

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

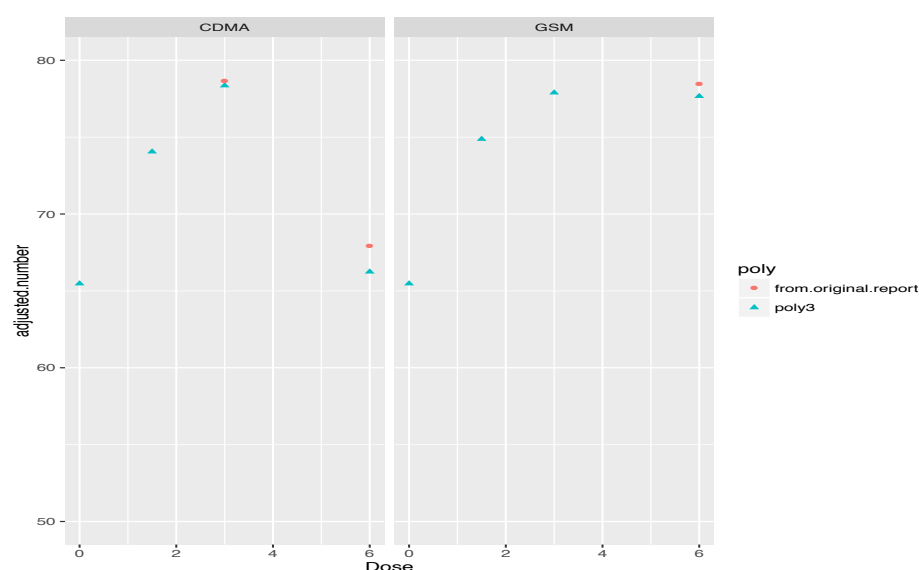
The numbers in from.original.report refers to the poly-3 adjusted rat number from Table 3 in the original report. The numbers in poly3 refers to the poly-3 adjusted rat numbers that I calculated from the raw data for heart schwannoma.

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

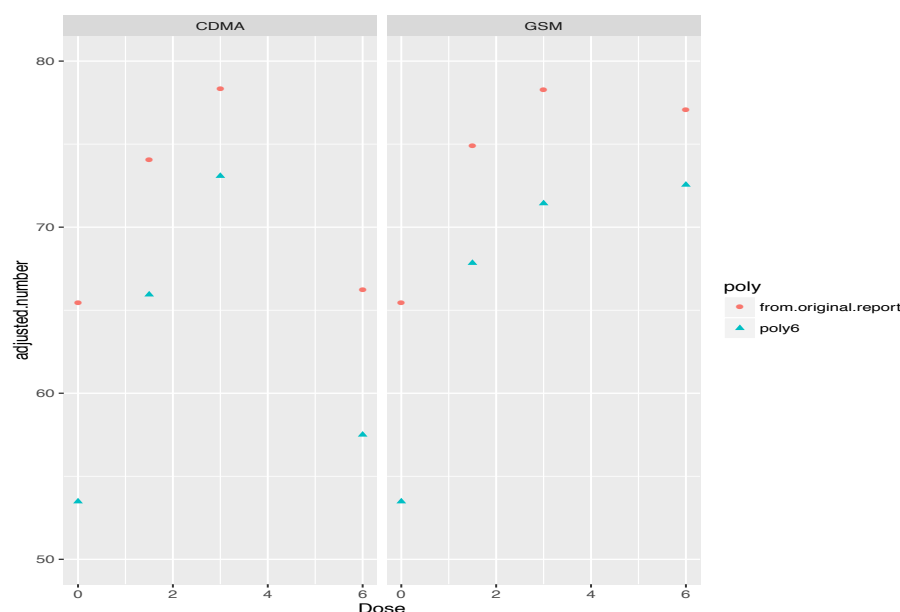
The numbers in from.original.report refers to the poly-6 adjusted rat number from Table 1 in the original report. The numbers in poly6 refers to the poly-6 adjusted rat numbers that I calculated from the raw data for brain gliomas.

Figure S1. Comparison of poly-3 adjusted rat numbers between those from the original report versus those calculated from the raw data.



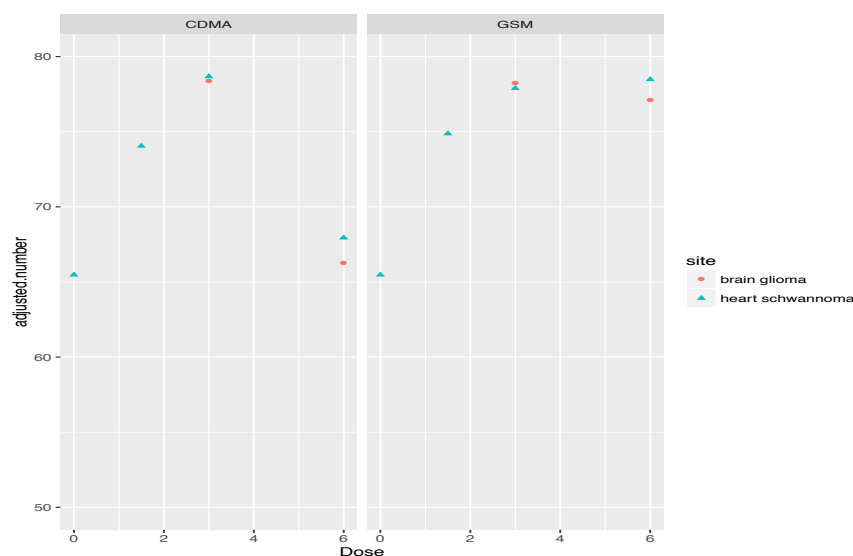
The poly-3 adjusted rat number from Table 3 of the original report is compare with the poly-3 adjusted rat number that I calculated from the raw data for heart schwannomas experiment

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.

