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Genetic Damage in Mammalian Somatic Cells Exposed to Radiofrequency Radiation: A Meta-analysis of Data from 63 Publications (1990–2005)

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During the last several decades, numerous researchers have examined the potential of *in vitro* and/or *in vivo* exposure of radiofrequency (RF) radiation to damage the genetic material in mammalian somatic cells. A meta-analysis of reported data was conducted to obtain a quantitative estimate (with 95% confidence intervals) of genotoxicity in RF-radiation-exposed cells compared with sham-exposed/unexposed control cells. The extent of genotoxicity was assessed for various end points, including single- and double-strand breaks in the DNA, incidence of chromosomal aberrations, micronuclei and sister chromatid exchanges. Among the several variables in the experimental protocols used in individual investigations, the influence of three specific variables related to RF-radiation exposure characteristics was examined in the meta-analysis: frequency, specific absorption rate, and exposure as continuous-wave, pulsed-wave and occupationally exposed/cell phone users. The overall data indicated that (1) the difference between RF-radiation-exposed and sham-/unexposed controls as well as the effect size or standardized mean difference due to RF-radiation exposure was small with very few exceptions; (2) at certain RF radiation exposure conditions, there were statistically significant increases in genotoxicity for some end points; and (3) the mean indices for chromosomal aberrations and micronuclei in RF-radiation-exposed and sham-/unexposed controls were within the spontaneous levels reported in the historical database. Considerable evidence for publication bias was found in the meta-analysis. © 2008 by Radiation Research Society

INTRODUCTION

Meta-analysis uses several quantitative statistical methods for the review, reduction and analysis of large bodies of data. It is widely used in biomedical research, especially when the outcomes in different investigations are contradictory. The main difficulty in integrating the results from different investigations stems from the diverse designs and methods used. Some experiments could have been conducted under well-controlled conditions while the others might not have been, and the results might not have been similar. Furthermore, when the sample sizes are different, each study will have a different sampling error. Armitage (*1*) emphasized the importance of using precise methods to analyze the data to draw inferences from heterogeneous but logically related studies.

Induction of damage to the DNA in somatic cells can lead to the development of cancer and/or cell death. During the last several decades, researchers have investigated the extent of genetic damage in mammalian somatic cells exposed *in vitro* and/or *in vivo* to radiofrequency (RF) radiation in the range of 300 MHz to 300 GHz. The damage was assessed using one or more end points, including single- and double-strand breaks (SSBs/DSBs), chromosomal aberrations, micronuclei and sister chromatid exchanges (SCE). Vijayalaxmi and Obe (*2*) made a qualitative assessment of the data from 53 peer-reviewed scientific publications during 1990–2003. They concluded that the results of a majority of the studies (58%) did not indicate significantly increased damage in RF-radiation-exposed cells compared with sham-/unexposed cells (hereafter referred to as controls). However, an increase in such damage in RF-radiation-exposed cells was reported in some investigations (23%). The observations from the other studies (19%) were inconclusive. The details presented in the publications revealed several differences among the investigations, including differences in RF-radiation exposure conditions and experimental protocols, which could have contributed to the contradictory observations (*3–5*).

This paper describes a meta-analysis of genotoxicity data published in peer-reviewed scientific journals during the years 1990–2005. The objectives were to (1) obtain a good overall quantitative estimate of the damage reported in RF-radiation-exposed cells compared with controls, (2) study the correlation between certain specific RF-radiation exposure characteristics (see below) and increased genotoxicity that is larger than the random variability, (3) examine whether the damage indices in RF-radiation-exposed cells were within the spontaneous levels reported in the historical database, (4) use multiple regression analysis to determine

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the combined effects of the characteristics of RF radiation on genotoxicity, and (5) test for heterogeneity of residual variability to determine whether other factors that were not considered in the meta-analysis could explain the effects reported in the publications.

MATERIALS AND METHODS

The methods used for the meta-analysis were based on the recommendations made in several standard textbooks (*6–9*). All publications in peer-reviewed scientific journals in English from 1990 to 2005 were assembled. A combination of key/search words including non-ionizing radiation, radiofrequency radiation, comet assay, chromosome aberrations, micronuclei, SCE, *in vitro* and/or *in vivo* studies, animals, rodents, rats, mice and humans were used for a systematic search in the Medline, PubMed and Ovid databases. The contents/papers listed in several scientific journals and Science Citation Index and information from colleagues in national and international laboratories also helped in this effort. Abstracts printed in scientific journals were not considered since they did not provide detailed results. The list contained a total of 63 publications (*10–72*).

Each publication was examined in detail by both authors to record the information in an Excel spreadsheet. The results reported as numbers in the tables were documented as such, while the figures were enlarged 200% to enter the data nearer to the actual numbers. Both authors assessed the quality of investigations/publications, i.e., whether the investigator(s) included sham-exposed/unexposed/positive controls and blind evaluations and provided detailed descriptions of dosimetry, experimental protocols, data collection procedures, appropriate statistical analyses, and consistent (yes or no) conclusions from results in the text, tables and figures. This was done to assess whether the quality of the investigations and publications in RF-radiation research has improved over the years; it was not intended to "rank" the publications either to exclude or include the data in the meta-analysis and was used only to interpret the heterogeneity of the results. The information in the spreadsheet was checked and rechecked three times for each publication to ensure that no errors were made during the recording process.

Investigators have examined different numbers of cells in the same/different experiments for the same genotoxicity end point. For example, the incidence of micronuclei was reported for 500, 1000, 2000 or 4000 cells. Fleiss *et al.* (*73*) suggested a method using raw data to calculate the mean, standard deviation (SD) and variance from varying numbers of cells examined in different experiments (when averaging over experiments and cells within experiments). However, it is almost impossible to obtain the raw data from individual investigators. Thus a standardized "unit" was obtained for each end point and used as a more homogeneous measure. The standardized unit for chromosome aberrations was in 100 cells; i.e., if the incidence was reported from 200 cells, it was divided by two to obtain the unit as chromosome aberrations/100 cells. Similarly, the standardized units were micronuclei/1000 cells and SCE/cell. Since limited data were reported for DSBs, they were pooled with SSBs to obtain a standardized unit for the comet tail length as SSBs measured in micrometers and comet tail moment as SSBs expressed as a ratio. When the investigator(s) reported the results as mean and standard error (SE), the SD was calculated by multiplying the SE by the square root of the number of experiments. When the results were from only one experiment or did not include the SD, all data in the RF-radiation exposure subgroups (see below) in the spreadsheet were pooled to obtain the SD. When the results were from two separate experiments, the numbers for RF-radiation-exposed cells were combined to obtain the mean and SD ($n = 2$). Similar methods were used for controls. The units for RF-radiation-exposed cells were integrated to the obtain overall mean and SD to assign it to the RF-radiation-exposed group, while similar data for controls were assigned to the control group. These are the descriptive data for the standardized units from which the meta-analysis was conducted.

