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Minireview

Genetic damage in human cells exposed to non-ionizing radiofrequency fields: A meta-analysis of the data from 88 publications (1990–2011)

Vijayalaxmi [a,*], Thomas J. Prihoda [b]

[a] Department of Radiology, University of Texas Health Science Center, San Antonio, TX 78229, USA
[b] Department of Pathology, University of Texas Health Science Center, San Antonio, TX 78229, USA

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ABSTRACT

Based on the 'limited' evidence suggesting an association between exposure to radiofrequency fields (RF) emitted from mobile phones and two types of brain cancer, glioma and acoustic neuroma, the International Agency for Research on Cancer has classified RF as 'possibly carcinogenic to humans' in group 2B. In view of this classification and the positive correlation between increased genetic damage and carcinogenesis, a meta-analysis was conducted to determine whether a significant increase in genetic damage in human cells exposed to RF provides a potential mechanism for its carcinogenic potential. The extent of genetic damage in human cells, assessed from various end-points, viz., single-/double-strand breaks in the DNA, incidence of chromosomal aberrations, micronuclei and sister chromatid exchanges, reported in a total of 88 peer-reviewed scientific publications during 1990–2011 was considered in the meta-analysis. Among the several variables in the experimental protocols used, the influence of five specific variables related to RF exposure characteristics was investigated: (i) frequency, (ii) specific absorption rate, (iii) exposure as continuous wave, pulsed wave and occupationally exposed/mobile phone users, (iv) duration of exposure, and (v) different cell types. The data indicated the following. (1) The magnitude of difference between RF-exposed and sham-/un-exposed controls was small with some exceptions. (2) In certain RF exposure conditions there was a statistically significant increase in genotoxicity assessed from some end-points: the effect was observed in studies with small sample size and was largely influenced by publication bias. Studies conducted within the generally recommended RF exposure guidelines showed a smaller effect. (3) The multiple regression analyses and heterogeneity goodness of fit data indicated that factors other than the above five variables as well as the quality of publications have contributed to the overall results. (4) More importantly, the mean indices for chromosomal aberrations, micronuclei and sister chromatid exchange end-points in RF-exposed and sham-/un-exposed controls were within the spontaneous levels reported in a large data-base. Thus, the classification of RF as possibly carcinogenic to humans in group 2B was not supported by genotoxicity-based mechanistic evidence.

Contents

Abbreviations: RF, radiofrequency fields; SBM, DNA single-/double-strand breaks measured as comet tail length in microns; SBR, DNA single-/double-strand breaks assessed from comet tail moment/factor/ratio; CA, chromosomal aberrations; MN, micronuclei; SCE, sister chromatid exchanges; E–C, magnitude of difference between RF-exposed and controls; ES, effect size or standardized mean difference.

* Corresponding author at: Department of Radiology, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA.
Tel.: +1 210 861 8189; fax: +1 210 567 5541.
E-mail address: vijay@uthscsa.edu (Vijayalaxmi).

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1. Introduction

A multitude of devices that emit non-ionizing electromagnetic radiofrequency fields (RF) in the frequency range of 300 MHz to 300 GHz are used in medicine, military, industry and a variety of consumer products. The introduction of wireless communication devices resulted in a remarkable increase in the number of people exposed to RF. Consequently, there is growing concern in the general public regarding potential adverse health effects from exposure to RF. The undesirable effects of RF exposure on the genetic material (DNA) are important. Any un-repaired and/or mis-repaired primary lesions in the DNA such as single-/double-strand breaks (SSB/DSB) can lead to the formation of chromosomal aberrations (CA), micronuclei (MN), sister chromatid exchanges (SCE) and mutations which may lead to carcinogenesis or cell death. Hence, during the last several decades, extensive research efforts were made to determine whether acute and long-term in vitro and in vivo RF exposures result in excessive genetic damage in eukaryotic and prokaryotic cells. Several reviews were already published [1–8]. However, the variables in animal and human investigations, viz., RF exposure facility, transmission as continuous wave (CW) or pulsed wave (PW), specific absorption rate (SAR), duration of continuous and/or intermittent exposure, freshly collected and cultured animal and human cells, genotoxicity end-points, statistical methods, etc. have made direct comparison of the data obtained by the same investigators in different experiments and between independent researchers almost impossible and, might have contributed to the controversial results in the published literature [9].

Meta-analysis is widely used in biomedical research and utilizes several quantitative statistical methods for large data review, especially when the outcomes in different investigations are controversial. Vijayalaxmi and Prihoda [10] conducted such analyses of genetic damage data, in animal and human cells exposed in vitro and in vivo to RF, reported in 63 peer-reviewed scientific publications during 1990–2005. The authors conclusions were: (i) with few exceptions, the magnitude of difference between RF-exposed and sham-/un-exposed controls as well as the 'effect size' or standardized mean difference due to RF exposure was small, (ii) at certain RF exposure conditions, a small but statistically significant increase in genotoxicity was observed in some end-points, and (iii) the mean indices for CA and MN in RF-exposed and controls were within the spontaneous levels reported in a large historical data-base.

More recently, the International Agency for Research on Cancer (IARC) invited a group of scientists to evaluate all peer-reviewed scientific publications related to the carcinogenic potential of RF exposure [11]. Human epidemiological investigations, long-term studies in experimental animals as well as the studies examining the other relevant end-points such as apoptosis, blood brain barrier, gene and protein expression, genotoxicity, immune function and oxidative stress which might provide a mechanistic basis were considered in the evaluation. Although the RF exposure effect was noticed in some relevant end-points, the conclusion was that the overall the data from other relevant end-points provided 'weak' mechanism for RF-induced carcinogenesis. Based on the 'limited' evidence for excess cancers in some animal studies and, from the 'limited' evidence in humans suggesting a positive association between RF emitted from mobile phones and two types of brain cancer (glioma and acoustic neuroma), the IARC classified RF as 'possibly carcinogenic' to humans in group 2B [11]. Considering this classification, human cells were the main focus in this meta-analysis. The main aim was to examine whether significantly increased genetic damage in human cells exposed to RF provides a potential mechanism for its carcinogenic potential. The overall objectives were to: (i) obtain a good overall 'quantitative' estimate of the genetic damage reported in freshly collected and cultured human cells exposed in vitro to RF as well as freshly collected cells from personnel who are occupationally exposed RF and/or individuals using mobile phones that emit RF and, compare with those in control cells, (ii) study the correlation between some RF exposure characteristics (see below) and increased genotoxicity that is larger than the random variability; (iii) examine whether the genotoxicity indices in RF-exposed cells were significantly higher than the spontaneous levels in healthy individuals reported in a large data-base, (iv) use multiple regression analysis to determine the combined effects of RF exposure characteristics (each adjusted for the others) on genotoxicity; and (v) test for heterogeneity of residual variability to indicate if factors other than those considered in the meta-analysis could explain the RF effects reported in the publications.

2. Materials and methods

A combination of key words including human; non-ionizing electromagnetic fields; radiofrequency fields; DNA strand breaks; CA; MN; SCE; in vitro and in vivo studies; etc. were used for systematic search for publications in Medline; PubMed and Ovid data-bases. Several colleagues also helped in the search. The data reported in each of 88 peer-reviewed publications in scientific journals during 1990–2011 [12–99 in chronological order] were recorded in an Excel spreadsheet (Microsoft; WA). The quality of the investigations; i.e., inclusion of sham and/or un-exposed controls; positive-controls; detailed descriptions of dosimetry; experimental protocols; data collection procedures; 'blind' evaluations; appropriate statistical analyses; concurrence of the conclusions in the abstract and in the text with the data presented in tables and figures; etc. were also included in the spreadsheet. The results presented for SSB and DSB were considered as SBM (comet tail length in microns); SBR (comet tail moment/factor/ratio) and foci/cell. The data reported for aneuploidy; MN and spindle disturbances were considered together as MN since they are inter-related and consequential end-points. When the investigators examined different numbers of cells to determine CA; MN and SCE indices in the same and/or different experiments; a standardized 'unit' was obtained as a homogeneous measure: CA/100 cells; MN/1000 cells and SCE/cell. Such units in RF-exposed cells were integrated to obtain overall mean and standard deviation (SD); and designated to the 'RF-exposed group' while similar units in controls were assigned to the 'control group'. These were the 'descriptive' data from which the meta-analysis was conducted using the Statistical

Analysis System; Version 9.2 for Windows [100]. Extensive details were described earlier [10].

3. Meta-analysis

The recommendations in several standard textbooks, including: (i) 'Statistical Methods for Meta-analysis' [101], (ii) 'Practical Meta-Analysis' [102], (iii) 'Methods of Meta-Analysis: Correcting Error and Bias in Research Findings' [103] and (iv) 'How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers' [104] were the basis for the meta-analysis. Among the several variables in individual RF publications, five were selected to determine their effect on different genotoxicity end-points: RF frequency, SAR, RF exposure as CP-CW-PW (CP are occupationally exposed individuals and mobile phone users exposed to RF, CW and/or PW), duration of RF exposure and cell types. Each of these selected variables was further classified into sub-groups and many of them were arbitrary. (1) Frequency: (a) all frequencies, (b) ≤2000 MHz generally used for wireless communication systems, and (c) >2000 MHz. (2) SAR: (a) all SARs, (b) papers in which SAR not reported (NR), (c) ≤2 W/kg, (d) >2–5 W/kg, and (e) >5 W/kg which is above the generally recommended SAR for human exposures. (3) RF exposure: (a) CP-CW-PW, (b) CP, (c) CW and (d) PW. (4) Duration of RF exposure: (a) all durations, (b) ≤2 h, (c) >2–72 h, (d) year(s). (5) Cell types: (a) all cells, (b) blood lymphocytes (BL, the most studied freshly collected cell type), (c) other cultured cells (amniotic cells, brain tumor cells, glioblastoma cells, human-hamster hybrid cells, lymphoblastoid cells, lens epithelial cells, lung fibroblasts, neuroblastoma cells, skin fibroblasts, sperm cells, stem cells, trophoblast cells) including buccal cells. In addition, several researchers have conducted in vitro experiments using a known genotoxic agent before, during and/or after RF exposure to investigate the effect of combined exposures, as occurs in real life situations: the data reported in a total of 22 such publications were considered in a separate meta-analysis.