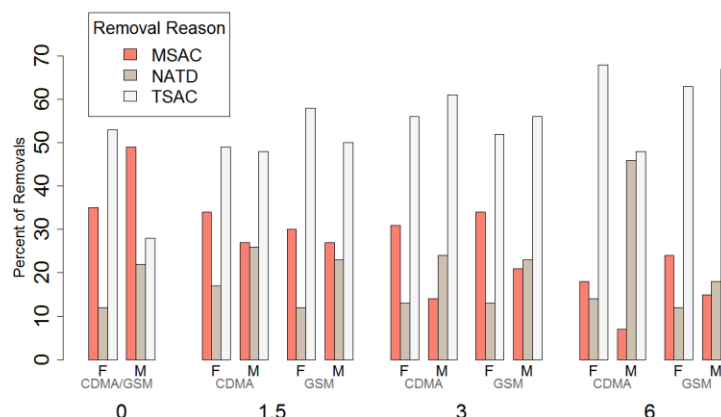
Median survival						TSAC percentage					
CDMA	Female	Male	GSM	Female	Male	CDMA	Female	Male	GSM	Female	Male
0	737	662.5	0	737	662.5	0	53	28	0	53	28
1.5	734	719	1.50	738	729	1.5	49	48	1.5	58	50
3	737	731	3	737	730	3	56	61	3	52	56
6	738.5	717	6	738	731	6	68	48	6	63	67

- 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. Environmental Research. Dr. Ron Melnick; 2019



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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.

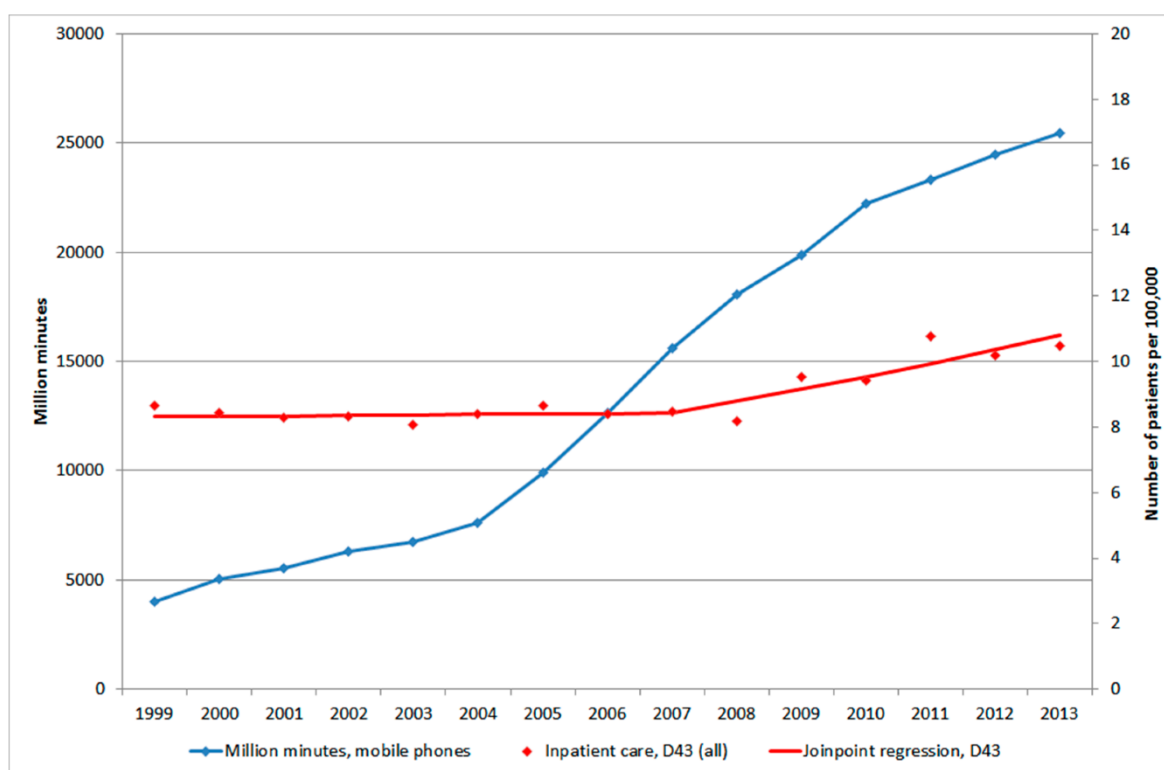


Figure 1. Number of out-going mobile phone minutes in millions during 1999–2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf> ; accessed on 1 April 2015) and joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish National Inpatient 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.