Meta-analysis

Vijayalaxmi and Obe (*2*) identified several variables in the experimental protocols used by different investigators in different countries. It is beyond the scope and goals of this meta-analysis to address the effect of all such variables. Three specific variables related to RF-radiation exposure characteristics, frequency, specific absorption rate (SAR), and exposure as continuous wave (CW), pulsed wave (PW), and occupationally exposed/cell phone users, were selected to determine their potential influence on genotoxicity end points. Each characteristic was further classified into subgroups. RF-radiation frequency was classified as: all frequencies, ≤2000 MHz, and >2000 MHz. SAR was classified as information not reported, all together, ≤2 W/kg, ≤5 W/kg and >5 W/kg. The exposure was classified as all together, CW, PW and occupationally exposed/cell phone user. In real life, people are exposed to a variety of environmental insults simultaneously and/or sequentially. Theoretically, it may be that RF-radiation exposure itself is not genotoxic but could enhance the damage induced by other genotoxic agents (i.e., the effect could be epigenetic). This issue was examined in rodent and human cells that were treated with a known genotoxic agent prior to, during and/or after RF-radiation exposure; these observations, reported in 11 publications, were also subjected to meta-analysis.

The Statistical Analysis System [SAS, ref. (*74*)] Version 9.1 for Windows was used for all the analyses described below.

Magnitude of Difference between RF-Radiation-Exposed and Controls

Fixed-effects models were first used to calculate the differences between the RF-radiation-exposed and control groups (*7*). These models assume a single fixed effect that every study will approximate within each subgroup. This is a conservative approach that provides very narrow confidence intervals (CIs) and is more likely to find significant differences between RF-radiation-exposed and control groups (compared to random effects models, which yield wider CI and would not find such differences). The sample size in RF-radiation-exposed and control groups was not always the same. Also, the results were variable from one experiment to another within the same laboratory and also from one laboratory to another. These factors were taken into consideration to provide a weight that is based on the sample size and variance in RF-radiation-exposed and control groups in each publication (*7*). Separate statistical analyses were performed for each genotoxicity end point because of the differences in their standardized units. This analysis was applied to pool the data from all publications. The pooled weighted SE was obtained from all publications and was then used to compute the 95% CI to obtain a quantitative estimate of the difference between exposed and control groups. The method is described in detail in the Supplementary Information.

Effect Size or Standardized Mean Difference

Another method regularly used in the meta-analysis is to determine "unit-less" measure called "effect size" (effect size or standardized mean difference) between RF-radiation-exposed and control groups in each publication. Random effects models suggested by Hunter and Schmidt (*8*) were used to calculate the effect size. These models are more accurate than the traditional random effects models and have several advantages. They allow for the possibility that P values vary from one study to another, make fewer assumptions, are more conservative, use weighting by sample size (which is critical for meta-analysis), and are recommended by the National Research Council (*75*). Thus the data reported in each publication were considered as an independent random sample with some degree of variability. The results were weighted before the data from all publications were pooled, the rationale being that studies with narrow CIs with more precise estimates were weighted more heavily than studies with greater uncertainty (*76*). The method also corrected for bias in the estimated effect size and provided weights for the data in each publication. This analysis was applied to pool the data from all publications. The pooled weighted SE was obtained from all publications and was then used to compute the 95% CI to obtain a quantitative estimate of the

difference between exposed and control groups. The SE of pooled weighted bias was then used to compute the 95% CI to obtain a quantitative estimate of effect size. The method is described in detail in the Supplementary Information.

Multiple Regression Analysis

Since the meta-analysis considered the influence of several subgroups in RF-radiation exposure characteristics on each end point, the percentage contribution of each subgroup for the outcomes in the difference between exposed and control groups and effect size was examined using the standard output of weighted multiple regression analysis with the adjustments described by Hedges and Olkin (*6*). Seven predictor variables in RF-radiation exposure characteristics [RF-radiation frequency subgroups (≤2000 MHz and >2000 MHz) as one predictor variable; SAR subgroups (all unreported SARs, ≤2 W/kg, 2–5 W/kg and >5 W/kg) as three predictor variables; CW/PW/occupationally exposed/cell phone user subgroups as two predictor variables] adjusted for each other provided weighted regression coefficients and sums of squares for the difference between exposed and control groups (*7*) and for effect size (*8*). The weighted regression coefficients and sums of squares for each predictor variable, for residual variability, and for total variability in the regression were obtained using SAS software (*74*). The SE of these regression coefficients from SAS was adjusted (*6*) for the weighted meta-analysis of subgroup effects. The percentage variance due to the predictor variables was calculated from each of the weighted sums of squares as a percentage of their total. The percentage contribution of each subgroup to the effect/outcome observed on the difference between exposed and control groups and effect size on each genotoxicity end point was estimated.

Heterogeneity

Since meta-analyses examine the results of several related studies, the degree of homogeneity or heterogeneity in the results can influence the overall conclusions. This was examined in the weighted multiple regression analysis (*6*) using the random error for testing heterogeneity of effects to verify the validity of the models used for both the difference between exposed and control groups and effect size. The residual weighted sums of squares were used in the chi-square goodness-of-fit test (heterogeneity in the difference between exposed and control groups and effect size values obtained for each end point) with appropriate degrees of freedom (*6*). When the goodness-of-fit test was not rejected, the regression model was adequate. When the test gave significant results, the data indicated heterogeneity; i.e., factors that were not considered in this meta-analysis had an influence on the differences between RF-radiation-exposed and control conditions. Such data were examined further to explain which subgroup RF-radiation exposure characteristic contributed to the heterogeneity, to compare minimum and maximum effects with those in controls, and to determine the magnitude of heterogeneity.

Publication Bias

Publication bias refers to the fact that studies with statistically significant results, even with a small sample size, are more likely to be published than those without statistically significant results (*77*). A simple graphical funnel plot (*8*) was used to determine whether a publication bias existed in the meta-analysis database. When the data with no publication bias were presented in a figure, studies with small sample size would have the same mean effect size as in those with a large sample size but would show a greater variability with wider dispersion of low and high effect size values around the mean effect size. In contrast, if there is publication bias, the smaller effect size in studies with small sample size would be disproportionately absent since such studies will fail to reach statistical significance ($P < 0.05$). This graphical method with a non-parametric test (*8*) was used to assess the publication bias.

Historical Database

To provide a proper perspective in the evaluation of potential adverse effects of RF-radiation exposure, the genotoxicity indices reported in RF-radiation research investigations were compared with the spontaneous indices in normal cells published in a large historical database. A simple descriptive meta-analysis was performed by pooling the spontaneous incidence of chromosome aberrations, micronuclei or SCE reported in normal cells in several studies (*78–92*) and weighted by the sample size and variance. The spontaneous indices obtained for each end point were compared with those in RF-radiation-exposed and controls in the meta-analysis database.

DATA PRESENTATION

Supplementary Table 1 is a list of 63 publications (*10–72*) in chronological order. Although the DNA fragment size (*20*), chromosomal recombination (*42*) and aneuploidy (*56*) were related to genotoxicity, the data were not included in the meta-analysis since no similar data were available for comparison. Since the results for SCE were reported in only three publications (*19, 26, 71*), the meta-analysis data are discussed briefly in the text.

