1994 and 2003 involving people who are electrosensitive (See Section 24 - Lyskov et al, 1995; Lyskov et al, 1998; Sandstrom et al, 1994; Sandstrom et al, 1995;

Sandstrom et al, 1997; Sandstrom et al, 2003). Sandstrom et al (2003) presented evidence that heart rate variability is impaired in people with electrical hypersensitivity and showed disruption of the autonomic nervous system.

“EHS patients had a disturbed pattern of circadian rhythms of HRF and showed a relatively ‘flat’ representation of hourly-recorded spectral power of the HF component of HRV”. This research team also found that “EHS patients have a dysbalance of the autonomic nervous system (ANS) regulation with a trend to hyper-sympathotonia, as measured by heart rate (HR) and electrodermal activity, and a hyperreactivity to different external physical factors, as measured by brain evoked potentials and sympathetic skin responses to visual and audio stimulation.” (Lyskov et al, 2001 a,b; Sandstrom et al, 1997).

The reports referenced above provide evidence that persons who report being electrosensitive differ from others in having some abnormalities in the autonomic nervous system, reflected in measures such as heart rate variability.

F. Evidence for Effects from Cell Tower-Level RFR Exposures

Very low exposure RFR levels are associated with bioeffects and adverse health effects. At least five new cell tower studies are reporting bioeffects in the range of 0.001 to 0.05 $\mu\text{W}/\text{cm}^2$ at lower levels than reported in 2007 (0.05 to 0.1 uW/cm^2 was the range below which, in 2007, effects were not observed). Researchers report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. Public safety standards are 1,000 – 10,000 or more times higher than levels now commonly reported in mobile phone base station studies to cause bioeffects.

Since 2007, five new studies of base station level RFR at intensities ranging from less than 0.001 uW/cm^2 to 0.05 uW/cm^2 report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults.

G. Evidence for Effects on the Blood-brain Barrier (BBB)

The Lund University (Sweden) team of Leif Salford, Bertil Persson and Henrietta Nittby has done pioneering work on effects of very low level RFR on the human brain's protective lining – the barrier that protects the brain from large molecules and toxins that are in the blood.

THE BLOOD-BRAIN BARRIER IS AT RISK

The BBB is a protective barrier that prevents the flow of toxins into sensitive brain tissue. Increased permeability of the BBB caused by cell phone RFR may result in neuronal damage. Many research studies show that very low intensity exposures to RFR can affect the blood-brain barrier (BBB) (mostly animal studies). Summing up the research, it is more probable than unlikely that non-thermal EMF from cell phones and base stations do have effects upon biology. A single 2-hr exposure to cell phone radiation can result in increased leakage of the BBB, and 50 days after exposure, neuronal damage can be seen, and at the later time point also albumin leakage is demonstrated. The levels of RFR needed to affect the BBB have been shown to be as low as 0.001 W/kg, or less than holding a mobile phone at arm's length. The US FCC standard is 1.6 W/kg; the ICNIRP standard is 2 W/kg of energy (SAR) into brain tissue from cell/cordless phone use. Thus, BBB effects occur at about 1000 times lower RFR exposure levels than the US and ICNIRP limits allow.

(Salford et al, 2012 - Section 10)

H. Evidence for Effects on Brain Tumors

The Orebro University (Sweden) team led by Lennart Hardell, MD, an oncologist and medical researcher, has produced an extraordinary body of work on environmental toxins of several kinds, including the effects of radiofrequency/microwave radiation and cancer. Their 2012 work concludes:

“Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings.
(Hardell et al, 2012 – Section 11)

“There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts. There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results. Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen. Based on our own research and review of other evidence the existing FCC/IEE and ICNIRP public safety limits and reference levels are not adequate to protect public health. New public health standards and limits are needed.
(Hardell et al, 2012 – Section 11)

I. Evidence for Genotoxic Effects (Genotoxicity)

Genetic Damage (Genotoxicity Studies): There are at least several hundred published papers that report EMF (ELF/RFR) can affect cellular oxidative processes (oxidative damage). Increased free radical activity and changes in enzymes involved in cellular oxidative processes are the most consistent effects observed in cells and animals after EMF exposure. Aging may make an individual more susceptible to the detrimental effects of ELF EMF from oxidative damage, since anti-oxidants may decline with age. Clearly, the preponderance of genetic studies report DNA damage and failure to repair DNA damage.

One hundred fourteen (114) new papers on genotoxic effects of RFR published between 2007 and early 2014 are profiled. Of these, 74 (65%) showed effects and 40 (35%) showed no effects. (Lai, 2014 – Section 6)

Fifty nine (59) new ELF-EMF papers and two static magnetic field papers that report on genotoxic effects of ELF-EMF published between 2007 and early 2014 are profiled. Of these, 49 (83%) show effects and 10 (17%) show no effect. (Lai, 2014 – Section 6)

Factors that act directly or indirectly on the nervous system can cause morphological, chemical, or electrical changes in the nervous system that can lead to neurological effects. Both RF and ELF EMF affect neurological functions and behavior in animals and humans.