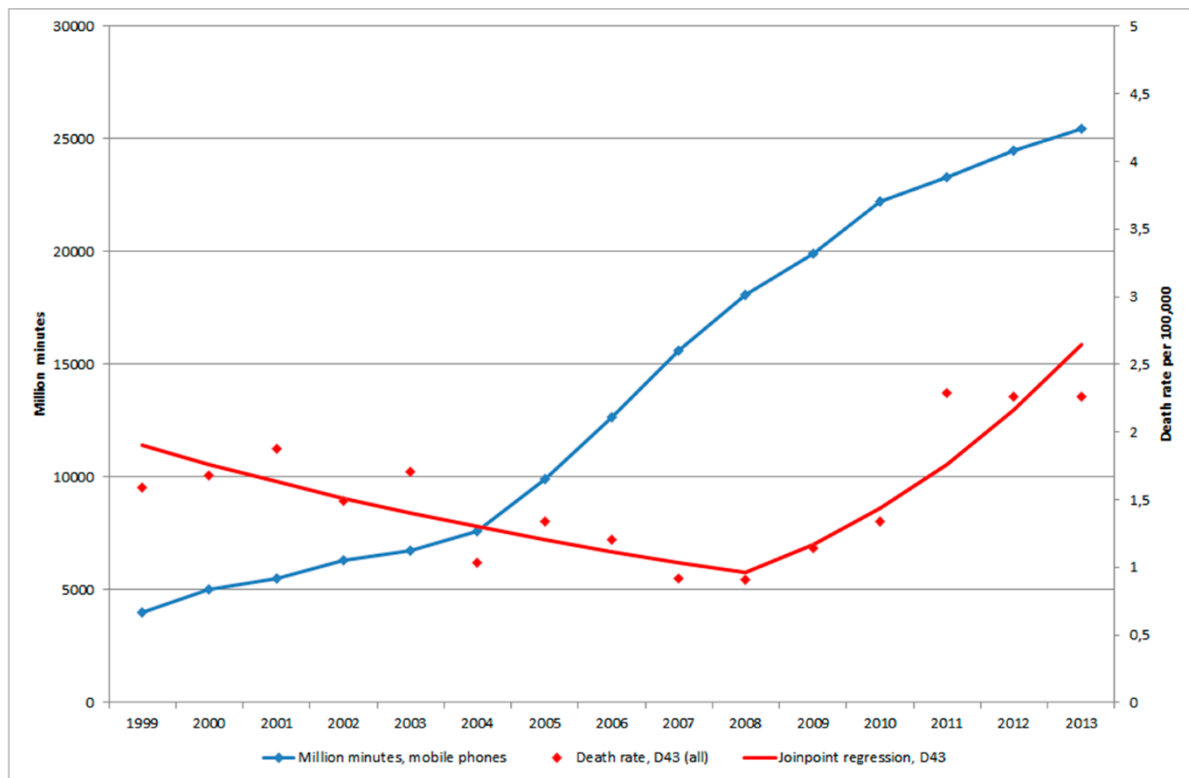


Figure 2. Number of out-going mobile phone minutes in millions during 1999–2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf> ; accessed on 1 April 2015) and joinpoint regression analysis of age-standardized death rates per 100,000 inhabitants according to the Swedish Causes 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.

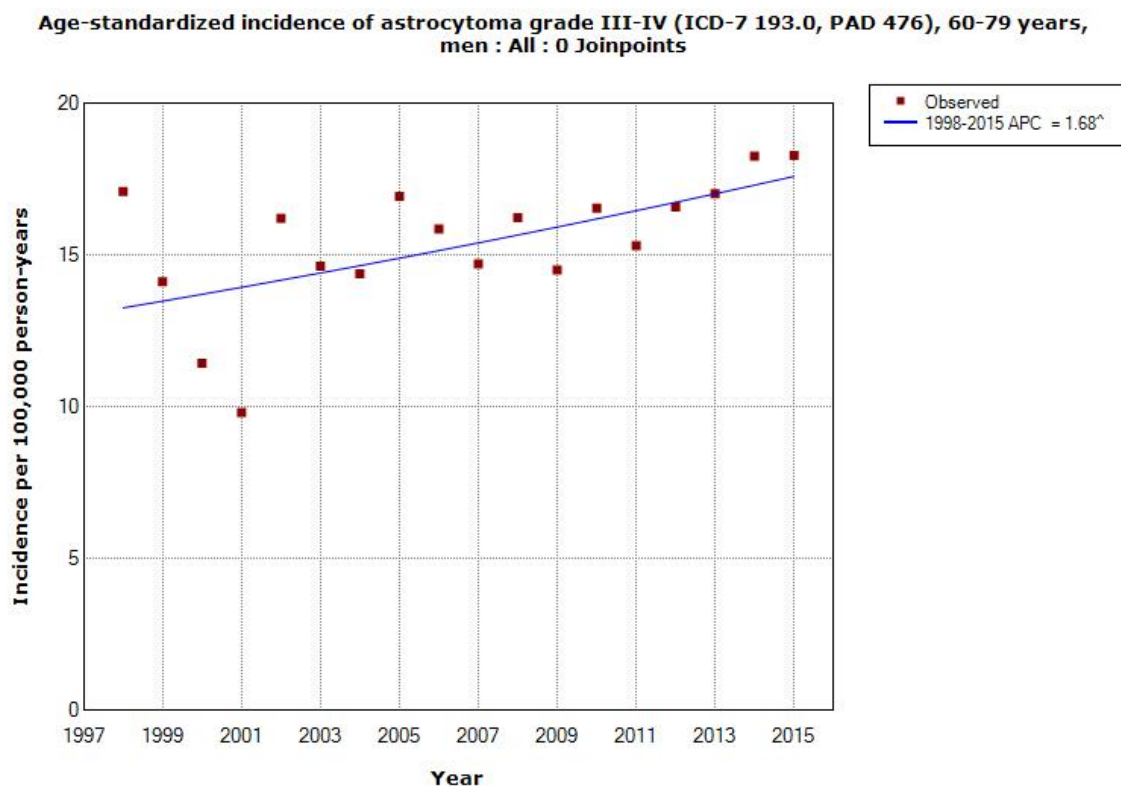


Figure 3. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC +1.68 %, 95 % CI +0.39, +2.99 %. (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>). <https://doi.org/10.1371/journal.pone.0185461.g005>