Examination of detailed publication characteristics (Supplementary Table 2) indicated that the number of publications increased over the years and reached a maximum of eight in 2005. The geographical distribution showed that many of the reports were from Europe (43%) followed by the U.S. (33%). Nearly equal numbers of studies used ≤2000 MHz (used for cell phones, 51%) and >2000 MHz (49%). SAR was not reported in 21% of the papers, while the influence of one, two or more SARs was examined in 40, 17 and 22% of the studies, respectively. The RF-radiation transmission was used as CW (32%) or PW (35%); other studies included both CW and PW (19%) as well as individuals who were exposed occupationally and were also cell phone users (14%). DNA strand breaks, chromosome aberrations, micronuclei and SCE were studied in 22, 10, 27 and 5% of the reports, respectively. The remaining reports included two (21%) and three (11%) different end points. A majority of the investigations were conducted using freshly collected human blood lymphocytes (54%); rodent cells that were freshly collected (17%) or cultured (16%) were used in one-third of the studies, while a few studies used two (8%) or more (2%) different cell types. The genotoxic potential of *in vitro* RF-radiation exposures was examined using rodent (10%) and/or human cells (33%), while whole-body RF-radiation exposure of rodents (21%) and occupationally exposed individuals and cell phone users (14%) was also investigated. The epigenetic effects of RF-radiation exposures were examined *in vitro* using rodent (6%) and human (8%) cells. There was a substantial improvement in the quality of publications over the years.

The meta-analysis data obtained for comet tail and chromosomal aberrations/micronuclei are presented in Tables 1 and 2, respectively; results from epigenetic investigations are given in Table 3. The last two columns show the computed values that would be required to achieve a statistically significant difference between RF-radiation-exposed and controls when the sample size is 6 or 12.

TABLE 1
Meta-analysis of the Magnitude of Difference between Data for RF-Radiation-Exposed and Control Groups based on Sample Size and Variance) for DNA Strand Breaks Evaluated as Comet Tail Length in μm (SBM) and Comet Tail Moment Expressed as Ratio (SBR)

		Control group				RF-radiation-exposed group					Exposed − Computed				Exposed − control	
RFR Exposure	End point	*N*	Mean	SD	CI (95%)	*N*	Mean	SD	CI (95%)	*P* value	Total *N*	Mean	SE	CI (95%)	If *N* = 6	If *N* = 12
Frequency																
All frequencies	SBM	522	57.7	18.1	56.2–59.3	509	57.3	18.5	55.6–58.9	0.349	1031	0.44	1.1	−1.8–2.7	30	21
≤2000 MHz	SBM	288	26.2	7.0	25.4–27.0	302	27.4	7.4	26.6–28.2	0.305	590	0.30	0.6	−0.9–1.5	12	8
>2000 MHz	SBM	234	96.6	24.8	93.4–99.8	207	100.9	26.7	97.3–104.6	0.203	441	2.05	2.5	−2.8–6.9	42	30
SAR																
All SARs	SBM	522	57.7	18.1	56.2–59.3	509	57.3	18.5	55.6–58.9	0.349	1031	0.44	1.1	−1.8–2.7	30	21
≤2 W/kg	SBM	394	66.7	19.8	64.7–68.6	381	66.1	20.3	64.0–68.1	0.309	775	0.72	1.4	−2.1–3.5	32	23
≤5 W/kg	SBM	469	61.0	18.8	59.3–62.7	456	60.4	19.2	58.7–62.2	0.372	925	0.41	1.3	−2.0–2.9	31	22
>5 W/kg	SBM	53	28.5	8.8	26.1–30.9	53	29.8	10.5	26.9–32.7	0.367	106	0.64	1.9	−3.0–4.3	16	11
CW/PW/CP[a]																
All	SBM	521	57.7	18.1	56.1–59.3	508	57.2	18.5	55.6–58.9	0.350	1029	0.44	1.1	−1.8–2.7	30	21
CW	SBM	188	37.2	25.9	33.4–40.9	189	41.7	26.0	37.0–45.4	0.467	377	0.22	2.7	−5.0–5.5	42	30
PW	SBM	323	71.2	12.3	69.9–72.6	295	69.7	13.1	68.2–71.2	0.484	618	−0.04	1.0	−2.1–2.0	21	15
CP	SBM	10	8.1	0.0	8.0–8.1	24	26.7	3.7	25.2–28.2	0.000	34	18.60	0.7	−17.1–20.1	3	2
Frequency																
All frequencies	SBR	660	1.6	4.4	1.3–2.0	660	1.7	4.2	1.4–2.0	0.461	1320	0.02	0.2	−0.4–0.5	7	5
≤2000 MHz	SBR	575	1.5	1.3	1.4–1.6	575	1.6	1.5	1.4–1.7	0.388	1150	0.02	0.1	−0.1–0.2	2	2
>2000 MHz	SBR	85	2.7	11.2	0.3–5.1	85	2.8	10.5	0.5–5.1	0.498	170	0.01	1.7	−3.3–3.3	18	12
SAR																
All SARs	SBR	660	1.6	4.4	1.3–2.0	660	1.7	4.2	1.4–2.0	0.461	1320	0.02	0.2	−0.4–0.5	7	5
≤2 W/kg	SBR	473	1.8	5.1	1.4–2.3	473	1.9	4.8	1.5–2.3	0.471	946	0.02	0.3	−0.6–0.7	8	6
≤5 W/kg	SBR	578	1.7	4.7	1.3–2.1	578	1.8	4.4	1.4–2.1	0.465	1156	0.02	0.3	−0.5–0.6	7	5
>5 W/kg	SBR	82	1.3	2.2	0.8–1.8	82	1.3	2.5	0.8–1.9	0.493	164	0.01	0.4	−0.7–0.7	4	3
CW/PW/CP																
All CW-PW	SBR	660	1.6	4.4	1.3–2.0	660	1.7	4.2	1.4–2.0	0.461	1320	0.02	0.2	−0.4–0.5	7	5
CW	SBR	273	1.2	6.7	0.4–2.0	273	1.2	6.3	0.5–2.0	0.485	546	0.02	0.6	−1.1–1.1	11	7
PW	SBR	387	2.0	1.5	1.8–2.1	387	2.0	1.7	1.9–2.2	0.405	774	0.03	0.1	−0.2–0.3	3	2

[a]cp = occupationally exposed/cell phone users.