3.1. Magnitude of difference between RF-exposed and controls (E–C)

The magnitude of difference between RF-exposed and controls (E–C) was obtained using the fixed-effects model [102]. This approach provides very 'narrow' confidence intervals (CI) and more likely to find significant differences between RF-exposed and control groups. Differences in sample size as well as the variable results from one experiment to another within the same laboratory and also from one laboratory to another were taken into consideration to provide a 'weight' for each effect measuring the E–C. The pooled weighted mean and variances were used to obtain the standard error (SE) which was then used to compute the 95% CI to obtain a quantitative estimate of E–C [102]. The p-value for significant differences, if any, between RF-exposed and control groups was also calculated. The step-by-step method was described in detail earlier [a link for the details is provided at the end of the text in Ref #10].

3.2. Effect size (ES) or standardized mean difference (d)

Meta-analysis regularly uses a 'unit-less' measure to calculate the effect size (ES) or standardized mean difference (d) between RF-exposed and controls. The random-effects model [103] which is recommended by the National Research Council [105] was used in the meta-analysis. This model has several advantages such as the use of weighting by sample size (which is critical for meta-analysis), makes fewer assumptions and considers the possibility that p values can vary from one study to another. The data in each publication were considered as an independent random sample with some degree of variability, 'weighted' and corrected for 'bias'. The pooled weighted SE was then used to compute the 95% CI to obtain a quantitative estimate of ES. The step-by-step method was described in detail earlier [a link for the details is provided at the end of the text in Ref# 10].

3.3. Multiple regression analysis

The meta-analysis considered the influence of several sub-groups in each RF exposure characteristic on each genotoxicity end-point investigated. The % contribution of each sub-group from the total variability for the outcomes in E–C and ES were examined using the weighted multiple regression analysis with adjustments [101]. The 9 predictor variables in RF exposure characteristics (1 for frequency-<2000 MHz and >2000 MHz; 3 for SAR-NR, <2 W/kg, 2–5 W/kg and >5 W/kg; 2 for CP, CW and PW; 2 for exposure duration-≤2 h, >2–72 h and years; 1 for cell types-blood lymphocytes and other cultured cells), adjusted for each other, provided 'weighted' regression coefficients and sums of squares for E–C [102] and for ES [103]. The weighted regression coefficients and the sums of squares for each predictor variable, residual and total variability, and SE in multiple regressions were all obtained from SAS software [100]. The significance due to each of the predictor variables was calculated from the weighted sums of squares. This was estimated for each sub-group effect for the outcomes observed for E–C and ES for each genotoxicity end-point studied.

3.4. Heterogeneity

The degree of homogeneity or heterogeneity among the results, which is known to influence the overall conclusions, was examined in the weighted multiple regression analysis [101] using the random error for testing heterogeneity of effects to verify the validity of the models used for both E–C and ES. The residual weighted sums of squares were used in the chi-square 'goodness of fit' test (heterogeneity in E–C and ES values obtained for each end-point) with appropriate degrees of freedom [101]. When the goodness of fit test was not rejected, the regression model used was considered as adequate. When the test gave significant results, the data indicated heterogeneity, i.e., factors which were not considered in this meta-analysis had an influence on the differences between RF-exposed and control groups. Such data were further examined to explain which sub-group RF exposure characteristic contributed to the heterogeneity, to compare minimum and maximum effects in RF-exposed with those in controls, and also to interpret the magnitude of heterogeneity.

3.5. Publication 'bias'

Publication 'bias' refers to the fact that studies with statistically significant results, even with small sample size, are more likely to be published than those without statistically significant results [106]. A simple graphical 'funnel plot' [103] was used to determine whether or not a publication bias existed in the meta-analysis data-base. The data with 'no' publication bias in studies with small sample size would have the same mean ES as in those with large sample size. However, such data would indicate greater variability with wider dispersion of low and high ES values around the mean ES. On the other hand, if there is a publication bias, the smaller ES in studies with small sample size would be disproportionately absent since such studies will fail to accomplish statistical significance ($p < 0.05$).

3.6. Historical data-base

A much larger and an up-dated data-base was obtained by pooling the CA, MN and SCE indices in control cells in this meta-analysis

with those reported in Vijayalaxmi and Prihoda [10] as well as similar observations in more recent publications. The overall data obtained for each of these end-points was weighted by the sample size and variance to perform a simple descriptive meta-analysis. The overall incidence obtained for each end-point in control cells was compared with that in RF-exposed cells to provide a proper perspective in the evaluation of potential 'adverse' effects of RF exposure.

4. Data presentation

The compiled list of 88 publications, in which researchers have examined the genotoxicity in freshly collected and cultured human cells exposed to RF, was presented in chronological order in Table 1 and a summary was given in Table 2. The maximum number of publications was in the year 2008 (10/88) and, the highest number was from Italy (18/88) followed by USA (10/88). A great majority of researchers have used ≤2000 MHz RF which is utilized for wireless communication systems (71/88). The influence ≤2 W/kg SAR was examined in 37/88 studies while it was not reported in 17 papers: >2–5 and >5 W/kg SARs were investigated in 10 and 6 papers, respectively. The other 18 studies examined two or three different SARs. Investigations using PW RF exposures were the majority (45/88) while those in individuals who are occupationally exposed and mobile phone users were 14/88 papers. SBM/SBR/Foci, CA, MN and SCE were studied in 27, 9, 22 and 2 of the 88 reports, respectively. Several studies examined more than one genotoxicity end-point: 22, 5 and 1 of 88 papers for 2, 3 and 4 different end-points, respectively. Freshly collected human blood lymphocytes were the choice cell-type for many researchers (60/88 studies) while cultured cells were used in another 25/88 studies. Two different cell types were also used in 3/88 investigations. In vitro studies formed the great majority (52/88) while the combined effects of RF + a known genotoxic agent were investigated in a total of 22 studies.

The meta-analysis data obtained for the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control groups for SBM, SBR, foci, CA, MN and SCE end-points at different RF frequencies, SARs, CP-CW-PW, exposure durations and cell-types were presented in Tables 3–8, respectively. The sequence of the data presented across the columns in Tables 3–8 was: sample size (N), mean, SD and 95% CI for control and RF-exposed groups, p-value for E–C and consolidated/total sample size, E–C, SE and 95% CI. The effect size (ES or standardized difference, d), SE and 95% CI calculated for all end-points at different RF frequencies, SARs, CP-CW-PW, exposure durations and cell types were presented in Table 9. The meta-analysis data obtained for E–C (based on the sample size and variance) in cells exposed to RF + a known genotoxic agent were given in Table 10. The multiple regression analysis and goodness of fit data for E–C and ES, and % contribution of each RF exposure characteristic for each genotoxicity end-point were presented in Table 11 along with the details of significant effects in the footnotes. The heterogeneity test results were given in Table 12. The publication 'bias' in RF investigations was displayed in Fig. 1.

5. Results

5.1. Magnitude of difference between RF-exposed and control groups (E–C)

The data presented in Table 3 indicated significantly increased SBM in RF-exposed group in 9 among the 19 tests ($p < 0.05$). However, the E–C (weighted mean difference) in all tests was small and ranged between −0.05 and 3.6 μm. The observations in Table 4 also showed significantly increased SBR in RF-exposed group in 14 out of 19 tests ($p < 0.05$) although the E–C in all tests was small and ranged between −0.00 and 2.39. There was a significant decrease in foci in all 12 tests ($p < 0.05$) and the E–C in all tests was small ranging from −0.56 to −0.69 foci/cell (Table 5). In the case of CA, 12 among the 19 tests indicted significant increases in RF-exposed group ($p < 0.05$); however, the E–C in other cell types was significantly decreased (−6.50) while it was extremely small in other tests and ranged between −0.04 and 0.82 aberrations/cell (Table 6). The MN indices were similar in RF-exposed and controls in all 19 tests ($p > 0.05$) with a very small E–C ranging between 0.24 and 3.24 micronuclei/1000 cells (Table 7). The observations for SCE indicated significant increases for the RF-exposed group in 6 of 17 tests ($p < 0.05$) and the E–C in all tests was small and ranged between 0.30 and 1.02 SCE/cell (Table 8).

5.2. Standardized difference between RF-exposed and control groups (ES or, d)

The overall ES, SE and 95% CI obtained for SBM, SBR, CA, MN and SCE was very small and ranged from −1.5 to 1.2 (Table 9). The exception was 6.7 obtained for SBM (in NR, CP and years of RF exposure). The pattern of large or small ES values was similar to the corresponding large and small E–C between RF-exposed and control groups in Tables 3–8.

5.3. RF + known genotoxic agent

The mean values between the cells exposed to a known genotoxic agent alone and those exposed to RF + known genotoxic agent were not significantly different suggesting no synergistic or additive effect from the combined exposure (Table 10).

5.4. Multiple regression analysis

The multiple regression analysis data for each genotoxicity end-point for E–C and ES (or standardized difference, d) values were presented in Table 11.

In the case of E–C, except for SBM, the overall contribution to the variability observed for all other end-points due to RF frequency, SAR, CP-CW-PW, duration of RF exposure and in different cell types, was of smaller magnitude (range between 0.022% and 15.917%) as compared with that obtained for goodness of fit test (range between 82.4% and 96.8%). For SBM, the contribution due to RF exposure duration was 55.176% and the regression analysis of goodness of fit test was 44.7%. Nonetheless, most of them indicated significant effects due to one or the other RF exposure characteristic ($p < 0.05$) and such effects were explained in detail by the regression coefficients given in the footnotes in Table 11. For SBM, the effect due to <2000 MHz frequency, CW, ≤2 h exposure was lower than that due >2000 MHz frequency, PW and years of exposure, respectively ($p < 0.001$), and the effect due to 2–5 W/kg SAR was higher than that due to >5 W/kg SAR ($p = 0.007$). For SBR, the effect due to <2000 MHz, 2–5 W/kg SAR, ≤2 h exposure and BL was lower than that due to >2000 MHz, >5 W/kg SAR, years of exposure and other cell types respectively ($p < 0.001$), and the effect in the publications where SAR was not reported and CW was higher than that of >5 W/kg SAR and PW, respectively ($p < 0.001$). For foci, the effect due to ≤2 h exposure was lower than that observed in >2–72 h exposure ($p = 0.008$). For CA, the effect observed in CP was lower than that observed in PW exposure ($p = 0.002$), and the effect observed in reports where SAR was not reported, ≤2 h exposure and BL was higher than that due to >5 W/kg SAR, years of exposure and other cell types ($p < 0.001$, $p = 0.006$ and $p = 0.009$), respectively. For MN, the effect due to <2000 MHz frequency, <2 W/kg SAR, CW and BL was lower than that due >2000 MHz frequency, >5/kg SAR, PW respectively and other cell types ($p < 0.001$), and the effect

Table 1
List of publications during 1990–2011 in chronological order.