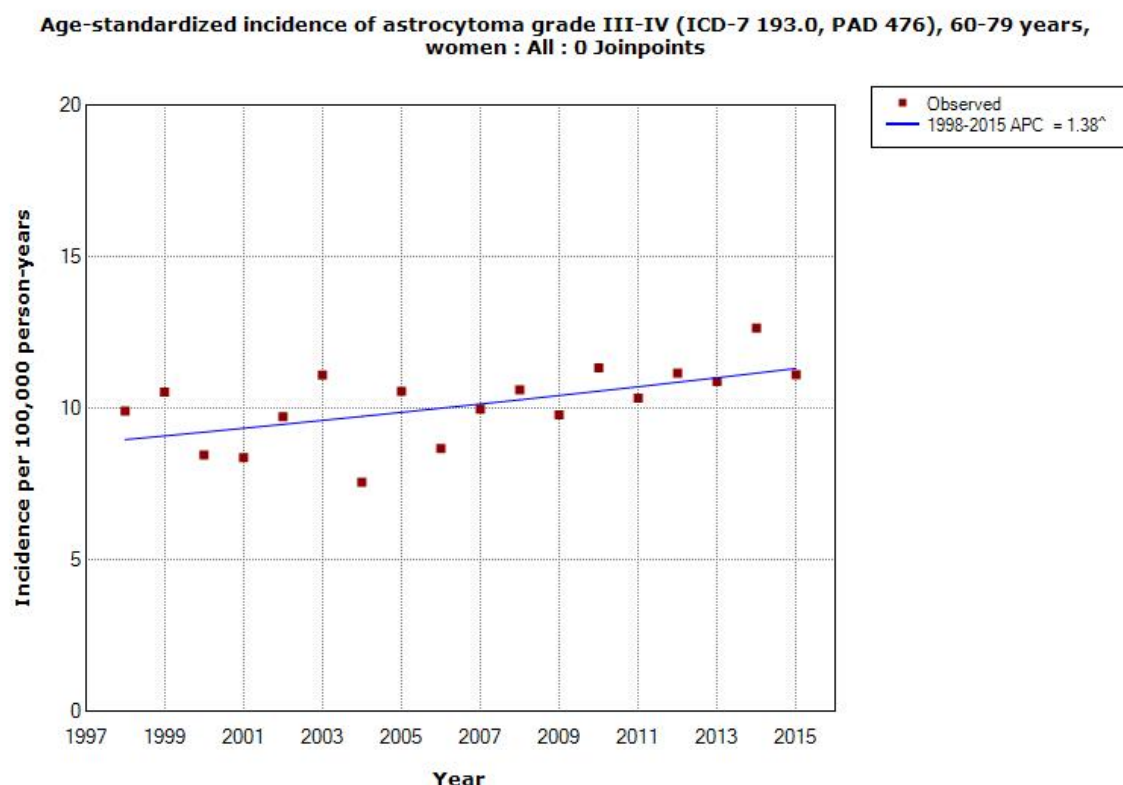


Figure 4. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in women aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC + 1.38 %, 95 % CI +0.32, +2.45 %. (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>). <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 since 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.

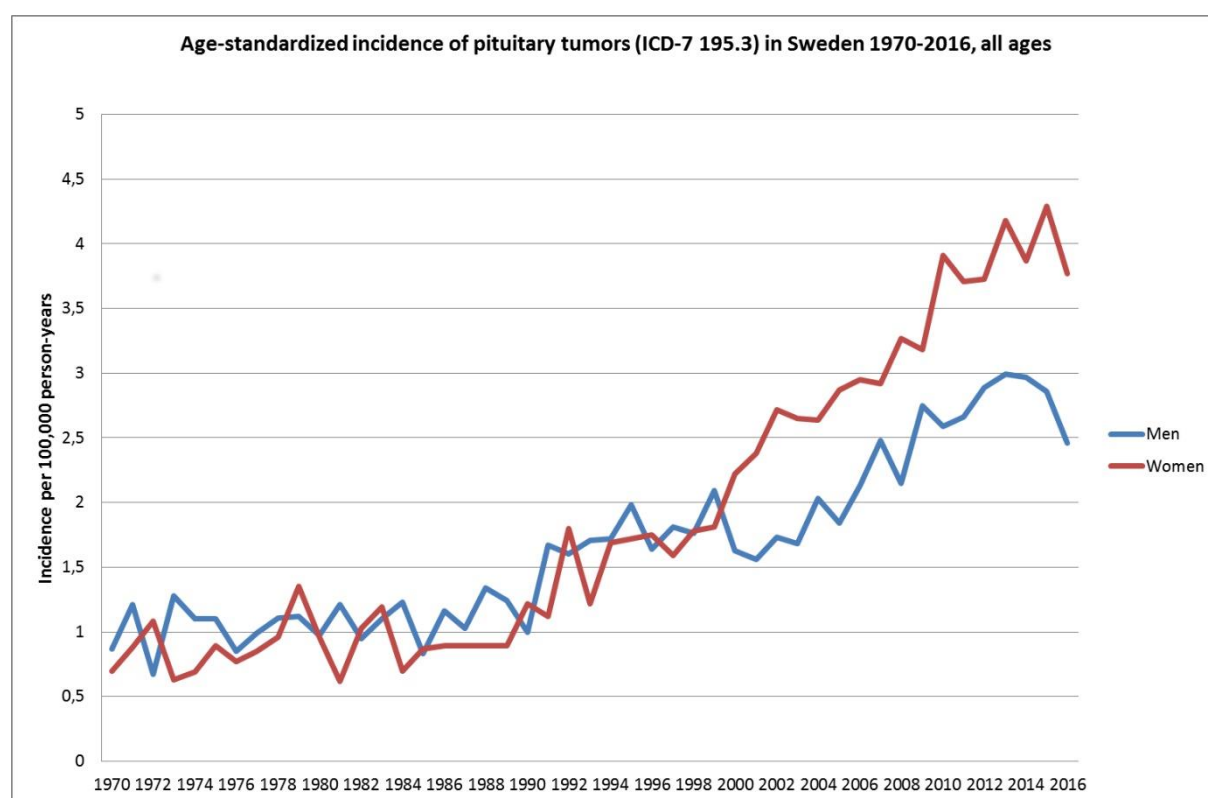


Figure 5. Age-standardized incidence of pituitary tumors (ICD-7 195.3) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

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 significantly 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.