RESULTS

The difference between exposed and control groups meta-analysis results for comet tail length and comet tail moment (Table 1) indicated similar means and SD in RF-radiation-exposed and control groups in 20 of 21 total tests ($P > 0.05$); the exception was for comet tail length (occupationally exposed/cell phone users, $P < 0.05$). The weighted mean difference between exposed and control groups was not significant in most cases and ranged between −0.04 and 2.05 μm for comet tail length (except for occupationally exposed/cell phone users, 18.60 μm) and between 0.01 and 0.03 for comet tail moment. The data on chromosome aberrations (Table 2) indicated similar means and SD in RF-radiation-exposed and control groups ($P > 0.05$). The weighted mean difference between exposed and control groups was not significant and ranged from 0.10 to 0.92 (i.e., <1 aberration in 100 cells). The results for micronuclei (Table 2) indicated similar means and SD in RF-radiation-exposed and control groups ($P > 0.05$). However, there were significant differences between the two groups for ≤2000 MHz and several SARs and PW/occupationally exposed/cell phone users exposures ($P < 0.05$). The weighted mean of the difference between exposed and control groups ranged from 0.06 to 6.13 (i.e., <6.5 micronuclei/1000 cells). Observations from epigenetic investigations (Table 3) of SSBs were reported in only two publications; a synergistic effect of RF radiation + mitomycin C (MMC) was observed in human blood lymphocytes (*50*), and an effect was found with two chemical mutagens (MMC and 4-nitroquinoline-1-oxide) but not with two other mutagens (bleomycin and methyl methane sulfonate) (*65*). The difference between exposed and control groups data for chromosome aberrations, micronuclei and SCE showed no synergistic effect. A significant increase in genotoxicity was evident in cells treated with the mutagens alone.

Overall, the effect size, SE and 95% CI obtained for comet tail length, comet tail moment, chromosome aberrations and micronuclei (Table 4, Part A), and for different

TABLE 2
Meta-analysis of Magnitude of Difference between Data for RF-Radiation-Exposed and Control Groups (based on Sample Size and Variance) for Chromosomal Aberrations (CA)/100 Cells and Micronuclei (MN)/1000 Cells

RF-radiation characteristics	End point	Control group				RF-radiation-exposed group				P value	Exposed − control				Exposed − control	
		N	Mean	SD	CI (95%)	N	Mean	SD	CI (95%)		Total N	Mean	SE	CI (95%)	If N = 6	If N = 12
All frequencies	CA	174	1.5	2.6	1.1–1.9	174	2.8	4.2	2.2–3.5	0.198	348	0.32	0.4	−0.4–1.1	6	4
≤2000 MHz	CA	68	2.0	3.5	1.2–2.9	68	1.7	0.9	1.4–1.9	0.363	136	0.15	0.4	−0.7–1.0	4	3
>2000 MHz	CA	106	1.1	1.9	0.7–1.5	106	3.6	5.2	2.6–4.6	0.186	212	0.48	0.5	−0.6–1.5	6	4
All SARs	CA	151	1.4	2.8	1.0–1.9	151	2.0	2.9	1.6–2.5	0.201	302	0.28	0.3	−0.4–0.9	5	3
NR-SARs[a]	CA	82	1.4	3.6	0.6–2.2	82	2.2	3.8	1.3–3.0	0.057	164	0.92	0.6	−0.2–2.1	6	4
≤2 W/kg	CA	20	1.7	0.5	1.4–1.9	20	1.9	0.8	1.6–2.3	0.233	40	0.16	0.2	−0.3–0.6	1	1
≤5 W/kg	CA	29	1.5	0.5	1.3–1.7	29	1.7	0.7	1.4–2.0	0.255	58	0.11	0.2	−0.2–0.4	1	1
>5 W/kg	CA	40	1.5	1.0	1.2–1.9	40	2.1	0.9	1.8–2.4	0.099	80	0.27	0.2	−0.1–0.7	2	1
All CW-PW	CA	174	1.5	2.6	1.1–1.9	174	2.8	4.2	2.2–3.5	0.198	348	0.32	0.4	−0.4–1.1	6	4
CW	CA	31	1.5	0.2	1.5–1.6	31	6.3	7.9	3.5–9.2	0.350	62	0.54	1.4	−2.2–3.3	9	6
PW	CA	61	1.6	0.8	1.3–1.8	61	2.0	0.9	1.7–2.2	0.486	122	0.10	0.2	−0.3–0.3	1	1
CP	CA	82	1.4	3.6	0.6–2.2	82	2.2	3.8	1.3–3.0	0.057	164	0.92	0.6	−0.2–2.1	6	4
All frequencies	MN	1940	5.0	2.4	4.8–5.1	2053	5.7	6.2	5.4–6.0	0.155	3993	0.15	0.2	−0.1–0.4	8	5
≤2000 MHz	MN	1616	4.8	2.4	4.6–4.9	1682	5.0	3.0	4.9–5.2	0.003	3298	0.26	0.1	0.1–0.5	4	3
>2000 MHz	MN	324	5.9	2.1	5.7–6.1	371	8.8	13.4	7.5–10.2	0.438	695	0.11	0.7	−1.3–1.5	15	11
All-SAR	MN	1934	4.9	2.4	4.8–5.0	2047	5.6	6.2	5.4–5.9	0.154	3981	0.15	0.2	−0.1–0.4	7	5
NR-SARs[a]	MN	195	5.2	1.7	4.9–5.4	194	10.9	18.8	8.3–13.6	0.482	389	0.06	1.4	−2.6–2.7	22	15
≤2 W/kg	MN	778	3.8	1.6	3.7–3.9	892	4.2	2.0	4.1–4.3	0.000	1670	0.36	0.1	0.2–0.5	3	2
≤5 W/kg	MN	1135	5.4	2.4	5.3–5.6	1249	5.5	2.9	5.4–5.7	0.014	2384	0.24	0.1	0.0–0.5	4	3
>5 W/kg	MN	604	3.9	2.4	3.7–4.1	604	4.1	2.8	3.9–4.3	0.001	1208	0.46	0.2	0.2–0.8	4	3
All CW-PW	MN	1940	5.0	2.4	4.8–5.1	2053	5.7	6.2	5.4–6.0	0.155	3993	0.15	0.2	−0.1–0.4	8	5
CW	MN	507	8.1	3.5	7.8–8.4	555	9.0	4.1	8.6–9.3	0.356	1062	0.09	0.2	−0.4–0.5	6	4
PW	MN	1358	3.7	1.9	3.6–3.8	1412	3.7	2.5	3.6–3.9	0.004	2770	0.22	0.1	0.1–0.4	4	3
CP	MN	75	5.7	1.4	5.4–6.1	86	17.0	26.2	11.4–22.6	0.015	161	6.13	2.8	0.6–11.7	29	20

Notes. Incidence of chromosomal aberrations reported in the historical database: Mean 1.5/100 cells (SD = 3.7; n = 15,594). Incidence of micronuclei reported in the historical database: Mean 9.0/1000 cells (SD = 8.0; n = 8,667).

[a] NR-SARs: SARs were not reported in some publications.

years of publication (Table 4, part B) were very small and ranged from 0 to 0.9. The two exceptions were for comet tail length and micronuclei with maximum means of 5.9 and 2.1 (occupationally exposed/cell phone users), respectively (Table 4, part A). The pattern of larger/smaller effeet size values (Table 4, part A) was similar to the corresponding large/small difference between exposed and control groups in Tables 3 and 4.

Sample Size

It must be emphasized that the difference between exposed and control groups values obtained for different end points were based on large sample size by consolidating the results from all publications (Tables 1 and 2). When the experiments were conducted with a smaller sample size, the difference between exposed and control groups must be severalfold larger to yield a statistically significant difference between RF-radiation-exposed and control groups ($P < 0.05$), with a power of 0.80 at a two-tailed significance level of 0.05 based on a two-sample t test and the pooled data (last two columns of Tables 1 and 2).