Pub#	First Author, Year	Country	Study	Frequency, MHz	SAR, W/kg	CP, CW, Pw[a]	Cells[b]	End point[c]	Addition[d]
1	Garaj-Vrhovac, 1990	Croatia	InVIVO	2000	NR	CP	BL	CA, MN	
2	Garson, 1991	Australia	InVIVO	2000	NR	CP	BL	CA	
3	Fucic, 1992	Croatia	InVIVO	2000	NR	CP	BL	MN	
4	Garaj-Vrhovac, 1992	Croatia	InVitro	7700	NR	CW	BL	CA, MN	
5	Garaj-Vrhovac, 1993	Croatia	InVIVO	1250–1350	NR	CP	BL	CA	
6	Maes, 1993	Belgium	InVitro	2450	75.0	PW	BL	CA, MN, SCE	
7	d'Ambrosio, 1995	Italy	InVitro	9000	90.0	CW	BL	MN	
8	Maes, 1995	Belgium	InVIVO/ InVitro	450–900, 954	1.56	CP, PW	BL	CA	
9	Eberle, 1996	Germany	InVitro	440	4.0	PW	BL	CA, MN, SCE	
10	Maes, 1996	Belgium	InVitro-PM	954	1.5	PW	BL	SCE	MC
11	Antonopoulos, 1997	Germany	InVitro	380, 900, 1800	0.08, 0.2, 1.7	PW	BL	SCE	
12	Maes, 1997	Belgium	InVitro-PM	935.2	0.3–0.4	PW	BL	SBM, SBR, CA, SCE	MC
13	Malyapa, 1997a	USA	InVitro	2450	0.7–1.9	CW	GB	SBM, SBR	
14	Malyapa, 1997b	USA	InVitro	835.6, 847.7	0.6	CW, PW	GB	SBM, SBR	
15	Vijayalaxmi, 1997	USA	InVitro	2450	12.5	CW	BL	CA, MN	
16	Phillips, 1998	USA	InVitro	813.6, 836.6	0.0024, 0.0026, 0.024, 0.026	PW	LB	SBR	
17	Garaj-Vrhovac, 1999	Croatia	InVIVO	1250–1350	NR	CP	BL	MN	
18	Maes, 2000	Belgium	InVitro-PM	455.7	6.50	PW	BL	SCE, CA	MC, XR
19	Vijayalaxmi, 2000	USA	InVitro	2450	2.1	PW	BL	SBM, SBR	
20	Zotti-Martelli, 2000	Italy	InVitro	2450, 7700	NR	CW	BL	MN	
21	Lalic, 2001	Croatia	InVIVO	8000	NR	CP	BL	CA	
22	Maes, 2001	Belgium	InVIVO/ InVitro-PM	900	1.5–10	PW	BL	SCE, CA	MC, XR
23	Othman, 2001	Egypt	InVIVO	2000	NR	CP	BL	Aneuploidy	
24	Vijayalaxmi, 2001a	USA	InVitro	835.6	4.4, 5	CW	BL	CA, MN	
25	Vijayalaxmi, 2001b	USA	InVitro	847.7	4.9, 5.5	PW	BL	CA, MN	
26	d'Ambrosio, 2002	Italy	InVitro	1748	5.0	CW, PW	BL	MN	
27	Cavallo, 2002	Italy	InVIVO	1800	NR	CP	BL	SBR	
28	McNamee, 2002a	Canada	InVitro	1900	0.1, 0.3, 0.9, 2.4, 10	CW	BL	MN, SBM, SBR	
29	McNamee, 2002b	Canada	InVitro	1900	0.1, 0.3, 0.9, 2.4, 10	PW	BL	MN, SBM, SBR	
30	Miyakoshi, 2002	Japan	InVIVO	2450	50, 100	CW	BT	SBR	
31	Tice, 2002	USA	InVitro	837, 1909.8	1, 1.6, 2.5, 2.9, 5, 10	CW, PW	BL	MN, SBM, SBR	
32	Zang, 2002	China	InVitro-PM	2450	2.0	PW	BL	SBM, MN	MC
33	Gadhia, 2003	India	InVIVO/ InVitro-PM	960	NR		BL	CA, SCE	MC
34	Mashevich, 2003	Israel	InVitro	830	2.0, 2.9,4.3, 8.2	CW	BL	Aneuploidy	
35	McNamee, 2003	Canada	InVitro	1900	0.1, 0.3, 0.9, 2.4, 10	CW, PW	BL	MN, SBM, SBR	
36	Othman, 2003	Egypt	InVIVO	2000	NR	CP	BL	CA, SCE	
37	Scarfi, 2003	Italy	InVitro	120,000, 140,000	2.0	PW	BL	MN	
38	Zeni, 2003	Italy	InVitro	900	1.6	CW, PW	BL	MN	
39	Figueiredo, 2004	Brazil	InVitro-PM	2500, 10,500	626.7	CW	BL	CA	GR
40	Hook, 2004	USA	InVitro	813.6, 835.6, 836.5, 847.7	0.0024, 0.0026, 0.024, 0.026, 3.2	CW, PW	LB	SBM, SBR	
41	Baohong, 2005	China	InVitro-PM	1800	3.0	PW	BL	SBM, SBR	BL, MC, MS, 4NQ
42	Belyaev, 2005	Sweeden	InVitro	915	0.04	PW	BL	FOCI	
43	Diem, 2005	Austria	InVitro	1800	1.2, 2	CW, PW	SF	SBR	
44	Gandhi, 2005a	India	InVIVO	1800	NR	CP	BC, BL	CA, MN	
45	Gandhi, 2005b	India	InVIVO	1800	NR	CP	BL	MN, SBM	
46	Markova, 2005	Sweeden	InVitro	905, 915	0.04	PW	BL	FOCI	
47	Zeni, 2005	Italy	InVitro	900	0.3, 1	PW	BL	SBR, CA, SCE	
48	Zotti-Martelli, 2005	Italy	InVitro	1800	NR	CW	BL	MN	
49	Chemeris, 2006	Russia	InVitro	8800	1600.0	PW	BL	SBM	
50	Lixia, 2006	China	InVitro	1800	1, 2, 3	PW	LE	SBM, SBR	

Table 1 (*Continued*)

Pub#	First Author, Year	Country	Study	Frequency, MHz	SAR, W/kg	CP, CW, Pw[a]	Cells[b]	End point[c]	Addition[d]
51	Maes, 2006	Belgium	InVIVO/ InVitroPM	900	NR	CP	BL	SBM, CA, SCE	MC
52	Sakuma, 2006	Japan	InVitro	2000	0.08, 0.25, 0.8	CW, PW	GB, LF	SBM, SBR	
53	Sannino, 2006	Italy	InVitro	1950	0.5, 2	PW	BL	SBR	
54	Scarfi, 2006	Italy	InVitro	900	1, 5, 10	PW	BL	MN	
55	Stronati, 2006	Italy	InVitro-PM	935	2.0	PW	BL	CA, MN, SCE, SBM, SBR, SCE	XR
56	Vijayalaxmi, 2006	USA	InVitro	2450, 8200	2.1, 20.73	CW	BL	CA, MN	
57	Baohong, 2007	China	InVitro-PM	1800	3.0	PW	BL	SBM, SBR	UV
58	Schmid, 2007	Germany	InVitro	835	0.01	PW	HH	Spindle	
59	Speit, 2007	Germany	InVitro	1800	2.0	CW	SF	SBR, MN	
60	Zeni, 2007	Italy	InVitro	12,000, 13,000	0.0004	PW	BL	MN, SBM, SBR	
61	Korenstein-Ilan, 2008	Israel	InVitro	10,000	2.0	CW	BL	Aneuploidy	
62	Manti, 2008	Italy	InVitro-PM	1950	0.5, 2	PW	BL	CA	XR
63	Mazor, 2008	Israel	InVitro	800	2.9, 4.1	CW	BL	Aneuploidy	
64	Schrader, 2008	Germany	InVitro	835	0.0115	PW	HH	Spindle	
65	Schwarz, 2008	Austria	InVitro	1950	0.05, 0.1, 0.5, 1, 2	PW	SF	SBR, MN	
66	Tiwari, 2008	India	InVitro-PM	835	1.17	PW	BL	SBM, SBR	APC
67	Valbonesi, 2008	Italy	InVitro	1817	2.0	PW	TR	SBM, SBR	
68	Yadav, 2008	India	InVitro	1800	NR	PW	BC	MN	
69	Yao, 2008	China	InVitro-PM	1800	1, 2, 3, 4	PW	LE	SBM, SBR	NOISE
70	Zeni, 2008	Italy	InVitro	1950	2.2	PW	BL	MN, SBM, SBR	
71	Belyaev, 2009	Sweeden	InVitro	905, 915, 1947	0.145	PW	BL	FOCI	
72	DeLuliis, 2009	Australia	InVitro	1800	0.4, 1, 2, 5, 10, 27.5	PW	SP	SBR	
73	Garaj-Vrhovac, 2009	Croatia	InVIVO	1350	NR	CP	BL	CA, SBM, SBR	
74	Hansteen, 2009a	Norway	InVitro-PM	1650, 1800	2.5	CW	BL	CA	MC+/-CAF
75	Hansteen, 2009b	Norway	InVitro-PM	2300	2.5	CW	BL	CA	MC
76	Luukkonen, 2009	Finland	InVitro-PM	872	5.0	CW, PW	NB	SBR	MEN
77	Sannino, 2009a	Italy	InVitro-PM	900	1.25	PW	BL	MN	MC
78	Sannino, 2009b	Italy	InVitro-PM	900	1.00	PW	BL	SBM, SBR	MX
79	Zhijian, 2009	China	InVitro-PM	1800	2.0	PW	BL	SBR	XR
80	Bourthoumieu,2010	France	InVitro	900	0.3	PW	AC	CA	
81	Franzellitti, 2010	Italy	InVitro	1800	2.0	CW, PW	TR	SBM, SBR	
82	Hintzsche, 2010	Germany	InVitro	1800	NR	PW	BC	MN	
83	Luukkonen, 2010	Finland	InVitro-PM	872	5.0	CW, PW	NB	SBR	FE+DEM
84	Markova, 2010	Sweeden	InVitro	905, 915, 1947	0.037, 0.039	PW	SF, ST	FOCI	
85	Zhijian, 2010	China	InVitro-PM	1800	2.0	PW	LB	SBR	DOX
86	Bourthoumieu,2011	France	InVitro	900	0.25, 1, 2, 4	PW	AC	Aneuploidy	
87	Hintzsche, 2011	Germany	InVitro	10,600	0.0115	PW	HH	Spindle	
88	Schrader, 2011	Germany	InVitro	900	0.0115	PW	HH	Spindle	

[a] CP: Occupationally exposed/mobile phone users; CW: Continuous Wave; PW: Pulsed Wave.
[b] AC: Amniotic Cells; BC: Buccal Cells; BL: Blood Lymphocytes; BT: Brain Tumor Cells; GB: Glio-Blastoma Cells; HH: Human-Hamster Hybrid Cells; LB: Lympho-Blastoid Cells; LE: Lens Epuithelial Cells; LF: Lung Fibroblasts; NB: Neuro-Blastoma Cells; SF: Skin Fibroblasts; SP: Sperm Cells; ST: Stem Cells; TR: Trophoblast Cells.
[c] SSB/SBR/FOCI: DNA sinlge and double strand breaks; CA: Chromosomal Aberrations; MN: Micronuclei; SCE: Sister Chromatid Exchanges.
[d] APC: Aphidicolin; BL: Bleomycin; CAF: Caffeine; DEM: Diethyl Maleate; DOX: Doxorubicin; FE: Ferric Chloride; GR: Gamma-Rays; MEN: Menadione; MC: Mitomycin C; MS: Methyl Methane Sulfonate; MX: 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5h)-furanone; 4-NQO: 4-NitroQuinoline-1-Oxide; UV: UltraViolet Light; XR: X-rays.