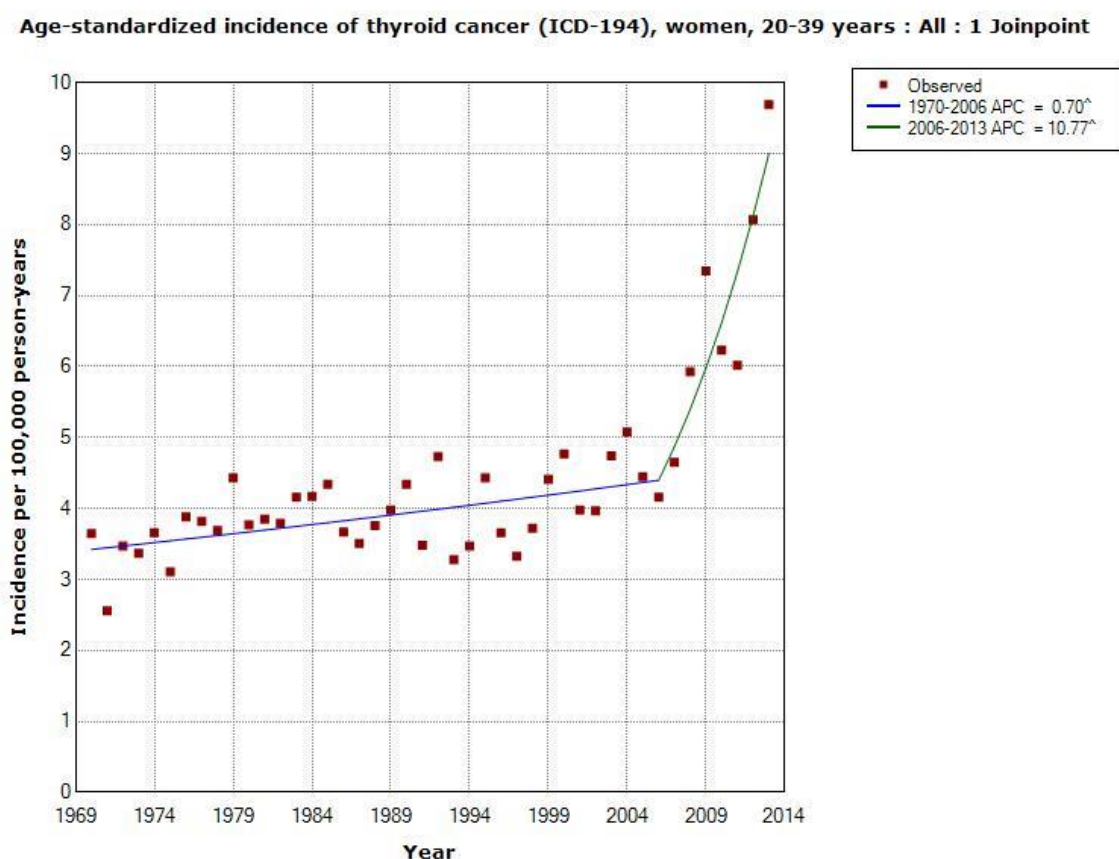


Figure 6. Joinpoint regression analysis of age-standardized incidence of thyroid cancer for women, aged 20–39 years, 1970–2013. Incidence per 100,000 inhabitants for ICD-7 code 194 according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>)

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%).