Multiple Regression Analysis and Heterogeneity

The results of the multiple regression analysis data are presented in Table 5. The overall percentage contributions to the variability observed in the difference between exposed and control groups and effect size for all end points due to frequency, SAR and CW/PW/occupationally exposed/cell phone users were smaller than those obtained for the goodness-of-fit test. Nonetheless, some were significant ($P < 0.05$; see the footnote in the table).

For comet tail length, the variability in effect size due to SAR was not significant, while those due to frequency and CW/PW/occupationally exposed/cell phone users and to the difference between exposed and control groups for SAR were significant ($P < 0.05$). For comet tail moment, the variability in the difference between exposed and control groups due to frequency was not significant while those due to SAR and CW/PW/occupationally exposed/cell phone users were significant ($P < 0.05$). The variabilities in effect size due to frequency, SAR and CW/PW/occupationally exposed/cell phone users were not significant. For chromosome aberrations, the variability in the difference between

TABLE 3
Meta-analysis of Magnitude of Difference between Data for RF-Radiation-Exposed and Control Groups (based on Sample Size and Variance) for DNA Strand Breaks (SSB), Chromosomal Aberrations (CA)/100 Cells, Micronuclei (MN)/1000 Cells and Sister Chromatid Exchanges (SCE)/Cell in Epigenetic Investigations

RF-radiation characteristics	End point	Control group				RF-radiation-exposed group				P value	Exposed − control)				Exposed − control	
		N	Mean	SD	CI (95%)	N	Mean	SD	CI (95%)		Total N	Mean	SE	CI (95%)	If N = 6	If N = 12
RF radiation alone	SSB	10	5.6	0.8	5.1–6.2	10	6.1	1.0	5.4–6.8		20	0.11	0.4	−0.7–0.9	1	1
Mutagen alone	SSB	40	5.6	0.8	5.4–5.9	40	19.3	1.7	18.8–19.9		80	1.36	0.3	0.8–1.9	2	2
RF radiation + Mutagen	SSB	102	8.0	1.1	7.8–8.3	102	10.2	1.5	9.9–10.4	0.001	204	0.38	0.2	0.0–0.7	2	1
RF radiation alone	CA	61	2.2	1.1	1.9–2.4	61	3.1	1.5	2.7–3.5		122	0.53	0.2	0.2–1.0	2	2
Mutagen alone	CA	2	4.0	2.8	21.4–29.4	2	44.5	6.4	−12.7–101.7		4	40.50	4.9	30.9–50.2	8	6
RF radiation + Mutagen	CA	25	34.4	4.0	32.8–36.0	25	40.1	5.8	37.7–42.5	0.304	50	4.86	1.4	2.1–7.6	8	6
RF radiation alone	MN	25	40.3	10.1	36.1–44.5	25	60.3	9.0	56.5–64.0		50	15.56	2.7	10.3–20.9	15	11
Mutagen alone	MN	12	39.7	6.9	35.3–44.1	12	124.7	22.9	110.1–139.3		24	59.48	6.9	45.9–73.0	27	19
RF radiation + Mutagen	MN	29	105.8	17.3	99.3–112.4	29	128.0	20.2	120.3–135.7	0.457	58	17.81	4.9	8.1–27.5	30	22
RF radiation alone	SCE	51	5.0	1.0	4.7–5.3	51	5.6	0.9	5.3–5.8		102	0.61	0.2	0.3–1.0	1	1
Mutagen alone	SCE	37	6.7	0.9	6.4–7.0	37	31.5	7.1	29.1–33.9		74	18.02	1.2	15.7–20.3	8	6
RF radiation + Mutagen	SCE	51	25.3	6.1	23.6–27.0	51	29.4	4.9	28.1–30.8	0.406	102	1.76	1.1	−0.4–3.9	9	6

Notes. Incidence of chromosomal aberrations reported in the historical database: Mean 1.5/100 cells (SD = 3.7; n = 15,594). Incidence of micronuclei reported in the historical database: Mean 9.0/1000 cells (SD = 8.0; n = 8,667). Incidence of SCE reported in the historical database: Mean 7.6/cell (SD = 1.6; n = 4,576).

exposed and control groups due to frequency was not significant, while those due to SAR and CW/PW/occupationally exposed/cell phone users were significant ($P < 0.05$). However, the variabilities in effect size due to RF-radiation frequency, SAR and CW/PW/occupationally exposed/cell phone users were not significant. For micronuclei, the variabilities in the difference between exposed and control groups and effect size due to RF-radiation frequency, SAR and CW/PW/occupationally exposed/cell phone users were all significant ($P < 0.05$) except for that due to SAR for effect size. All of the multiple regression data for comet tail length, comet tail moment and chromosome aberrations were similar to the results of the univariate analyses in Tables 1 and 2; the data for micronuclei sometimes differed from the results in Table 2.

Random error accounted for most of the variability observed in the difference between exposed and control groups and effect size for each end point (goodness-of-fit data, last column in Table 5). Significant deviations ($P < 0.05$) indicate that factors other than the three RF-radiation exposure characteristics might explain the variability in end points. Further details of the goodness-of-fit tests are presented for the differences between exposed and control group in Table 6. No values were outside the normal range in comet tail moment. Although nearly all of the differences between exposed and control group effects for comet tail length, chromosome aberrations and micronuclei were within normal range of the controls, there was some heterogeneity of effects for these regression models. For comet tail length, the 3.6% is very close to the expected 2.5% out of the normal range. All of the publications for chromosome aberrations and most of those for micronuclei did not provide complete information on dosimetry, and this might explain the larger the difference between exposed and control group effects for chromosome aberrations and micronuclei. The few papers with complete dosimetry for micronuclei (1.1%) that were outside the normal range for 97.5% of controls were also well within the expected 2.5% out of normal range.

A considerable reduction in residual variability with improved goodness-of-fit was obtained when the description of dosimetry (complete or incomplete) in each publication was considered in the weighted multiple regression analysis (results not shown). Determination of the contributions of other variables in the experimental protocols to the heterogeneity/variability in the difference between exposed and control groups and effect size for different genotoxicity end points requires further analyses.