Table 2
Publications characteristics.

			Publications
1	Year	1990-1; 1991-1; 1992-2; 1993-2; 1994-0; 1995-2; 1996-2; 1997-5; 1998-1; 1999-1; 2000-3; 2001-5; 2002-7; 2003-6; 2004-2; 2005-8; 2006-8; 2007-4; 2008-10; 2009-9; 2010-6; 2011-3.	88
2	Country	Australia-2; Austria-2; Belgium-7; Brazil-1; Canada-3; China-7; Croatia-7; Egypt-2; Finland-2; France-2; Germany-8; India-5; Israel-3; Italy-18; Japan-2; Norway-2; Russia-1; Sweden-4; USA-10.	88
3	RF Frequencies	≤2000 MHz-71; >2000 MHz-17.	88
4	SAR	NR: 17; ≤2–37; >2–5–10; >5–6; Two SARs-9; Three SARs-9.	88
5	RF transmission	CP (occupational and mobile phone users)-14; Continuous Wave-16; Pulsed Wave-45; CP and PW-1; CW and PW-12.	88
6	Genotoxicity End-points	SBM/SBR/FOCI-27; CA-9; MN-22; SCE-2; Two endpoints-22; Three endpoints-5; Four endpoints-1.	88
7	Cell types	Amniotic Cells-2; Buccal Cells-2; Blood Lymphocytes-60; Brain Tumor Cells-1; Glio-Blastoma Cells-2; Human-Hamster-Hybrids-4; Lympho-Blastoid Cells-3; Lens Epithelial Cells-2; Neuro-Blastoma Cells-2; Skin Fibroblasts-4; Sperm Cells-1; Trophoblast Cells-2; Two cell types-3.	88
8	Studies	In VIVO-13; InVIVO/InVitro-1; InVIVO/InVitro+known gentoxic agent(s)-3; In Vitro-52; In Vitro+known gentoxic agent(s)-19	88

Table 3
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for SBM.

End point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
SBM-All data														
SBM	All-Freq	424	17.0	13.1	15.73–18.23	438	18.5	13.8	17.17–19.75	ns	862	1.32	0.9	−0.47–3.11
SBM	All-SARs	424	17.0	10.6	15.97–17.99	438	18.5	11.2	17.41–19.51	ns	862	1.32	0.7	−0.14–2.77
SBM	CP-CW-PW	424	17.0	6.3	16.37–17.59	438	18.5	6.7	17.83–19.09	*	862	1.31	0.4	0.44–2.18
SBM	All-Expo	424	17.0	6.4	16.37–17.59	438	18.5	6.8	17.82–19.10	*	862	1.20	0.4	0.32–2.07
SBM	All-Cells	424	17.0	6.3	16.37–17.59	438	18.5	6.8	17.82–19.10	*	862	1.31	0.4	0.43–2.19
Frequency-MHz														
SBM	≤2000	367	17.2	13.7	15.83–18.65	381	18.9	14.4	17.47–20.37	ns	748	1.32	1.0	−0.69–3.34
SBM	>2000	57	15.3	8.2	13.13–17.48	57	15.4	8.2	13.19–17.56	ns	114	−0.05	1.5	−3.07–2.97
SAR-W/kg														
SBM	SAR NR	20	11.2	0.1	11.10–11.20	34	23.9	3.1	22.78–24.95	*	54	3.07	0.5	2.02–4.11
SBM	≤2	266	15.7	8.1	14.75–16.70	266	16.4	9.0	15.36–17.54	ns	532	1.33	0.7	−0.12–2.79
SBM	>2–5	81	22.3	18.6	18.20–26.44	81	23.0	19.3	18.68–27.23	ns	162	0.41	3.0	−5.44–6.26
SBM	>5	57	17.3	7.8	15.22–19.36	57	18.2	9.3	15.75–20.71	ns	114	−0.08	1.6	−3.24–3.08
CP-CW-PW														
SBM	CP	20	11.2	0.1	11.10–11.20	34	23.9	3.1	22.78–24.95	*	54	3.07	0.5	2.02–4.11
SBM	CW	113	17.7	4.1	16.96–18.49	113	18.5	3.9	17.75–19.22	ns	226	0.65	0.5	−0.40–1.69
SBM	PW	291	17.1	7.2	16.26–17.92	291	17.8	7.8	16.91–18.72	*	582	1.31	0.6	0.08–2.53
Exposure duration														
SBM	≤2 h	202	13.4	5.3	12.66–14.14	202	13.6	5.0	12.89–14.27	ns	404	0.01	0.5	−1.0–1.02
SBM	>2–72 h	202	21.1	7.6	20.09–22.18	202	22.4	8.7	21.22–23.63	*	404	3.56	0.8	1.97–5.14
SBM	year(s)	20	11.2	0.1	11.10–11.20	34	23.9	3.1	22.78–24.95	*	54	3.07	0.5	2.02–4.11
Cell types														
SBM	BL	225	19.3	8.3	18.20–20.37	239	21.2	8.7	20.13–22.34	ns	464	0.41	0.8	−1.14–1.95
SBM	Other Cells	199	14.4	2.1	14.07–14.67	199	15.1	2.2	14.81–15.44	*	398	1.32	0.2	0.89–1.75

due to 2–5 W/kg SAR and CP (occupational/mobile phone users) was higher than that due to >5 W/kg SAR and in PW ($p = 0.001$), respectively. Overall, for all end-points, the effect observed in blood lymphocytes was significantly lower than that recorded in other cell types ($p < 0.001$).

In the case of ES, the overall contribution to the variability observed for all end-points due to RF frequency, SAR, CP-CW-PW, duration of RF exposure and in different cell types, was of smaller magnitude (range between 0.000% and 5.996%) as compared with that obtained for goodness of fit test (range between 82.0% and 97.4%). For SBM, the effect observed in the publications where SAR was not reported was higher than that due to >5 W/kg SAR ($p < 0.001$). In contrast, for SBR, the effect observe in the publications where SAR was not reported and BL was lower than that due to >5 W/kg SAR ($p = 0.043$) and other cell types ($p = 0.002$). For foci, the effect due to ≤2 h exposure and BL was higher than that observed in >2–72 h exposure ($p = 0.028$) and other cell types ($p = 0.042$). For CA, the effect observed in reports where SAR was not reported was higher than that due to >5 W/kg SAR ($p = 0.038$). For MN, the effect due to >2–5 W/kg SAR, CP, CW, ≤2 h and >2–72 h exposures were higher than that due >5/kg SAR, PW and years of exposure ($p = 0.025$, $p < 0.001$, $p < 0.001$, $p < 0.030$ and $p < 0.026$) respectively. The effect in BL was lower than in other cell types ($p < 0.001$). Similar to the E–C data, for all these end-points, the ES effect observed

Table 4
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for SBR.

End point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
SBR-All data														
SBR	All-Freq	902	3.9	1.7	3.75–3.96	940	4.2	1.6	4.07–4.28	*	1842	1.09	0.1	0.93–1.24
SBR	All–SARs	902	3.9	1.5	3.76–3.96	940	4.2	1.5	4.08–4.28	*	1842	1.09	0.1	0.95–1.23
SBR	CP-CW-PW	902	3.9	1.3	3.77–3.94	940	4.2	1.2	4.10–4.26	*	1842	1.08	0.1	0.96–1.19
SBR	All-Expo	902	3.9	1.3	3.77–3.94	940	4.2	1.2	4.10–4.26	*	1842	1.08	0.1	0.96–1.19
SBR	All-Cells	902	3.9	1.3	3.77–3.94	940	4.2	1.2	4.10–4.26	*	1842	1.08	0.1	0.96–1.19
Frequency-MHz														
SBR	≤2000	857	3.9	1.7	3.82–4.05	895	4.3	1.7	4.16–4.38	*	1752	1.09	0.1	0.93–1.25
SBR	>2000	45	2.3	0.6	2.12–2.48	45	2.3	0.8	2.08–2.57	ns	90	0.03	0.1	−0.26–0.32
SAR-W/kg														
SBR	SAR NR	61	7.4	3.0	6.60–8.15	99	4.3	0.9	4.16–4.53	*	160	2.39	0.4	1.61–3.17
SBR	≤ 2	628	3.3	1.1	3.18–3.35	628	3.8	1.4	3.65–3.88	*	1256	1.15	0.1	1.01–1.29
SBR	>2–5	129	3.6	2.0	3.23–3.92	129	4.0	2.2	3.63–4.39	ns	258	0.04	0.3	−0.47–0.54
SBR	>5	84	6.2	1.5	5.84–6.50	84	7.3	1.8	6.95–7.72	ns	168	−0.00	0.3	−0.50–0.50
CP-CW-PW														
SBR	CP	61	7.4	3.0	6.60–8.15	99	4.3	0.9	4.16–4.53	*	160	2.39	0.4	1.61–3.17
SBR	CW	230	4.4	1.3	4.19–4.52	230	4.6	1.4	4.37–4.73	*	460	1.48	0.1	1.23–1.72
SBR	PW	611	3.3	0.8	3.25–3.38	611	4.0	1.2	3.92–4.11	*	1222	0.76	0.1	0.64–0.87
Exposure duration														
SBR	≤2 h	340	3.1	1.0	3.02–3.24	340	3.7	1.2	3.61–3.87	ns	680	0.02	0.1	−0.15–0.19
SBR	>2–72 h	501	3.9	1.0	3.84–4.01	501	4.4	1.3	4.33–4.56	*	1002	1.48	0.1	1.34–1.62
SBR	year (s)	61	7.4	3.0	6.60–8.15	99	4.3	0.9	4.16–4.53	*	160	2.39	0.4	1.61–3.17
Cell types														
SBR	BL	492	5.0	1.6	4.89–5.18	530	4.6	1.4	4.51–4.74	ns	1022	0.04	0.1	−0.15–0.22
SBR	Other Cells	410	2.4	0.5	2.40–2.50	410	3.6	1.0	3.51–3.70	*	820	1.12	0.1	1.01–1.23

Table 5
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for foci.