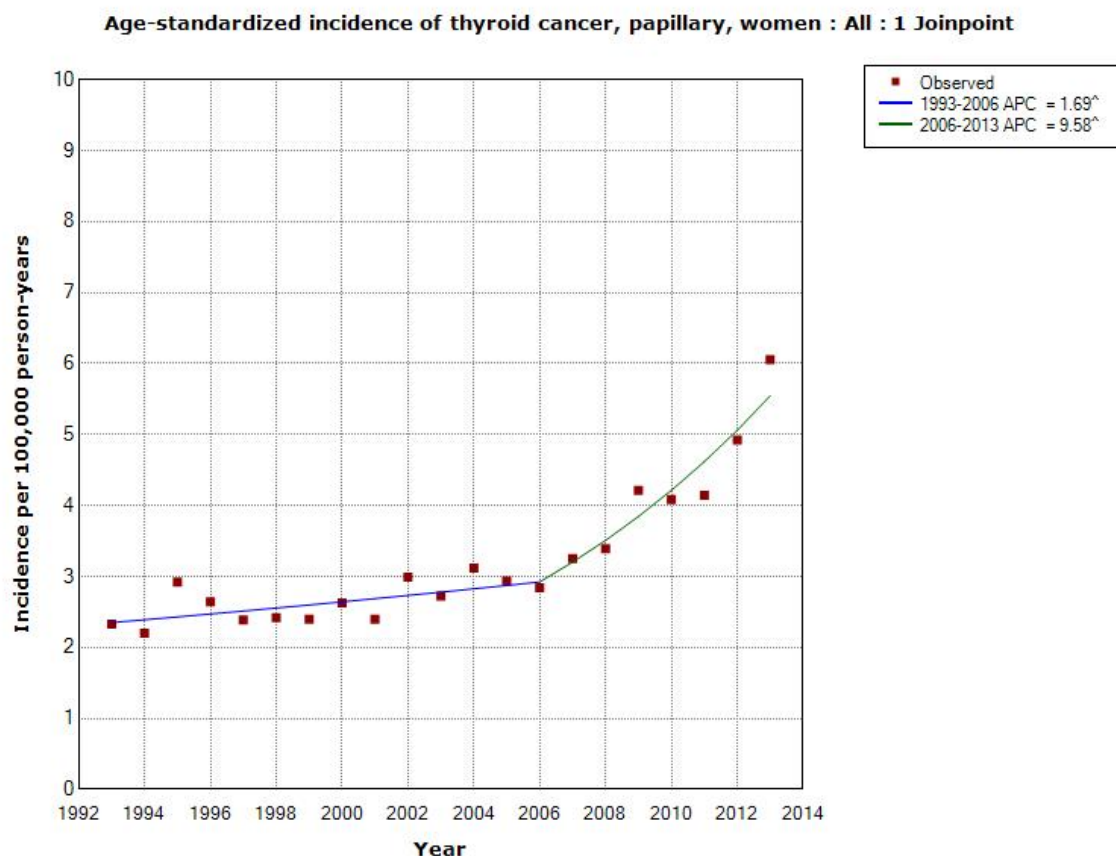


Figure 7. Joinpoint regression analysis of age-standardized incidence of papillary thyroid cancer for women, all ages, 1993–2013. Incidence per 100,000 inhabitants for ICD-7 code 194; data obtained from the Swedish Cancer Register

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.

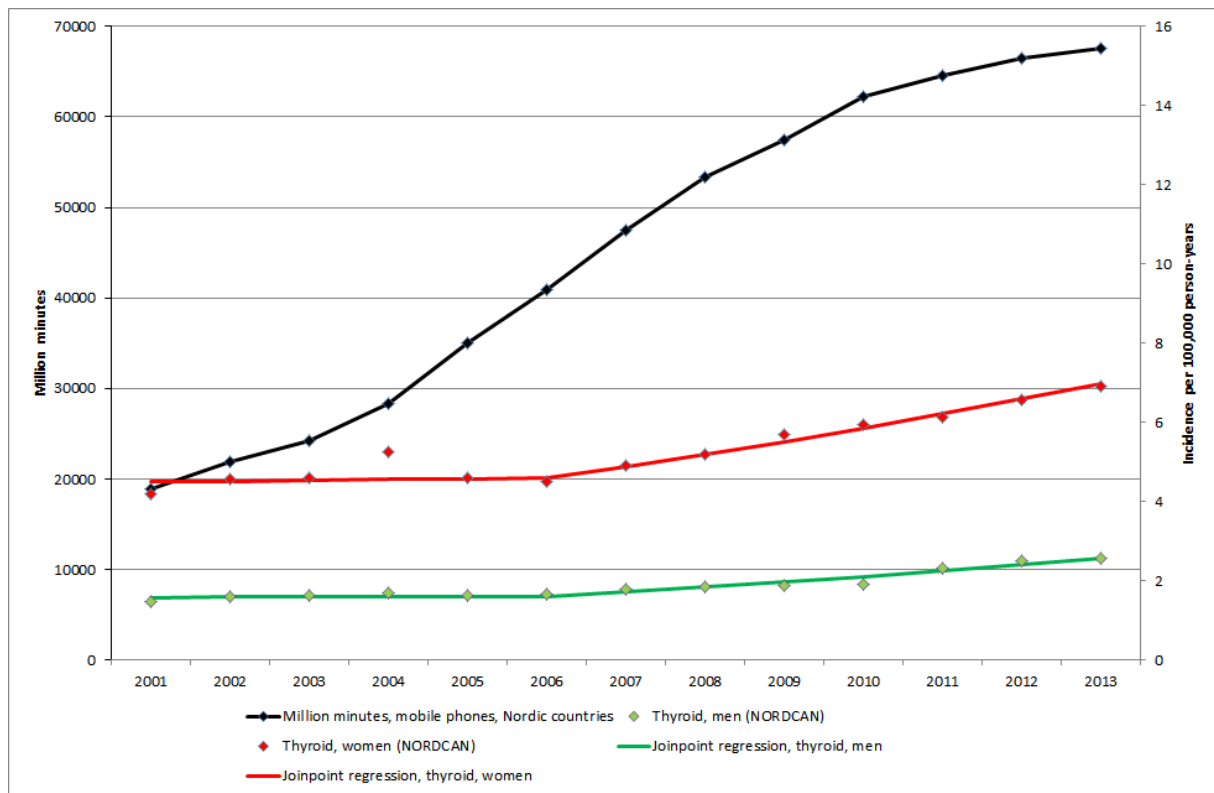


Figure 8. Number of out-going mobile phone minutes and incidence of thyroid cancer 2001–2013. Mobile phone minutes in millions in the Nordic countries (<http://statistik.pts.se/PTSnordic/NordicBaltic2014/>) and incidence per 100,000 person-years for all ages 2001–2013 according to NORDCAN (<http://www-dep.iarc.fr/NORDCAN/english/frame.asp>). 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.

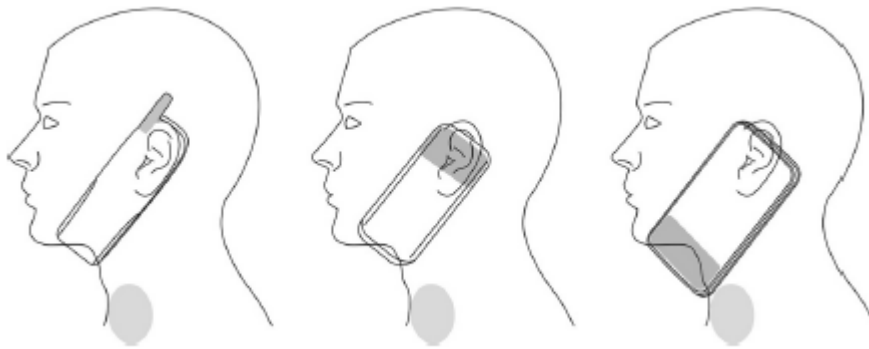


Figure 9. Mobile phone antenna placements in regard to the thyroid gland

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.