Two hundred eleven (211) new papers that report on neurological effects of RFR published between 2007 and early 2014 are profiled. Of these, 144 (68%) showed effects and 67 (32%) showed no effects.

One hundred five (105) new ELF-EMF papers (including two static field papers) that report on neurological effects of ELF-EMF published between 2007 and early 2014 are profiled. Of these, 95 (90%) show effects and 10 (10%) show no effect. (Lai, 2014 – Section 9)

K. Evidence for Cancer (Childhood Leukemia)

With overall 42 epidemiological studies published to date, power frequency ELF-EMF is among the most comprehensively studied environmental factors. Except ionizing radiation no other environmental factor has been as firmly established to increase the risk of childhood leukemia.

Sufficient evidence exists from epidemiological studies of an increased risk from exposure to EMF (power frequency ELF-EMF magnetic fields) and cannot be attributed to chance, bias or confounding. Therefore, according to the rules of IARC such exposures can be classified as a **Group 1 carcinogen (Known Carcinogen)**.

There is no other risk factor identified so far for which such unlikely conditions have been put forward to postpone or deny the necessity to take steps towards exposure reduction. As one step in the direction of precaution, measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG. This value is arbitrary at present and only supported by the fact that in many studies this level has been chosen as a reference. (Kundi, 2012 – Section 12)

L. Melatonin, Breast Cancer and Alzheimer's Disease

MELATONIN AND BREAST CANCER: Eleven (11) of the 13 published epidemiologic residential and occupational studies are considered to provide (positive) evidence that high ELF magnetic fields (MF) exposure can result in decreased melatonin production. The two negative studies had important deficiencies that may certainly have biased the results. There is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production.

There is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production, which may increase risk for breast cancer. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production. New research indicates that ELF MF exposure, in vitro, can significantly decrease melatonin activity through effects on MT1, an important melatonin receptor. Five longitudinal studies have now been conducted of low melatonin production as a risk factor for breast cancer. There is increasingly strong longitudinal evidence that low melatonin production is a risk factor for at least post-menopausal breast cancer.

(Davanipour and Sobel, 2012 – Section 13)

ALZHEIMER’S DISEASE: There is now evidence that a) high levels of peripheral amyloid beta are a risk factor for AD, and b) medium to high ELF MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high ELF MF exposure to brain cells likely also increases these cells’ production of amyloid beta. There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

There is strong epidemiologic evidence that exposure to ELF MF is a risk factor for AD. There are now twelve (12) studies of ELF MF exposure and AD or dementia. Nine (9) of these studies are considered positive and three (3) are considered negative. The three negative studies have serious deficiencies in ELF MF exposure classification that results in subjects with rather low exposure being considered as having significant exposure. There are insufficient studies to formulate an opinion as to whether radiofrequency MF exposure is a risk or protective factor for AD.

There is now evidence that (i) high levels of peripheral amyloid beta are a risk factor for AD and (ii) medium to high ELF MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high ELF MF exposure to brain cells likely also increases these cells’ production of amyloid beta.

There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

(Davanipour and Sobel, 2012 – Section 13)

M. Stress, Stress Proteins and DNA as a Fractal Antenna

Any agent (EMF, ionizing radiation, chemicals, heavy metals, heat and other factors) that continuously generates stress proteins is not adaptive, and is harmful, if it is a constant provocation. The work of Martin Blank and Reba Goodman of Columbia University has established that stress proteins are produced by ELF-EMF and RFR at levels far below what current safety standards allow. Further, they think DNA is actually a very good fractal RF-antenna which is very sensitive to low doses of EMF, and may induce the cellular processes that result in chronic ‘unrelenting’ stress. That daily environmental levels of ELF-EMF and RFR can and do throw the human body into stress protein response mode (out of homeostasis) is a fundamental and continuous insult. Chronic exposures can then result in chronic ill-health.

“It appears that the DNA molecule is particularly vulnerable to damage by EMF because of the coiled-coil configuration of the compacted molecule in the nucleus. The unusual structure endows it with the self similarity of a fractal antenna and the resulting sensitivity to a wide range of frequencies. The greater reactivity of DNA with EMF, along with a vulnerability to damage,

underscores the urgent need to revise EMF exposure standards in order to protect the public. Recent studies have also exploited the properties of stress proteins to devise therapies for limiting oxidative damage and reducing loss of muscle strength associated with aging.” (Blank, 2012- Section 7)

- DNA acts as a ‘fractal antenna’ for EMF and RFR. The coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies.
- The structure makes DNA particularly vulnerable to EMF damage.
- The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false).
- Many EMF frequencies in the environment can and do cause DNA changes.
- The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.
- EMF stimulates stress proteins (indicating an assault on the cell).
- EMF efficiently harms cells at billions of times lower levels than conventional heating.
- Safety standards based on heating are irrelevant to protect against EMF-levels of exposure. There is an urgent need to revise EMF exposure standards. Research has shown thresholds are very low (safety standards must be reduced to limit biological responses). Biologically-based safety standards could be developed from the research on the stress response. (Blank, 2012 – Section 7).