When only the publications with complete description of dosimetry were considered in the meta-regression analysis, the goodness-of-fit test (heterogeneity) for comet tail length and comet tail moment remained significant while that for chromosome aberrations ($P = 0.174$) and micronuclei ($P = 0.184$) was reduced to nonsignificant levels. The Higgins measure of heterogeneity effects remained substantial (>50%) for comet tail length and comet tail moment but was 0% for chromosome aberrations and 13% for micronuclei (*78*). However, the magnitude of heterogeneity for

TABLE 4
Meta-analysis of the Data for Effect Size (ES) or Standardized Difference (d) Obtained for DNA Single- and Double-Strand Breaks Evaluated as Comet Tail Length (SBM) and Comet Tail Moment (SBR), Chromosomal Aberrations (CA) and Micronuclei (MN)

Exposure	SBM			SBR			CA			MN		
	ES (d)	SE	CI (95%)	ES (d)	SE	CI (95%)	ES (d)	SE	CI (95%)	ES (d)	SE	CI (95%)
Part A												
Frequency												
All Frequencies	0.4	0.1	0.2–0.5	0.0	0.1	−0.1–0.2	0.3	0.1	0.1–0.6	0.2	0.0	0.1–0.2
≤2000 MHz	0.2	0.1	−0.1–0.4	0.0	0.1	−0.2–0.2	0.1	0.2	−0.2–0.5	0.1	0.0	0.0–0.2
>2000 MHz	0.6	0.1	0.4–0.8	0.0	0.2	−0.3–0.4	0.4	0.2	0.1–0.8	0.6	0.1	0.4–0.8
SAR												
All SARs	0.4	0.1	0.2–0.5	0.0	0.1	−0.1–0.2	0.2	0.1	−0.1–0.5	0.2	0.0	0.1–0.2
NR-SARs[a]	—[b]	—	—	—	—	—	0.2	0.2	−0.1–0.6	0.9	0.1	0.6–1.2
≤2 W/kg	0.4	0.1	0.3–0.6	0.0	0.1	−0.2–0.2	0.3	0.3	−0.4–0.5	0.2	0.1	0.1–0.3
≤5 W/kg	0.4	0.1	0.2–0.5	0.0	0.1	−0.1–0.2	0.3	0.3	−0.4–0.9	0.1	0.0	0.0–0.2
>5 W/kg	0.2	0.2	−0.3–0.7	−0.1	0.2	−0.4–0.3	0.1	0.3	−0.4–0.6	0.0	0.1	−0.1–0.2
CW/PW/CP[c]												
All	0.4	0.1	0.2–0.5	0.0	0.1	−0.1–0.2	0.3	0.1	0.1–0.6	0.2	0.0	0.1–0.2
CW	0.3	0.1	0.0–0.5	0.0	0.1	−0.2–0.2	0.9	0.3	0.3–1.5	0.5	0.1	0.4–0.6
PW	0.3	0.1	0.1–0.5	0.0	0.1	−0.2–0.2	0.1	0.2	−0.3–0.5	−0.0	0.0	−0.1–0.1
CP	5.9	0.8	4.3–7.5	—	—	—	0.2	0.2	−0.1–0.6	2.1	0.3	1.6–2.6
Part B												
Year 1990	—	—	—	—	—	—	0.7	0.4	−0.2–1.5	0.6	0.7	−0.8–2.1
Year 1991	—	—	—	—	—	—	0.1	0.2	−0.3–0.5	0.7	0.6	−0.5–2.0
Year 1992	—	—	—	—	—	—	2.0	0.9	0.3–3.8	1.1	0.4	0.3–2.0
Year 1993	—	—	—	—	—	—	−0.3	0.6	−1.5–0.9	8.4	4.3	0.1–16.8
Year 1994	—	—	—	—	—	—	—	—	—	—	—	—
Year 1995	0.3	0.2	−0.2–0.7	—	—	—	0.4	0.3	−0.2–1.1	0.2	0.3	−0.5–0.9
Year 1996	2.4	0.4	1.7–3.1	—	—	—	—	—	—	—	—	—
Year 1997	0.5	0.2	0.2–0.8	0.0	0.2	−0.4–0.4	1.2	1.4	−1.5–3.8	0.7	0.1	0.4–0.9
Year 1998	0.1	0.3	−0.5–0.5	−0.2	0.2	−0.5–0.2	—	—	—	—	—	—
Year 1999	—	—	—	—	—	—	—	—	—	2.4	0.6	1.3–3.5
Year 2000	0.1	0.6	−1.1–0.3	0.0	0.6	−1.2–1.2	0.0	0.3	−0.5–0.6	1.0	0.5	0.0–1.9
Year 2001	0.2	0.3	−0.3–0.7	0.2	0.3	−0.3–0.7	1.1	0.5	0.2–2.0	0.3	0.3	−0.3–0.9
Year 2002	0.0	0.2	−0.4–0.4	−0.1	0.1	−0.4–0.2	—	—	—	0.1	0.1	−0.2–0.3
Year 2003	0.2	0.2	−0.2–0.7	−0.1	0.2	−0.4–0.3	−0.1	0.9	−1.9–1.6	0.0	0.1	−0.2–0.1
Year 2004	0.2	0.2	−0.2–0.5	0.2	0.2	−0.2–0.6	—	—	—	0.8	0.3	0.3–1.4
Year 2005	5.9	0.8	4.3–7.5	1.0	0.3	0.3–1.7	0.7	0.9	−1.0–2.4	0.2	0.1	0.1–0.3

[a] NR-SARs: SARs were not reported in some publications.
[b] No data in the publications.
[c] Occupationally exposed/cell phone users.

all individual end point effects was small and was within the normal range for controls.

Quality of Publications

The quality of publications increased from 2% during 1990–1995 to 48% during 2001–2005, indicating a substantial improvement in the quality of publications during recent years (see Supplementary Table 2).

Publication Bias

The publication bias is presented graphically in Fig. 1. Although there were 63 publications, some examined one or more end points in several different RF-radiation exposure conditions that are plotted separately. The data did not appear as a "bell" shape with the mean effect size approximately at the center of the negative and positive publications. Instead, the data were skewed, indicating a significant publication bias ($P < 0.0001$) toward positive publications even with small sample sizes, while negative papers were published only when the sample size was large. The skew was also due to a small SD in studies with a small sample size, which gives the appearance of large effect size values despite a small mean difference between exposed and control groups (the 37 largest effect size values were obtained from the comet tail moment and the pooled SD was much smaller for these effect size values). The large effect size values are misleading (due to small pooled SD), although the complete dosimetry data are still within the normal range (Table 6). The overall effect size and 95% CI obtained from meta-analysis was 0.161 to 0.165. The true effect size value at the peak was nearly zero despite the CI

TABLE 5

Multiple Regression Analysis of the Effects of RF-Radiation Exposure Characteristics on the Magnitude of Difference between RF-Radiation-Exposed and Control Groups (E − C, based on Sample Size and Variance) and Effect Size (ES) Observed for Comet Tail Length in μm (SBM), Comet Tail Moment (SBR), Chromosomal Aberrations (CA) and Micronuclei (MN)

			Percentage contribution due to			
End point		Number of effects examined	Frequency (MHz)	SAR W/kg	CW/PW/CP	Regression goodness-of-fit test
SBM	E − C	110	2.4[c]	0.8[g]	40.3[m]	56.4[a]
SBM	ES		5.1[d]	0.2	24.9[n]	69.8[a]
SBR	E − C	182	<0.01	0.01[h,i]	2.5[o]	97.5[a]
SBR	ES		0.03	0.25	0.01	99.7
CA	E − C	7	0.3	41.3[j]	14[p]	44.4[a]
CA	ES		5.4	14.2	15.2	65.3
MN	E − C	174	7.3[e]	1.7[k,l]	27.2[q,r]	63.8[a]
MN	ES		4.2[f]	0.6	23.9[s]	71.2

Note. Only univariate regression analysis was used for sister chromatid exchanges (SCE) due to small sample size [refs. (*19, 26, 71*)].

[a] $P \leq 0.05$ (heterogeneity in the predictors effects observed in RF radiation exposure characteristics).