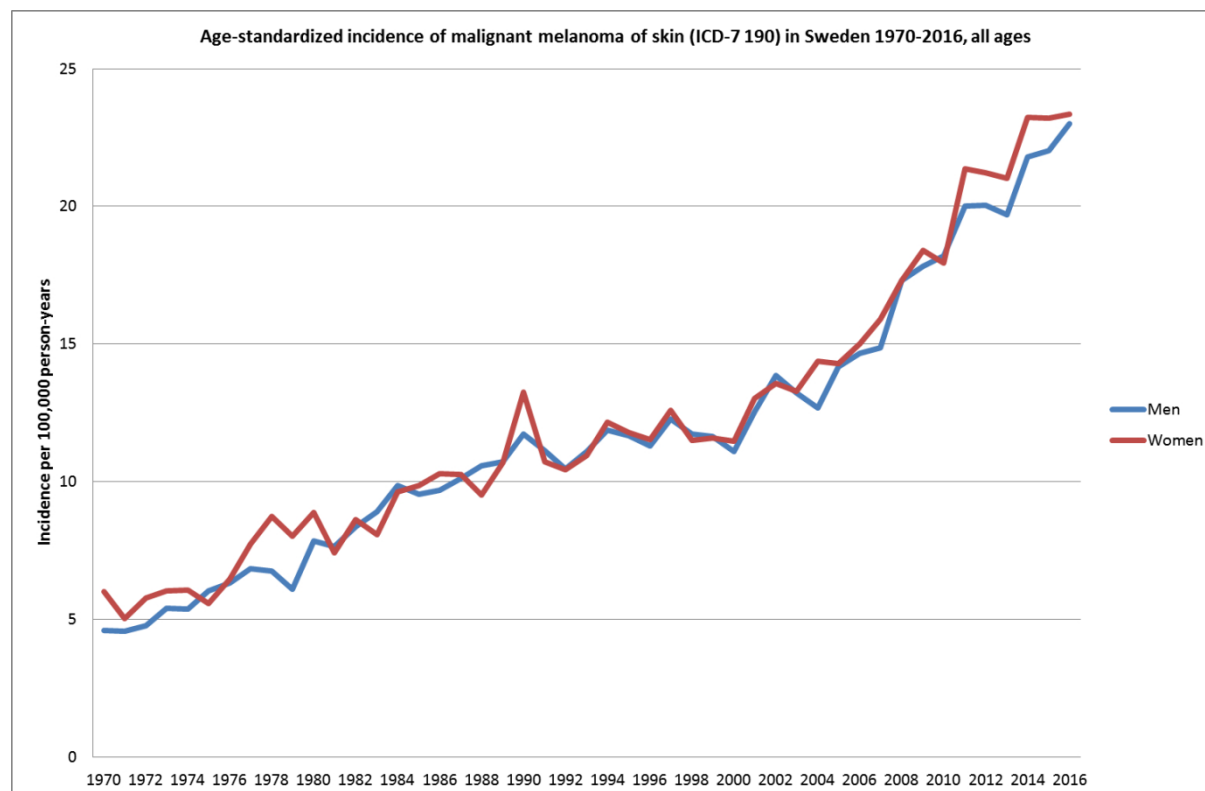


Figure 10. Age-standardized incidence of malignant melanoma (ICD-7 190) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

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/currentb6evalrationalle0706.php>)

Respectfully submitted
Pro Bono Publico



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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	– 0.0.3 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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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.

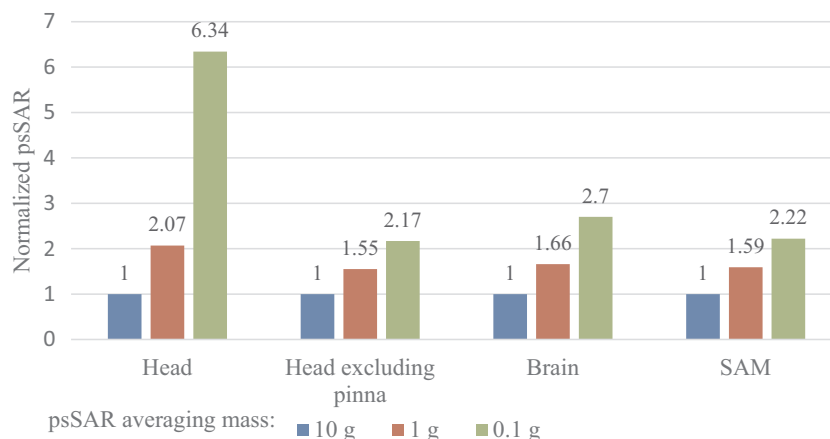


Fig. 1. psSAR averaged over cubic volumes containing 1 g and 0.1 g, relative to 10 g of continuous tissue. Values are normalized to the 10 g psSAR. Head including and excluding pinna, and brain psSAR values are averages of the psSAR obtained for 10 anatomical models. SAM is also presented.

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.