End Point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
FOCI-All data														
FOCI	All-Freq	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
FOCI	All-SARs	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
FOCI	CP-CW-PW	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
FOCI	All-Expo	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
FOCI	All-Cells	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
Frequency-MHz														
FOCI	≤2000	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
SAR-W/kg														
FOCI	≤2	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
CP-CW-PW														
FOCI	PW	186	1.4	0.5	1.32–1.47	186	0.7	0.7	0.62–0.83	*	372	−0.61	0.1	−0.74–0.48
Exposure duration														
FOCI	≤2 h	102	1.5	0.6	1.39–1.62	102	0.8	0.9	0.62–0.98	*	204	−0.69	0.1	−0.90–0.47
FOCI	>2–72 h	84	1.3	0.4	1.17–1.36	84	0.6	0.4	0.54–0.72	*	168	−0.56	0.1	−0.69–0.43
Cell types														
FOCI	BL	114	0.9	0.3	0.84–0.95	114	0.6	0.9	0.41–0.73	*	228	−0.60	0.1	−0.77–0.44
FOCI	Other Cells	72	2.2	0.8	2.02–2.38	72	1.0	0.5	0.85–1.07	*	144	−0.67	0.1	−0.88–0.46

in blood lymphocytes was lower than that recorded in other cell types ($p = 0.042$ to $p < 0.001$). All of these multiple regression data for SBM, SBR, foci, CA and MN were similar to the univariate analysis results in Tables 3–7 where as the MN data were either different or similar to the results in Table 2.

Considering the multiple regression analysis data from E–C and ES together, there was no consistent pattern in all RF exposure characteristics on all genotoxicity end-points. The goodness of fit test revealed that the factors other than those considered in the meta-analysis could explain the RF effects reported in the publications.

5.5. Heterogeneity

The heterogeneity test results were presented in Table 12. In general, the overall data indicated that all of the E–C effects for SBM, foci, CA, MN and SCE were within ~5% range in control cells: 0% for SBM (0 of 99), 7.6% for SBR (17 of 223), 2.5% for foci (1 of 40), 5.5% for CA (3 of 55) and 0% for SCE (0 of 16). For MN, however, 16% of the effects were outside the normal range (30 of 187). The footnotes in Table 11 described the details of significant heterogeneity effects.

Further analyses were focused on whether or not the investigations were free of observational and other 'biases' in data collection as well as in the management, and thus the overall quality of publications. The Excel spreadsheet contained the information whether or not the investigators included sham- and/or un-exposed controls, positive-controls, detailed descriptions of dosimetry and experimental protocols/methods, data collection procedures, 'blind' evaluations, appropriate statistical analyses, concurrence of the conclusions in the abstract and in the text with the data presented in tables and figures. When one or more of these was not mentioned, the publication was considered 'low' quality in the meta-analysis. (1) For SBR, when the investigators did not

Table 6
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for chromosomal aberrations/100 cells.

End point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
CA-All data														
CA	All-Freq	371	2.0	2.1	1.81–2.24	418	3.6	2.3	3.38–3.82	*	789	0.64	0.2	0.34–0.95
CA	All-SARs	371	2.0	2.1	1.81–2.24	418	3.6	2.3	3.38–3.82	*	789	0.64	0.2	0.34–0.95
CA	CP-CW-PW	371	2.0	2.1	1.81–2.24	418	3.6	2.3	3.38–3.82	*	789	0.64	0.2	0.34–0.95
CA	All-Expo	371	2.0	2.1	1.81–2.24	418	3.6	2.3	3.38–3.82	*	789	0.64	0.2	0.34–0.95
CA	All-Cells	371	2.0	2.1	1.81–2.24	418	3.6	2.3	3.38–3.82	*	789	0.64	0.2	0.34–0.95
Frequency-MHz														
CA	≤2000	332	1.9	2.1	1.69–2.15	380	3.6	2.3	3.36–3.82	*	712	0.64	0.2	0.32–0.97
CA	>2000	39	3.0	1.8	2.39–3.54	38	3.8	2.0	3.11–4.39	ns	77	0.62	0.4	−0.22–1.45
SAR-W/kg														
CA	SAR NR	197	1.5	2.4	1.11–1.79	245	4.0	2.4	3.74–4.34	*	442	0.82	0.2	0.36–1.27
CA	≤2	62	2.4	1.3	2.09–2.75	62	2.5	1.8	1.99–2.92	ns	124	−0.04	0.3	−0.60–0.53
CA	>2–5	63	3.0	1.8	2.58–3.49	63	3.5	2.4	2.85–4.07	ns	126	0.13	0.4	−0.61–0.88
CA	>5	49	2.6	1.5	2.11–3.00	48	3.0	1.7	2.55–3.52	ns	97	0.51	0.3	−0.13–1.14
CP-CW-PW														
CA	CP	192	1.5	2.5	1.10–1.80	240	4.0	2.4	3.70–4.32	*	432	0.81	0.2	0.35–1.28
CA	CW	29	1.9	0.7	1.62–2.15	28	2.7	1.0	2.30–3.05	ns	57	0.39	0.2	−0.05–0.83
CA	PW	150	2.8	1.6	2.53–3.05	150	3.1	2.1	2.78–3.45	ns	300	−0.02	0.2	−0.44–0.40
Exposure duration														
CA	≤2 h	111	2.5	1.4	2.21–2.73	110	3.2	1.9	2.87–3.57	*	221	0.62	0.2	0.19–1.06
CA	>2–72 h	68	2.9	1.8	2.50–3.36	68	2.8	2.2	2.23–3.30	ns	136	−0.04	0.3	−0.72–0.63
CA	year (s)	192	1.5	2.5	1.10–1.80	240	4.0	2.4	3.70–4.32	*	432	0.81	0.2	0.35–1.28
Cell types														
CA	BL	367	1.9	2.1	1.68–2.11	414	3.6	2.2	3.35–3.78	*	781	0.64	0.2	0.34–0.95
CA	Other Cells	4	14.0	4.0	7.64–20.36	4	7.5	3.7	1.56–13.44	*	8	−6.50	2.7	−11.86 to −1.14

In a large data-base, the damage indices in *human* blood lymphocytes: CA-2.2 in 100 cells (SD ± 2.5, $N = 25,775$); MN-8.6 in 1000 cells (SD ± 7.7, $n = 14,888$); SCE-7.5 in a cell (SD ± 1.9, $N = 6891$).

Table 7
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for micronuclei/1000 cells.

End point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total N	Mean	SE	CI (95%)
MN -All data														
MN	All-Freq	1357	21.8	10.4	21.29–22.40	1250	34.5	19.9	33.39–35.60	ns	2607	0.56	0.6	−0.67–1.80
MN	All-SARs	1357	21.8	10.4	21.29–22.40	1250	34.5	19.9	33.39–35.60	ns	2607	0.56	0.6	−0.67–1.79
MN	CP-CW-PW	1357	21.8	10.4	21.29–22.40	1250	34.5	19.9	33.40–35.60	ns	2607	0.56	0.6	−0.67–1.79
MN	All-Expo	1357	21.8	10.4	21.29–22.40	1250	34.5	19.9	33.40–35.60	ns	2607	0.56	0.6	−0.67–1.79
MN	All-Cells	1357	21.8	10.4	21.29–22.40	1250	34.5	19.9	33.40–35.60	ns	2607	0.56	0.6	−0.67–1.79
Frequency-MHz														
MN	≤2000	1177	17.4	9.0	16.92–17.95	1070	30.3	19.8	29.11–31.48	ns	2247	0.56	0.7	−0.74–1.85
MN	>2000	180	50.7	17.9	48.09–53.34	180	59.5	20.5	56.46–62.49	ns	360	3.24	2.0	−0.73–7.21
SAR-W/kg														
MN	SAR NR	577	3.3	2.1	3.09–3.43	470	17.9	19.4	16.17–19.70	ns	1047	0.63	0.9	−1.14–2.39
MN	≤2	475	27.6	12.7	26.43–28.72	475	33.7	15.0	32.35–35.05	ns	950	0.55	0.9	−1.21–2.32
MN	>2–5	220	62.4	18.5	59.89–64.82	220	79.2	30.1	75.17–83.16	ns	440	0.24	2.4	−4.43–4.91
MN	>5	85	11.1	5.9	9.86–12.41	85	14.9	6.9	13.46–16.43	ns	170	0.60	1.0	−1.33–2.53
CP-CW-PW														
MN	CP	95	10.3	2.2	9.86–10.77	158	29.9	29.8	25.21–34.57	ns	253	0.64	2.4	−4.02–5.31
MN	CW	472	49.6	16.6	48.11–51.12	472	62.3	23.8	60.18–64.48	ns	944	0.38	1.3	−2.24–3.00
MN	PW	790	6.6	5.2	6.28–7.00	620	14.5	11.4	13.58–15.39	ns	1410	0.55	0.5	−0.42–1.52
Exposure duration														
MN	≤2 h	344	23.6	10.7	22.45–24.73	344	28.9	14.8	27.32–30.46	ns	688	0.55	1.0	−1.38–2.48
MN	>2–72 h	441	44.6	16.2	43.04–46.08	441	56.2	23.3	54.00–58.36	ns	882	0.56	1.4	−2.09–3.21
MN	year (s)	572	3.3	2.1	3.11–3.45	465	18.1	19.5	16.30–19.86	ns	1037	0.63	0.9	−1.15–2.41
Cell types														
MN	BL	740	36.1	13.6	35.07–37.03	803	45.3	23.3	43.71–46.94	ns	1543	0.54	1.0	−1.35–2.43
MN	Other Cells	617	4.8	4.9	4.42–5.19	447	15.0	11.8	13.95–16.14	ns	1064	0.56	0.6	−0.60–1.72

In a large data-base, the damage indices in *human* blood lymphocytes: CA - 2.2 in 100 cells (SD ± 2.5, *N* = 25, 775); MN-8.6 in 1000 cells (SD ± 7.7, *N* = 14,888); SCE-7.5 in a cell (SD ± 1.9, *N* = 6891).

mention the inclusion of positive controls, 28.6% effects (12/42) were outside the range in control cells where as when such positive control cells were included in the study, only 2.8% effects (5/181) were outside the range in control cells. Also, 13% effects (17/131) were outside the range in control cells in 'low' quality publications while 0% effects (0/92) were outside the range in other publications. (2) For CA, 10% effects (2/20) and 2.9% effects (1/35) were outside the range in control cells in 'low' quality and other publications, respectively. (3) For MN end-point, when the authors did not mention 'blind' procedure during data collection, 42.2% effects (27/64) were outside the range in control cells and, when such procedure was used, only 2.4% effects (3/123) were outside the range in control cells. Also, 20% effects (27/135) and 5.8% effects (3/52) were outside the range in control cells in 'low' quality and in other publications, respectively. The latter 5.8% effects were observed in only one publication. Thus, the quality of publications had helped to explain the larger E–C effects for SBR (13.0–28.6%) and MN (20–42.2%). Furthermore, considerable reduction in residual variability with improved goodness of fit was obtained in the weighted multiple regression analysis when the inclusion of positive controls for SBR

Table 8
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between RF-exposed and control cells for sister chromatid exchanges/cell.