N. Effects of Weak-Field Interactions on Non-Linear Biological Oscillators and Synchronized Neural Activity:

A unifying hypothesis for a plausible biological mechanism to account for very weak field EMF bioeffects other than cancer may lie with weak field interactions of pulsed RFR and ELF-modulated RFR as disrupters of synchronized neural activity. Electrical rhythms in our brains can be influenced by external signals. This is consistent with established weak field effects on coupled biological oscillators in living tissues. Biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels (Buzsaki, 2006; Strogatz, 2003). The key to synchronization is the joint actions of cells that co-operate electrically and link populations of biological oscillators that couple together in large arrays and synchronize spontaneously. Synchronous biological oscillations in cells (pacemaker cells) can be disrupted by artificial, exogenous environmental signals, resulting in desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles (Strogatz, 1987). The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles (Strogatz, 2001, 2003)

“Rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance.” (Busaki, 2006)

III. EMF EXPOSURE AND PRUDENT PUBLIC HEALTH PLANNING

Chronic exposure to low-intensity RFR and to ELF-modulated RFR at today's environmental levels in many cities will exceed thresholds for increased risk of many diseases and causes of death (Sage and Huttunen, 2012). RFR exposures in daily life alter homeostasis in human beings. These exposures can alter and damage genes, trigger epigenetic changes to gene expression and cause de novo mutations that prevent genetic recovery and healing mechanisms. These exposures may interfere with normal cardiac and brain function; alter circadian rhythms that regulate sleep, healing, and hormone balance; impair short-term memory, concentration, learning and behavior; provoke aberrant immune, allergic and inflammatory responses in tissues; alter brain metabolism; increase risks for reproductive failure (damage sperm and increase miscarriage risk); and cause cells to produce stress proteins. Exposures now common in home and school environments are likely to be physiologically addictive and the effects are particularly serious in the young (Sage and Huttunen, 2012).

RECOMMENDED ACTIONS

A. Defining Preventative Actions for Reduction in RFR Exposures

ELF-EMF and RFR are Classified as Possible Cancer-causing Agents – Why Are Governments Not Acting?

The World Health Organization International Agency for Research on Cancer has classified wireless radiofrequency as a Possible Human Carcinogen (May, 2011)*. The designation applies to low-intensity RFR in general, covering all RFR-emitting devices and exposure sources (cell and cordless phones, Wi-Fi, wireless laptops, wireless hotspots, electronic baby monitors, wireless classroom access points, wireless antenna facilities). The IARC Panel could have chosen to classify RFR as a Group 4 – Not A Carcinogen if the evidence was clear that RFR is not a cancer-causing agent. It could also have found a Group 3 designation was a good interim choice (Insufficient Evidence). IARC did neither.

New Safety Limits Must Be Established – Health Agencies Should Act Now

Existing public safety limits (FCC and ICNIRP public safety limits) do not sufficiently protect public health against chronic exposure from very low-intensity exposures. If no mid-course corrections are made to existing and outdated safety limits, such delay will magnify the public health impacts with even more applications of wireless-enabled technologies exposing even greater populations around the world in daily life.

Scientific Benchmarks for Harm Plus Safety Margins = New Safety Limits that are Valid

Health agencies and regulatory agencies that set public safety standards for ELF-EMF and RFR should act now to adopt new, biologically-relevant safety limits that key to the lowest scientific benchmarks for harm coming from the recent studies, plus a lower safety margin. Existing public safety limits are too high by several orders of magnitude, if prevention of bioeffects and resulting adverse health effects are to be minimized or

eliminated. Most safety standards are a thousand times or more too high to protect healthy populations, and even less effective in protecting sensitive subpopulations.

Sensitive Populations Must Be Protected

Safety standards for sensitive populations will more likely need to be set at lower levels than for healthy adult populations. Sensitive populations include the developing fetus, the infant, children, the elderly, those with pre-existing chronic diseases, and those with developed electrical sensitivity (EHS).

Protecting New Life – Infants and Children

Strong precautionary action and clear public health warnings are warranted immediately to help prevent a global epidemic of brain tumors resulting from the use of wireless devices (mobile phones and cordless phones). Commonsense measures to limit both ELF-EMF and RFR in the fetus and newborn infant (sensitive populations) are needed, especially with respect to avoidable exposures like baby monitors in the crib and baby isolettes (incubators) in hospitals that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RFR are easily instituted.