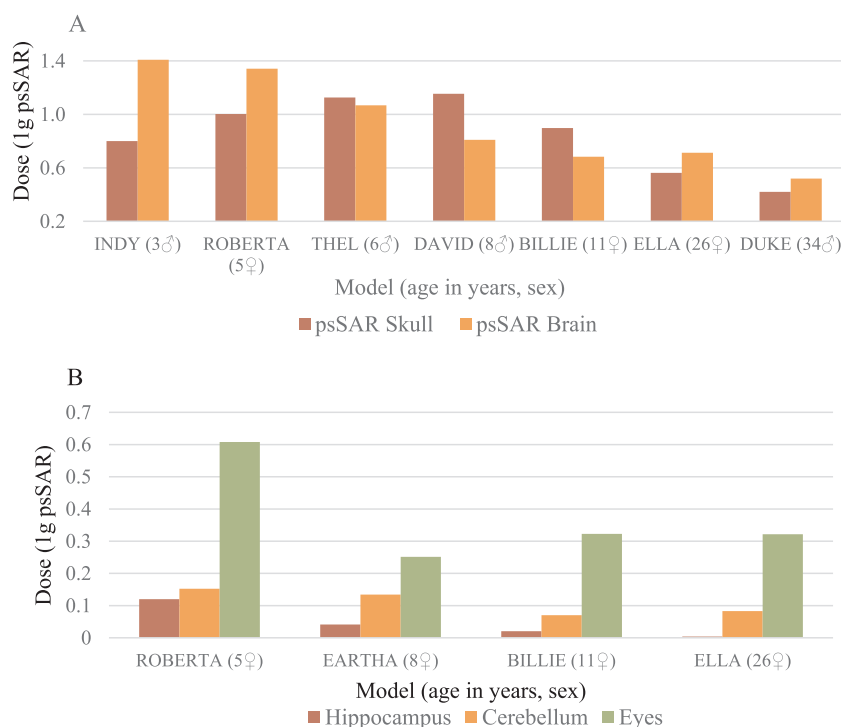


Fig. 2. psSAR in 1 g of specific tissues. A. the skull and brain and B. specific tissues in models with these features identified – hippocampus, cerebellum and eyes.

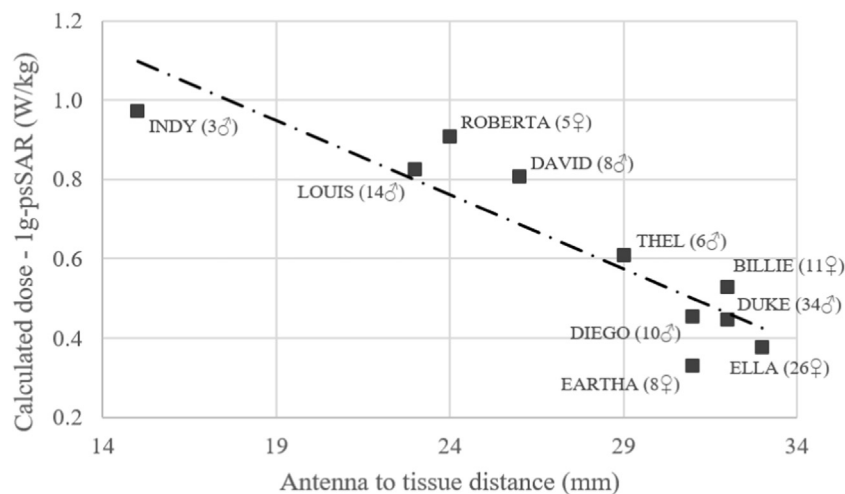


Fig. 3. Trend of psSAR in 1 g of grey matter, as a function of distance from the antenna to the brain, for phone in “talk” position.

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

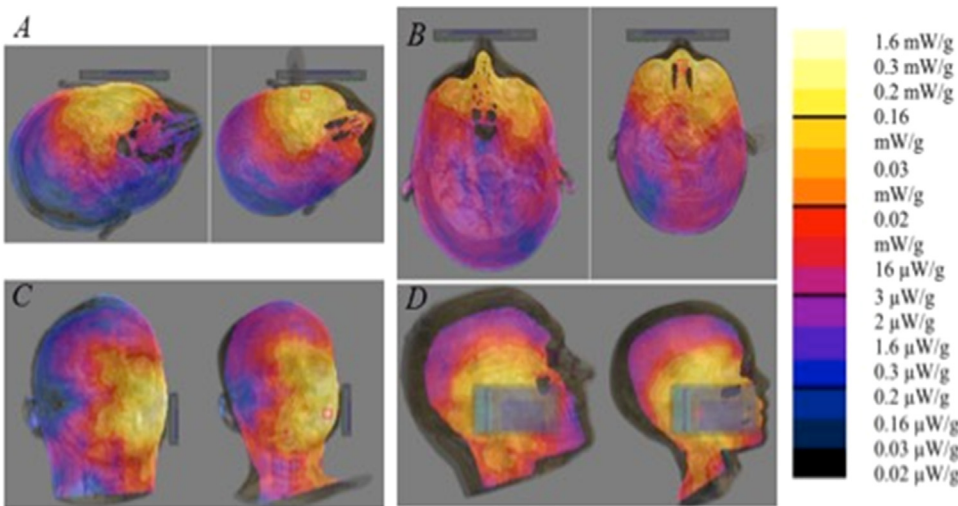


Fig. 4. SAR in cross-sectional views of child and adult male heads, with phone in talk and in virtual reality positions. A Axial slices (top view) of Thelonious (6 y) and Duke (34 y), with cell phone in cheek position, intersecting the eyes; B Axial slices (top view) of Thelonious (6 y) and Duke (34 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

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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 (NIEER) 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 NIEER 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).

Reasonant 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 then 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).

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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.

Otitoloju 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/m^2 [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 short-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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Prepared for the BioInitiative Working Group
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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.