End point		Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
SCE-All data														
SCE	All-Freq	140	4.5	4.9	3.67–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71
SCE	All-SARs	140	4.5	4.9	3.68–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71
SCE	CP-CW-PW	140	4.5	4.9	3.68–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71
SCE	All-Expo	140	4.5	4.9	3.68–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71
SCE	All-Cells	140	4.5	4.9	3.68–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71
Frequency-MHz														
SCE	≤2000	136	4.5	4.9	3.63–5.30	192	5.0	4.1	4.39–5.57	ns	328	0.71	0.5	−0.30–1.73
SCE	>2000	4	5.5	0.2	5.13–5.84	4	6.1	0.6	5.11–7.15	*	8	0.74	0.3	0.07–1.41
SAR-W/kg														
SCE	SAR-NR	55	3.8	0.9	3.52–4.00	111	4.8	1.0	4.64–5.00	*	166	1.02	0.2	0.72–1.31
SCE	≤2	65	4.6	7.1	2.82–6.35	65	4.8	7.1	3.02–6.55	ns	130	0.32	1.2	−2.13–2.77
SCE	>2–5	12	6.9	0.7	6.44–7.32	12	7.2	1.0	6.61–7.81	ns	24	0.33	0.3	−0.34–1.00
SCE	>5	8	5.2	0.3	4.95–5.52	8	6.0	0.7	5.43–6.52	*	16	0.78	0.3	0.27–1.29
CP-CW-PW														
SCE	CP	55	3.8	0.9	3.52–4.00	111	4.8	1.0	4.64–5.00	*	166	1.02	0.2	0.72–1.31
SCE	PW	85	5.0	6.3	3.61–6.33	85	5.2	6.3	3.87–6.60	ns	170	0.46	1.0	−1.44–2.36
Exposure duration														
SCE	≤2 h	36	6.0	0.8	5.75–6.28	36	6.4	1.0	6.10–6.79	*	72	0.56	0.2	0.14–0.99
SCE	>2–72 h	49	4.2	8.1	1.89–6.52	49	4.4	8.1	2.04–6.67	ns	98	0.30	1.6	−2.90–3.49
SCE	year (s)	55	3.8	0.9	3.52–4.00	111	4.8	1.0	4.64–5.00	*	166	1.02	0.2	0.72–1.31
Cell types														
SCE	BL	140	4.5	4.9	3.68–5.32	196	5.0	4.1	4.42–5.58	ns	336	0.72	0.5	−0.28–1.71

In a large data-base, the damage indices in *human* blood lymphocytes: CA - 2.2 in 100 cells (SD ± 2.5, *N* = 25, 775); MN-8.6 in 1000 cells (SD ± 7.7, *N* = 14,888); SCE-7.5 in a cell (SD ± 1.9, *N* = 6891).

Table 9
Meta-analysis data obtained for effect size (ES or standardized difference, *d*) for DNA strand breaks evaluated as comet tail length/moment/ratio/factor/foci (SBM/SBR/FOCI), chromosomal aberrations/100 cells (CA), micronuclei/1000 cells (MN) and sister chromatid exchanges/cell (SCE).

	SBM			SBR			FOCI			CA			MN			SCE		
	ES(*d*)	SE	CI (95%)	ES(*d*)	SE	CI (95%)	ES(*d*)	SE	CI (95%)	ES(*d*)	SE	CI (95%)	ES(*d*)	SE	CI (95%)	ES(*d*)	SE	CI (95%)
Frequency (MHz)																		
All	0.3	0.1	0.2–0.5	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.4–0.8
≤2000	0.4	0.1	0.2–0.6	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.3–0.8
>2000	0.0	0.2	−0.4–0.4	0.2	0.3	−0.4–0.7	–	–	–	0.5	0.4	−0.3–1.2	0.6	0.1	0.4–0.9	0.8	1.3	−1.7–3.3
SAR (W/kg)																		
All	0.3	0.1	0.2–0.5	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.4–0.8
NR	6.7	0.7	5.2–8.1	−0.6	0.2	−0.9 to −0.2	–	–	–	0.6	0.1	0.3–0.9	0.5	0.1	0.3–0.6	1.0	0.2	0.7–1.4
≤2	0.3	0.1	0.0–0.5	0.2	0.1	0.0–0.3	−1.2	0.1	−1.4 to −0.9	0.1	0.2	−0.3–0.5	0.6	0.1	0.4–0.8	0.1	0.2	−0.3–0.5
>2–5	0.4	0.2	−0.0–0.8	0.2	0.2	−0.1–0.5	–	–	–	0.2	0.3	−0.3–0.7	0.6	0.1	0.4–0.8	0.4	0.4	−0.5–1.2
>5	0.0	0.2	−0.4–0.4	0.0	0.2	−0.4–0.3	–	–	–	0.1	0.2	−0.4–0.6	0.2	0.2	−0.2–0.5	1.2	0.8	−0.3–2.6
CP-CW-PW																		
All	0.3	0.1	0.2–0.5	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.4–0.8
CP	6.7	0.7	5.2–8.1	−0.6	0.2	−0.9 to −0.2	–	–	–	0.6	0.1	0.3–0.9	1.0	0.2	0.7–1.4	1.0	0.2	0.7–1.4
CW	0.3	0.2	−0.0–0.6	0.1	0.1	−0.1–0.4	–	–	–	0.6	0.4	−0.2–1.5	0.7	0.1	0.5–0.8	–	–	–
PW	0.2	0.1	0.0–0.4	0.2	0.1	0.1–0.4	−1.2	0.1	−1.4 to −0.9	0.1	0.1	−0.1–0.4	0.4	0.1	0.2–0.5	0.2	0.2	−0.1–0.5
RF Exposure Duration																		
All	0.3	0.1	0.1–0.5	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.4–0.8
≤2 h	0.2	0.1	−0.0–0.4	0.2	0.1	−0.0–0.4	−1.0	0.2	−1.3 to −0.6	0.3	0.2	0.0–0.6	0.5	0.1	0.3–0.7	0.4	0.3	−0.2–0.9
>2–72 h	0.2	0.1	0.0–0.5	0.2	0.1	0.0–0.3	−1.4	0.2	−1.8 to −1.0	−0.2	0.2	−0.7–0.3	0.6	0.1	0.4–0.7	0.1	0.2	−0.4–0.5
year (s)	6.7	0.7	5.2–8.1	−0.6	0.2	−0.9 to −0.2	–	–	–	0.6	0.1	0.3–0.9	0.5	0.1	0.3–0.6	1.0	0.2	0.7–1.4
Cell types																		
All	0.3	0.1	0.1–0.5	0.1	0.1	−0.0–0.2	−1.2	0.1	−1.4 to −0.9	0.4	0.1	0.2–0.6	0.5	0.0	0.4–0.6	0.6	0.1	0.4–0.8
BL	0.2	0.1	0.0–0.5	−0.1	0.1	−0.2–0.1	−1.0	0.2	−1.4 to −0.7	0.4	0.1	0.2–0.6	0.6	0.1	0.4–0.7	0.6	0.1	0.4–0.8
Other Cells	0.4	0.1	0.2–0.7	0.4	0.1	0.2–0.6	−1.4	0.2	−1.9 to −1.0	−1.5	0.9	−3.3–0.4	0.5	0.1	0.3–0.6	–	–	–

and 'blind' microscopic analyses for MN in each publication was considered.

The contribution of other variables in the experimental protocols to the heterogeneity/variability in E–C and ES for different genotoxicity end-points requires further detailed multiple regression analysis. Overall, the magnitude of heterogeneity for all individual end-point effects was small and was within the normal, spontaneous range in controls.

5.6. Publication bias

The publication bias was graphically presented in Fig. 1. Although there were a total of 88 publications, some investigators have examined more than one end-point in several different RF exposure conditions. Consequently, both *X* and *Y* axis in Fig. 1 had several data points, each representing the ES value for each end-point and for each RF exposure condition and thus, gave a total of 627 effects examined. Overall, the mean ES values were not approximately at the center of 'negative' and 'positive' publications, i.e., absence or presence of a significant increase in RF-exposed cells compared with controls, respectively. The data did not appear as 'bell' shape and largely skewed towards the 'positive' publications. There were 191 data-points with −9.0 to 0.0 value (the average genotoxicity indices in control cells was higher than in RF-exposed cells), 30 data-points had 0.0 value (the average indices in RF-exposed and control cells was the same) and 406 data points had >0.0 to 365 value (the average indices in control cells was lower than in RF-exposed cells). Thus, the largely 'skewed' data indicated the existence of a significant publication bias, i.e., 'positive' publications were published even with small sample size while the 'negative' papers were published only when the sample size was large. Further detailed examination of the data indicated that 96 effects among the 627 total effects (15%) examined had ES values which were ≥2. Among these 96 effects, 75 effects (78%) were

Table 10
Meta-analysis of the magnitude of difference (E–C, based on the sample size and variance) between mutagen (known genotoxic agent) alone and RF + mutagen-exposed cells for different genotoxicity end-points.