Wireless laptops and other wireless devices should be strongly discouraged in schools for children of all ages.

Standard of Evidence for Judging the Science

The standard of evidence for judging the scientific evidence should be based on good public health principles rather than demanding scientific certainty before actions are taken.

Wireless Warnings for All

The continued rollout of wireless technologies and devices puts global public health at risk from unrestricted wireless commerce unless new, and far lower exposure limits and strong precautionary warnings for their use are implemented.

EMF and RFR are Preventable Toxic Exposures

We have the knowledge and means to save global populations from multi-generational adverse health consequences by reducing both ELF and RFR exposures. Proactive and immediate measures to reduce unnecessary EMF exposures will lower disease burden and rates of premature death.

B. Defining New ‘Effect Level’ for RFR

Section 24 concludes that RFR ‘effect levels’ for bioeffects and adverse health effects justify new and lower precautionary target levels for RFR exposure. New epidemiological and laboratory studies are finding effects on humans at lower exposure levels where studies are of longer duration (chronic exposure studies). Real-world experience is revealing worrisome evidence that sperm may be damaged by cell phones even on

stand-by mode; and people can be adversely affected by placing new wireless pulsed RFR transmitters (utility meters on the sides or interiors of homes), even when the time-weighted average for RFR is miniscule in both cases.

There is increasing reason to believe that the critical factor for biologic significance is the intermittent pulse of RF, not the time-averaged SAR. For example, Hansson Mild et al, (2012) concluded there could be no effect on sleep and testicular function from a GSM mobile phone because the “*exposure in stand-by mode can be considered negligible*”. It may be that we, as a species, are more susceptible than we thought to intermittent, very low-intensity pulsed RFR signals that can interact with critical activities in living tissues. It is a mistake to conclude that the effect does not exist because we cannot explain HOW it is happening or it upsets our mental construct of how things should work.

This highlights the serious limitation of not taking the nature of the pulsed RFR signal (high intensity but intermittent, microsecond pulses of RFR) into account in the safety standards. This kind of signal is biologically active. Even if it is essentially mathematically invisible when the individual RFR pulses are time-averaged, it is apparently NOT invisible to the human body and its proper biological functioning.

For these reasons, and in light of parallel scientific work on non-linear biological oscillators including the accepted mathematics in this branch of science regarding coupled oscillators (Bezsaki, 2006; Strogatz, 2001, 2003), it is essential to think forward about the ramifications of shifting national energy strategies toward ubiquitous wireless systems. And, it is essential to re-think safety standards to take into account the exquisite sensitivity of biological systems and tissue interactions where the exposures are pulsed and cumulatively insignificant over time-scale averaging, but highly relevant to body processes and functioning. If it is true that weak-field effects have control elements over synchronous activity of neurons in the brain, and other pacemaker cells and tissues in the heart and gut that drive essential metabolic pathways as a result, then this will go far in explaining why living tissues are apparently so reactive to very small inputs of pulsed RFR, and lead to better understanding of what is required for new, biologically-based public exposure standards.

A reduction from the BioInitiative 2007 recommendation of 0.1 uW/cm² (or one-tenth of a microwatt per square centimeter) for cumulative outdoor RFR down to something three orders of magnitude lower (in the low nanowatt per square centimeter range) is justified on a public health basis. We use the new scientific evidence documented in this Report to identify ‘effect levels’ and then apply one or more reduction factors to provide a safety margin. A cautionary target level for cumulative, outdoor pulsed RFR exposures for ambient wireless that could be applied to RFR sources from cell tower antennas, Wi-Fi, WiMAX and other similar sources is proposed. Research is needed to determine what is biologically damaging about intermittent pulses of RFR, and how to provide for protection in safety limits against it. With this knowledge it might be feasible to recommend a higher time-averaged number.

A scientific benchmark of 0.003 uW/cm² or three nanowatts per centimeter squared for ‘lowest observed effect level’ for RFR is based on mobile phone base station-level studies. Applying a ten-fold reduction to compensate for the lack of long-term exposure (to provide a safety buffer for chronic exposure, if needed) or for children as a sensitive subpopulation (if studies are on adults, not children) yields a 300 to 600 picowatts per

square centimeter precautionary action level. This equates to a 0.3 nanowatts to 0.6 nanowatts per square centimeter as a reasonable, precautionary action level for chronic exposure to pulsed RFR. Even so, these levels may need to change in the future, as new and better studies are completed. This is what the authors said in 2007 (Carpenter and Sage, 2007, BioInitiative Report) and it remains true today in 2012.

We leave room for future studies that may lower or raise today's observed 'effects levels' and should be prepared to accept new information as a guide for new precautionary action.