Multiple regression coefficients for significant effects ($P < 0.05$):

[b] Contribution due to factors other than the RF radiation characteristics.

Frequency (MHz) effects:

[c] Change in effect due to <2000 MHz RF radiation frequency was smaller than >2000 MHz (−2.52 ± 0.53).

[d] Change in effect due to <2000 MHz RF radiation frequency was smaller than >2000 MHz (−0.56 ± 0.18).

[e] Change in effect due to <2000 MHz RF radiation frequency was smaller than >2000 MHz (−2.67 ± 0.16).

[f] Change in effect due to <2000 MHz RF radiation frequency was smaller than >2000 MHz (−0.56 ± 0.18).

Specific absorption rates (SAR)—W/kg effects:

[g] Change in effect due to >5 W/kg was greater than >2 W/kg (1.12 ± 0.42).

[h] Change in effect due to >5 W/kg SAR was smaller than 2 W/kg SAR (−0.02 ± 0.003).

[i] Change in effect due to 2-5 W/kg SAR was smaller than <2 W/kg SAR (−0.02 ± 0.004).

[j] Change in effect due to non-reported SAR was greater than <2 W/kg SAR (3.17 ± 0.77).

[k] Change in effect due to >5 W/kg was greater than <2 W/kg SAR (0.30 ± 0.06).

[l] Change in effect due to non-reported SAR was greater than 5 W/kg SAR (31.03 ± 8.63).

CW/PW/CP effects:

[m] Change in effect due to CP was greater than PW (19.05 ± 1.00).

[n] Change in effect due to CP was greater than PW (5.83 ± 0.83).

[o] Change in effect due to CW was smaller than PW (−0.01 ± 0.0001).

[p] Change in effect due to CW was greater than PW (0.49 ± 0.17).

[q] Change in effect due to CP was greater than PW (6.36 ± 0.23).

[r] Change in effect due to CW was smaller than PW (−2.35 ± 0.17).

[s] Change in effect due to CP was greater than PW (3.48 ± 0.47).

being largely biased toward the positive studies with small sample sizes. Furthermore, the effect size value was smaller than that obtained in many of the positive studies with small sample size (right side of the peak effect size), which again emphasized the existence of publication bias. Finally, since the meta-analysis strongly suggested the presence of publication bias, conclusions drawn from it should be regarded as tentative.

Comparison of Meta-analysis Data with those in Historical Database for Chromosome Aberrations, Micronuclei and SCE

The mean spontaneous indices in freshly collected peripheral blood lymphocytes from normal individuals in the historical database (*79–93*) were as follows: chromosome aberrations, 1.5/100 cells (SD 3.7; $n = 15{,}594$); micronuclei, 9.0/1000 cells (SD 8.0; $n = 8667$); SCE, 7.6/cell (SD 1.6; $n = 4576$). The maximum indices obtained in RF-radiation-exposed and control groups in the meta-analysis were similar to the above indices in the historical database.

CYTOGENETIC END POINTS AS BIOMARKERS FOR CANCER RISK

To the best of our knowledge, there has been no systematic analysis of human health risks using the data obtained with the comet assay. The original technique (*94*) was modified (*95–98*) for different purposes (*37*). The damage is assessed using a computerized image analysis system or from manual/visual classification of comets (*99*). When

TABLE 6
Heterogeneity in RF-Radiation Exposure Characteristics on the Effects observed in Comet Tail Length Measured in μm (SBM), Comet Tail Moment (SBM), Chromosomal Aberrations (CA) and Micronuclei (MN)

End point		Number of E − C effects examined	RF-radiation research publications		
			Sample size	Controls (C)	RF-radiation-exposed (E)
SBM	Mean		522	57.7	57.3
	SD			18.1	18.5
	Upper limit[a]			36.1	
	E − C range[b]	110		−29.0 to 70.0 (4 of 110 = 3.6%)	
SBR	Mean		660	1.6	1.7
	SD			4.4	4.2
	Upper limit[a]			8.8	
	E − C range[b]	182		−2.3 to 5.0 (0 of 182 = 0%)	
CA/100 cells	Mean		174	1.5	2.8
	SD			2.6	4.2
	Upper limit[a]			5.3	
	E − C range[b]	17		−0.5 to 7.7 (3 of 17 = 17.6%)	
	Complete dosimetry[c]			−0.5 to 0.8 (0 of 12 = 0%)	
	Incomplete dosimetry[c]			2.05 to 7.68 (3 of 5 = 60%)	
MN/1000 cells	Mean		1940	5.0	5.7
	SD			2.4	6.2
	Upper limit[a]			4.7	
	E − C range[b]	174		−9.2 to 31.4 (10 of 174 = 5.8%)	
	Complete dosimetry[c]			−9.2 to 9.3 (2 of 161 = 1.2%)	
	Incomplete dosimetry[c]			−5.0 to 31.4 (8 of 13 = 61.5%)	

[a] Upper limit is 2 × SD above control mean, i.e. 97.5 percentile.
[b] RF radiation-exposed − Control (E − C) range is the minimum and maximum for all E − C values used in the multiple regression.
[c] The description of dosimetry, i.e., complete or incomplete, was considered as an example of high or poor quality of publication, respectively. The percentages in parentheses are the number of studies with differences (E − C) greater than the upper limit values.

comet data are collected using continuously growing, unsynchronized cultured cells exposed to RF radiation for prolonged periods, it is important to include cell cycle analysis to determine the numbers of cells in S phase and to enumerate apoptotic cells since such cells could be included as damaged cells (*100*). Since most cell types have inherent capacity to repair DNA strand breaks within few hours, the results from the comet assay would provide more meaningful information if the damage assessment included evaluation of DNA repair. It is worth mentioning genetic toxicology investigations (*101*) in which cells from eight different organs of mice treated with 208 chemicals selected from the carcinogenicity database of the International Agency for Research on Cancer and from the U.S. National Toxicology Program were examined. The results from comet assays were compared with those from other genotoxicity end points, e.g., Ames in several bacterial tester strains, chromosome aberrations, micronuclei and unscheduled DNA synthesis. The conclusion was that no single test was capable of detecting all relevant genotoxic/carcinogenic agents, and the recommendation was to conduct a battery of *in vitro* and *in vivo* tests for genotoxicity (*101*).

The incidence of chromosome aberrations has been used for several decades to monitor occupational and environmental exposures to genotoxic carcinogens. Several researchers have conducted a systematic analysis of the spontaneous incidence of chromosome aberrations as a biomarker to predict carcinogenic risk in humans. The advantage of using chromosome aberrations as a biomarker is that the experimental procedure was standardized, and very few modifications were made to the classical cytogenetic technique. Despite the fact that the analysis is time-consuming, chromosome aberrations are the most reliable biomarker to predict increased cancer risk in humans (*101–105*). Data from several studies have also shown that the aberration frequencies are increased even prior to the clinical manifestation of disease.