	End point	Control Group				RF-exposed Group				*p* value	RF-exposed Group–Control Group			
		N	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)		Total *N*	Mean	SE	CI (95%)
Control	SBM	40	5.0	1.7	4.48–5.59	40	4.9	1.6	4.35–5.37		80	0.23	0.4	−0.49–0.96
Mutagen alone	SBM	73	5.2	1.3	4.93–5.55	73	13.9	2.8	13.25–14.56		146	0.02	0.4	−0.70–0.73
RF + Mutagen	SBM	115	5.6	2.5	5.11–6.02	115	12.0	2.1	11.57–12.35	ns	230	0.00	0.3	−0.59–0.59
Control	SBR	179	1.4	0.4	1.36–1.48	217	1.4	0.8	1.24–1.47		396	0.01	0.1	−0.11–0.13
Mutagen alone	SBR	206	1.3	0.4	1.26–1.35	244	5.5	5.6	4.76–6.29		450	1.17	0.4	0.48–1.87
RF + Mutagen	SBR	286	4.9	5.1	4.28–5.46	286	5.0	3.0	4.63–5.34	ns	572	−0.04	0.3	−0.72–0.65
Control	CA	85	1.8	1.4	1.53–2.13	84	2.6	2.0	2.15–3.00		169	−0.02	0.3	−0.54–0.50
Mutagen alone	CA	64	2.2	1.6	1.84–2.62	62	30.7	12.8	27.47–33.88		126	11.47	1.6	8.26–14.69
RF + Mutagen	CA	88	25.8	10.2	23.61–27.93	87	25.8	10.9	23.47–28.09	ns	175	2.06	1.6	−1.07–5.19
Control	MN	21	9.0	3.2	7.55–10.50	21	9.4	3.0	7.99–10.72		42	1.27	1.0	−0.62–3.16
Mutagen alone	MN	27	7.9	3.0	6.73–9.09	27	58.3	11.1	53.91–62.72		54	7.84	2.2	3.48–12.19
RF + Mutagen	MN	41	64.2	11.1	60.68–67.69	39	56.8	9.0	54.00–59.66	ns	80	9.44	2.3	5.02–13.85
Control	SCE	55	4.2	0.9	3.97–4.44	93	5.0	0.8	4.80–5.25		148	0.79	0.1	0.51–1.07
Mutagen alone	SCE	45	5.3	0.8	5.11–5.57	83	33.4	9.6	30.57–36.32		128	2.75	1.1	0.68–4.82
RF + Mutagen	SCE	99	22.3	7.8	20.71–23.84	97	35.7	8.5	33.96–37.37	ns	196	1.58	1.2	−0.72–3.88

ns: not significant.
In a large data-base, the damage indices in huan blood lymphocytes: CA-2.2 in 100 cells (SD ± 2.5, *N* = 25,775); MN-8.6 in 1000 cells (SD ± 7.7, *N* = 14,888); SCE-7.5 in a cell (SD ± 1.9, *N* = 6891).

Table 11
Multiple regression analysis of the magnitude of difference (E–C) and effect size (ES) between RF-exposed and control cells for different genotoxicity endpoints. Detailed explanation is given in foot-notes.

End-point		Effects examined	Frequency, MHz	SAR, W/kg	CP-CW-PW	RF exposure duration	Cell types	Regression Goodness of Fit Test
SBM	E–C	99	0.003 [a1]	0.033 [b1]	0.077 [c1]	55.176 [d1]	0.034 [e1]	44.7
SBR	E–C	223	0.078 [a2]	0.479 [b2, b3]	0.685 [c2]	15.917 [d2]	0.472 [e2]	82.4
FOCI	E–C	40	ns	ns	ns	3.204 [d3]	0.033	96.8
CA	E–C	55	0.022	13.083 [b4]	0.005 [c3]	3.386 [d4]	4.128 [e3]	79.4
MN	E–C	187	6.786 [a3]	1.736 [b5, b6]	1.614 [c4, c5]	0.143	1.008 [e4]	88.7
SCE	E–C	16	0.207	5.946	ns	0.155	ns	93.7
SBM	ES	99	1.192	0.152 [f1]	0.168	0.018	2.306	96.2
SBR	ES	223	0.212	0.002 [f2]	0.069	0.025	2.32 [i1]	97.4
FOCI	ES	40	ns	ns	ns	3.66[h1]	3.044 [i2]	93.3
CA	ES	55	2.716	0.01 [f3]	0.000	1.463	1.420	94.4
MN	ES	187	1.183	0.123 [f4]	10.24[g1, g2]	0.93 [h2, h3]	5.537 [i3]	82.0
SCE	ES	16	5.996	0.501	ns	0.206	ns	93.3

*$p \leq 0.05$ (heterogeneity in the predictor effects observed in RF exposure characteristics); ns is not significant, $p > 0.05$.
E–C: Significant changes ($p \leq 0.05$) in the effect due to:
a1: SBM: <2000 MHz RF was lower than >2000 MHz (-0.78 ± 0.23), $p < 0.001$.
b1: SBM: 2–5 W/kg SAR was higher than >5 W/kg SAR (0.58 ± 0.23), $p = 0.007$.
c1: SBM: CW was lower than PW (-2.91 ± 0.16), $p < 0.001$.
d1: SBM: ≤2 h RF exposure was lower than in year(s) (-4.25 ± 0.01), $p < 0.001$.
e1: SBM: BL are lower than in other cells (-0.71 ± 0.06), $p < 0.001$.
a2: SBR: <2000 MHz RF was lower than >2000 MHz (-0.59 ± 0.03), $p < 0.001$.
b2: SBR: not reported SAR was higher than >5 W/kg (1.60 ± 0.11), $p < 0.001$.
b3: SBR: 2–5 W/kg SAR was lower than >5 W/kg SAR (-0.43 ± 0.04), $p < 0.001$.
c2: SBR: CW was higher than PW (0.24 ± 0.00), $p < 0.001$.
d2: SBR: ≤2 h RF exposure was lower than in year(s) (-1.31 ± 0.01), $p < 0.001$.
e2: SBR: BL are lower than in other cells (-0.58 ± 0.01), $p < 0.001$.
d3: FOCI: ≤2 h RF exposure was lower than in >2–72 h exposure (-0.12 ± 0.05), $p = 0.008$.
b4: CA: not reported SAR was higher than >5 W/kg (3.23 ± 0.78), $p < 0.001$.
c3: CA: CP was lower than PW (-2.47 ± 0.83), $p = 0.002$.
d4: CA: ≤2 h RF exposure was higher than in year(s) (0.47 ± 0.22), $p = 0.016$.
e3: CA: BL are higher than in other cells (6.45 ± 2.73), $p = 0.009$.
a3: MN: <2000 MHz RF was lower than >2000 MHz (-3.44 ± 0.14), $p < 0.001$.
b5: MN: <2 W/kg SAR was lower then >5 W/kg SAR (-0.72 ± 0.06), $p < 0.001$.
b6: MN: 2–5 W/kg SAR was higher than >5 W/kg SAR (0.50 ± 0.08), $p < 0.001$.
c4: MN: CP was higher than PW (0.65 ± 0.13), $p < 0.001$.
c5: MN: CW was lower than PW (-0.92 ± 0.09), $p < 0.001$.
e4: MN: BL are lower than in other cells (-0.45 ± 0.05), $p < 0.001$.
ES: Significant changes ($p \leq 0.05$) in the effect due to:
f1: SBM: not reported SAR was higher than >5 W/kg (6.69 ± 0.80), $p < 0.001$.
f2: SBR: not reported SAR was lower than >5 W/kg (-0.48 ± 0.28), $p = 0.043$.
i1: SBR: BL are lower than other cells (-0.40 ± 0.14), $p = 0.002$.
h1: FOCI: ≤2 h RF exposure was higher than in >2–72 hr exposure (0.55 ± 0.29), $p = 0.028$.
i2: FOCI: BL are higher than other cells (0.52 ± 0.30), $p = 0.042$.
f3: CA: not reported SAR was higher than >5 W/kg (1.87 ± 1.06), $p = 0.038$.
f4: MN: >2–5 W/kg SAR was higher than >5 W/kg SAR (0.46 ± 0.23), $p = 0.025$.
g1: MN: CP was higher than PW (1.77 ± 0.30), $p < 0.001$.
g2: MN: CW was higher than PW (0.51 ± 0.14), $p < 0.001$.
h2: MN: ≤2 h RF exposure was higher than in year(s) (1.61 ± 0.86), $p = 0.030$.
h3: MN: >2–72 h RF exposure was higher than in year(s) (1.66 ± 0.85), $p = 0.026$.
i3: MN: BL are lower than other cells (-1.12 ± 0.24), $p < 0.001$.

observed in studies without positive controls and/or 'blind' analysis. In the remaining 21, only 7 effects (33%) had both ES and E–C values outside the normal range of ≥2 (with very small SDs) which contributed to the skewness for publication bias. Overall, the meta-analysis data strongly suggested the existence of a significant publication bias. Since the meta-analysis deals with the data from diverse investigations, the presence of publication bias should be considered as tentative and should be accepted in view of the reality that exists in practice in some laboratory investigations.

5.7. Comparison of CA, MN and SCE meta-analysis data with the spontaneous Indices in human blood lymphocytes

The CA, MN and SCE indices obtained in control cells in this meta-analysis were pooled together with the spontaneous frequencies reported in Vijayalaxmi and Prihoda [10] as well as similar observations reported in more recent publications. The up-dated overall spontaneous frequencies in this much larger data-base were as follows. CA: 2.2/100 cells (SD 2.5; $N = 25{,}775$); MN: 8.6/1000 cells (SD 7.7; $N = 14{,}888$) (with the exception of those studies where blind analysis was not mentioned); SCE: 7.5/cell (SD 1.9; $N = 6891$). These indices for CA, MN and SCE end-points were similar to the maximum frequencies observed in both RF-exposed and control groups in the meta-analysis.

6. Cytogenetic end-points as biomarkers for cancer risk

The importance of conducting genetic toxicology investigations is the well documented evidence for positive correlation between increased genetic damage and carcinogenesis. To the best of our knowledge, there have been no systematic analyses of DNA strand breaks with elevated carcinogenic risk. Numerous investigators have used the comet assay to examine SBM/SBR in RF-exposed cells and compared with those in control cells. The overall meta-analysis data in Tables 3 and 4 indicated significant increases in several RF exposure conditions. Some of the increases could be attributed to the modification of comet analyses and interpretation of the results [107] as well as the other issues mentioned in

Table 12
Heterogeneity in the effects observed in different genotoxicity endpoints between RF-exposed and control groups.