The existence of micronuclei as a separate entity, apart from the main nucleus in a cell, has been known for decades. Micronuclei may contain portions of broken chromosomes (clastogenic effect) or whole chromosomes that were not incorporated into daughter cells during cell division due to spindle disruption (aneugenic effect). Preliminary evidence has been presented that an increased incidence of micronuclei predicts enhanced risk of cancer in humans (*106*). Since micronuclei arise as a result of clastogenic and/or aneugenic effects, it is useful to determine the contents of each micronucleus (using fluorescence *in situ* hybridization techniques) for the absence in the case of the former or presence of whole chromosome in the case of the latter. However, the possibility of the presence of broken chromosomal fragments with intact centromere

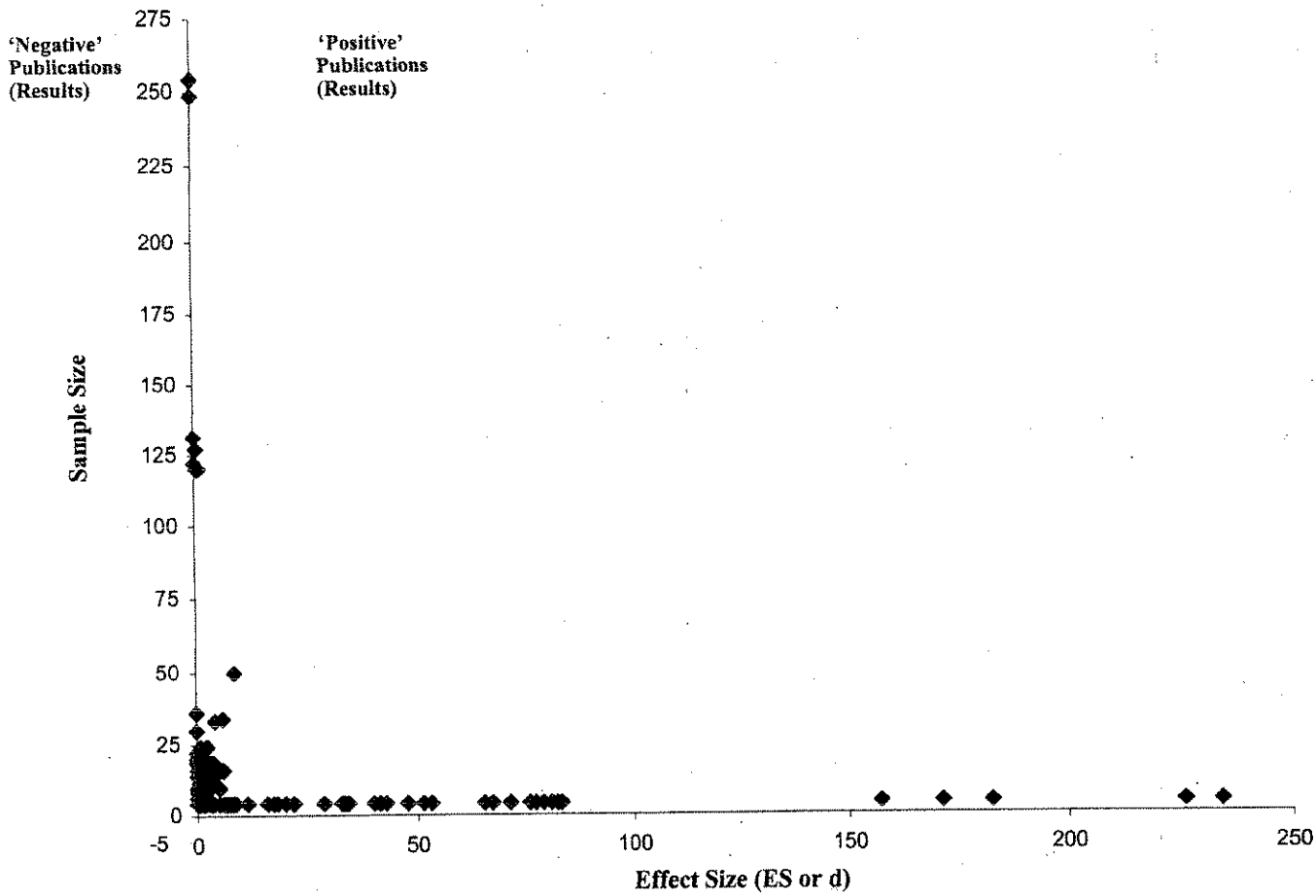

FIG. 1. The skewed publication bias reporting positive results (significant difference between experimental and control groups of cells) with small sample size. Each data point represents one effect from a group of exposed and control conditions, in one publication, for one genotoxicity end point. There were a total of 572 data points (175 data points <0, 17 data points of 0, and 380 data points >0). Detailed explanation is given in the text.

which gives the appearance of whole chromosome in micronuclei cannot be ruled out.

SCE are cytological manifestations of consequences of errors in DNA replication (*107*). Although SCE are more sensitive indicators of exposure to genotoxic agents than chromosome aberrations and micronuclei, the consolidated data reported in the literature did not appear to have a predictive value. Nonetheless, SCE would remain a valuable end point among the short-term assay systems because of the sensitivity and smaller effort needed for their analysis. The incidence of SCE was reported in only three publications (*19, 26, 71*) and the meta-analysis data, which were based on a very small sample size, indicated that the weighted mean difference between exposed and control groups (and effect size) was small, in the range between 0.74 and 1.26 (i.e., <1.5 SCE/cell).

PERSPECTIVE FROM META-ANALYSIS AND CONCLUSION

Cytogenetic investigations are important because most genotoxic agents are also carcinogens. Non-genotoxic agents can also contribute to the development of cancer by enhancing the damage induced by known genotoxic agents (epigenetic effect). To protect the general public and personnel who are occupationally exposed to RF radiation, organizations such as the ICNIRP (*108*) and IEEE (*109*) have recommended safety guidelines (based on 4 W/kg SAR, which is the threshold for heat generation). The following are the recommended whole-body average SARs: 0.4 W/kg for occupationally exposed personnel (1/10 safety factor) and 0.08 W/kg for the general public (1/50 safety factor). The SAR recommended for localized exposure is 1.6 W/kg, for example, for brain in mobile phone users. When the investigations were conducted under these recommended safety guidelines, the overall genotoxicity indices obtained in the meta-analysis were similar in RF-radiation-exposed and control groups (in certain RF-radiation exposure conditions, there was a statistically significant increase in damage assessed from some end points), and the mean differences (the difference between exposed and control groups) between the two groups as well as the effect size due to RF-radiation exposure were small. Also, the mean indices for chromosome aberrations and micronuclei

in RF-radiation-exposed and sham-/unexposed controls were within the spontaneous levels reported in the historical database. 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 (*104*), it is relevant to include more than one genotoxicity end point for assessment of DNA damage in future investigations of RF radiation.

SUPPLEMENTARY INFORMATION

Magnitude of Difference between RF-Radiation-Exposed and Controls (E − C), and Effect Size (ES) or Standardized Mean Difference (d). http://dx.doi.org/10.1667/RR0987.1.s1

Supplementary Table 1: List of Publications in Chronological Order. http://dx.doi.org/10.1667/RR0987.1.s2

Supplementary Table 2: Publication Characteristics. http://dx.doi.org/10.1667/RR0987.1.s3

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