End point	Number of effects examined	Controls group	RF-exposed group
SBM			
Sample size		424	438
Mean		17.00	18.50
SD		13.07	13.76
Upper limit		26.14	
E–C range	99	−4.2 to18.6 (0/99 = 0%)	
SBR			
Sample size		902	940
Mean		3.90	4.20
SD		1.66	1.64
Upper limit		3.32	
E–C range	223	−2.3 to 17.0 (17/223 = 7.6%)	
Pos.Controls-Not Mentioned	42	−2.3 to 17.0 (12/42 = 28.6%)	
Pos. Controls-Mentioned	181	−2.2 to 8.6 (5/181 = 2.8%)	
Low quality publications[a]	131	−2.3 to 17.0 (17/131 = 13.0%)	
Other publications	92	−2.2 to 1.5 (0/92 = 0%)	
FOCI			
Sample size		186	186
Mean		1.40	0.70
SD		0.53	0.74
Upper limit		1.06	
E–C range	40	−3.8 to 1.1 (1/40 = 2.5%)	
CA			
Sample size		371	418
Mean		2.00	3.60
SD		2.12	2.26
Upper limit		4.24	
E–C range	55	−6.5 to 7.7 (3/55 = 5.5%)	
Low quality publicationsa	20	−6.5 to 7.7 (2/20 = 10.0%)	
Other publications	35	−4.5 to 6.1 (1/35 = 2.9%)	
MN			
Sample size		1357	1250
Mean		21.80	34.50
SD		10.39	19.89
Upper limit		20.78	
E–C range	187	−10.6 to 57.0 (30/187 = 16.0%)	
Blind analysis-Not Mentioned	64	−10.6 to 52.2 (27/64 = 42.2%)	
Blind analysis-Mentioned	123	−10.0 to 57.0 (3/123 = 2.4%)	
Low quality publications[a]	135	−10.6 to 52.2 (27/135 = 20%)	
Other publications	52	−8.8 to 57.0 (3/52 = 5.8%)	
SCE			
Sample size		140	196
Mean		4.50	5.00
SD		4.91	4.12
Upper limit		9.82	
E–C range	16	−0.4 to 1.7 (0/16 = 0%)	

[a] When the investigators did not mention one or more of the following: sham- and/or un-exposed controls, positive-controls, detailed descriptions of dosimetry and experimental protocols/methods, data collection procedures, 'blind' evaluations, appropriate statistical analyses, concurrence of the conclusions in the abstract and in the text with the data presented in Tables and Figures.

Table 12. Regarding the foci, the technique appears to be more sensitive than the neutral comet assay for the evaluation of DSB. It is important to mention that the data presented in Table 5 was reported by one research group in only 4 publications [53,57,82,95]. The results were that 905 MHz RF exposure had no effect while 915 MHz RF significantly decreased number of foci (below the levels in control cells) immediately as well as several hours after exposure (repair foci). The authors mentioned that the latter RF frequency had induced long-lasting inhibition of DNA repair. Comparison of these data with those obtained using the neutral comet assay could not be made since there was only one such publication where the results reported were contradictory, i.e., significantly increased DSB in RF-exposed cells compared with that in controls [54].

Several researchers have conducted a systematic analysis of the spontaneous incidence of CA as a biomarker to predict carcinogenic risk in humans. The conclusions from several scientific reviews have indicated that the frequencies of CA were increased even prior to the clinical manifestation of disease indicating their correlation with increased cancer risk [108–116]. The meta-analysis results in Table 6 and the multiple regression analysis in Table 11 indicated significant increases in CA in several RF exposure conditions. However, the heterogeneity results (Table 12) indicated none of the E–C effects were outside of the range in control cells while 10% of the effects were in 'low' quality publications. More importantly, the indices in RF-exposed and control cells were within the spontaneous frequencies reported in the large data-base. Hence, caution should be exercised to interpret the elevated CA with increased brain cancer reported in human epidemiological investigations [11].

Several reviewers have presented the evidence that increased incidence of MN predicts enhanced cancer risk in humans [117–121]. It is well documented in the literature that MN arise as a result of clastogenic (chromosome breakage) and/or aneugenic (lagging and/or unequal segregation of whole chromosomes caused by spindle disturbances during cell division) action of genotoxic agent. Hence, a positive correlation is known to exist between MN and CA end-points. The meta-analysis data between MN and CA end-points did not indicate such positive correction in all of the tests: no significant differences were observed between RF-exposed and control cells in all 19 tests for MN where as 12 of

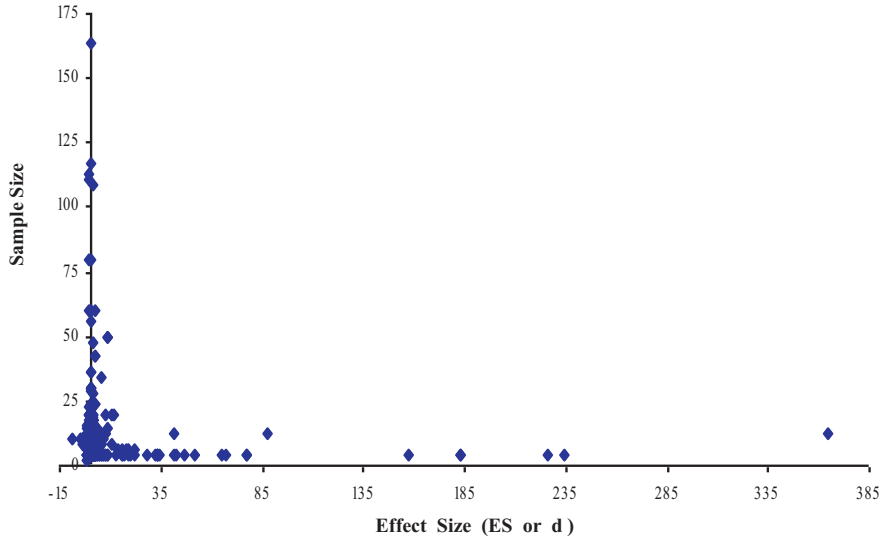

Fig. 1. The 'skewed' publication bias reporting 'positive' results (significant difference between RF-exposed and control groups of cells) with small sample size. In the figure, there are a total of 627 data-points. Each data-point represented one effect for each genotoxicity end-point in each publication in RF-exposed and control conditions: (i) 191 data-points indicated <0 value (the average genotoxicity indices in control cells was higher than in RF-exposed cells), 30 data-points had 0 value (the average indices in RF-exposed and control cells were the same) and, 406 data-points had >0 value (the average indices in control cells was lower than in RF-exposed cells). Detailed explanation is given in the text.

19 tests showed significant increases for CA. However, a more detailed multiple regression analysis (Table 11) and heterogeneity tests (Table 12) revealed significant increases in MN in certain exposure conditions: the quality of publications as well as the other factors that were not considered in the meta-analysis contributed to the increases in MN. Overall, the MN as well as CA indices in both RF-exposed and control cells were within the spontaneous indices in the large data-base and thus, there was, indeed, a positive correlation between the two end-points. Therefore, caution should be exercised to interpret the elevated MN with increased brain cancer reported in human epidemiological investigations [11].

The meta-analysis data indicated significant increases in SCE in several RF exposure conditions (Table 8) although the consolidated data reported in the literature did not appear to have a predictive value for increased cancer risk [122].

The data from the investigations in which human cells were exposed in vitro to a genotoxic agent before, during or after RF exposure indicated no significant synergistic or additive effects of the combined exposure (Table 10). Thus, RF exposure may not cause additional carcinogenic risk other than that exerted by the genotoxic agent(s).

Finally, the overall conclusions in the current meta-analysis were similar to those reported in our earlier meta-analysis publication [10]. The differences, if any, might be due to the fact that the observations reported in human cells only were considered in the former while those in both animal and human cells were considered together in the latter. An up-date of our earlier publication [10] will resolve if all of the former conclusions are still valid or would become stronger. Such an up-date is under-way now.

7. Perspective from meta-analysis and conclusion

The impetus for the meta-analysis of genotoxicity data in human cells came from the recent IARC classification of RF exposure as 'possibly carcinogenic to humans' in group 2B [11]. Since most genotoxic agents are also carcinogens and, non-genotoxic agents can contribute to the development of cancer by enhancing the damage induced by known genotoxic agents, the focus in this meta-analysis was human cells and to determine whether significant increases in genetic damage in RF-exposed human cells (compared to those in sham-/un-exposed controls) would provide a mechanistic basis for IARC classification. As mentioned above, there was no systematic analysis of SBM, SBR and foci data to predict carcinogenic risk. The CA, MN and SCE frequencies obtained in the meta-analyses indicated significant increases at certain RF exposure conditions and the quality of publications had a large impact on such increases. Overall, the genotoxicity indices in RF-exposed and un-exposed controls were within the spontaneous indices reported in the large data-base. Since no single genotoxic end-point, by itself, is capable of determining the genotoxic potential and the consequent cancer risk from occupational and environmental agents [123], it is relevant to include more than one genotoxicity end-point and good quality DNA damage assessments in future RF research investigations.

The International Commission for Non-Ionizing Radiation Protection [124] and the Institute of Electrical and Electronic Engineers [125] have recommended safety exposure guidelines (based on the threshold for behavior disruption at 4 W/kg whole body averaged SAR) to protect the personnel who are occupationally exposed to RF as well as the general public. The recommended whole body average SAR for occupationally exposed personnel was 0.4 W/kg (1/10th safety factor) while that for the general public was 0.08 W/kg (1/50th safety factor). For localized exposure for head/brain in mobile phone users, the recommendation was 2.0 W/kg/10 g average (10 W/kg/10 g average for professional two-way radios). When the investigations were conducted under these recommended safety guidelines, the overall genotoxicity indices obtained in the meta-analysis for all genotoxicity end-points were similar in RF-exposed and controls, and the mean differences (E–C) between the two groups due to RF exposure were small. The same is true for the effect size (ES) as well. It is important to mention again that the mean indices for CA and MN end-points in RF-exposed and controls were within the spontaneous levels reported in the large data-base. In a more recent meta-analysis and systematic review, Repacholi et al. [126] have concluded that the data from not only genotoxicity studies but also from in vivo oncogenicity, tumor promotion, brain and other head tumors do not support a causal relationship between RF exposure emitted from mobile phones and the incidence of brain cancer or other tumors of the head. Overall, the classification of RF as 'possibly carcinogenic to humans' in group

2B [11] was not supported by genotoxicity-based mechanistic evidence.

Conflict of interest

Both authors declare no conflict of interest.

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