Environment International 193 (2024) 109104

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Systematic Review

Genotoxicity of radiofrequency electromagnetic fields on mammalian cells *in vitro*: A systematic review with narrative synthesis

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ARTICLE INFO

Keywords:
Radiofrequency electromagnetic fields
Genotoxicity
In vitro
Systematic review

ABSTRACT

Background: Over the last decades, great concern has been raised about possible adverse effects to human health due to exposures to radiofrequency electromagnetic fields (RF-EMF, 100 kHz – 300 GHz) emitted by wireless communication technologies. In 2011 the International Agency for Research on Cancer classified RF-EMF as possibly carcinogenic to humans, highlighting that the evidence was weak and far from conclusive. Updated systematic reviews of the scientific literature on this topic are lacking, especially for mechanistic studies.
Objectives: To perform a systematic review of the scientific literature on genotoxic effects induced by RF-EMF in *in vitro* experimental models. The overall aim is to assess the confidence and level of evidence of the induced effects in mammalian cell cultures.
Methods: Full details regarding the eligibility criteria, information sources, and methods developed to assess risk of bias in the included study, are reported in our published protocol (Romeo et al. 2021). The databases NCBI PubMed, Web of Science, and EMF-Portal were used as information sources (last searched on 31st December 2022). In developing the systematic review, we followed the guidelines provided by the National Toxicology Program-Office of Health Assessment and Translation (NTP-OHAT), adapted to the evaluation of *in vitro* studies. A narrative synthesis of the body of evidence was performed by tabulating data classified according to meaningful groups (endpoints) and sub-groups (exposure parameters). This report, abstract included, conforms to the PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.
Results: Out of 7750 unique records identified, 159 articles were eligible for inclusion. From the extracted data, we identified 1111 experiments (defined as independent specific combinations of diverse biological and electromagnetic parameters). The large majority (80%) of experiments reviewed did not show statistically significant genotoxic effects of RF-EMF exposures, and most "positive" studies were rated as of moderate to low quality, with negative ratings in the key bias domains. A qualitative evidence appraisal was conducted at the endpoint level, and then integrated across endpoints.
Discussion: To the best of our knowledge, this is the first systematic review of the scientific literature on genotoxic effects in mammalian cell cultures in relation to RF-EMF exposure, which confirms and strengthens conclusions from previous syntheses of this specific topic thanks to the use of transparently reported methods, pre-defined inclusion criteria, and formal assessment of susceptibility to bias. Limitations of the evidence included the frequent reporting of findings in graphical display only, and the large heterogeneity of experimental data, which precluded a *meta*-analysis.
Conclusions: In the assessment restricted to studies reporting a significant effect of the exposure on the outcome, we reached an overall assessment of "low" confidence in the evidence that RF-EMF induce genotoxic effects in mammalian cells. However, 80% of experiments reviewed showed no effect of RF exposure on the large majority of endpoints, especially the irreversible ones, independently of the exposure features, level, and duration (moderate evidence of no effect). Therefore, we conclude that the analysis of the papers included in this review, although only qualitative, suggests that RF exposure does not increase the occurrence of genotoxic effects *in vitro*.
Framework and funding: This systematic review addresses one of the evidence streams considered in a larger systematic review of the scientific literature on the potential carcinogenicity of RF-EMF, performed by scientists

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https://doi.org/10.1016/j.envint.2024.109104
Received 13 September 2023; Received in revised form 16 October 2024; Accepted 24 October 2024
Available online 26 October 2024

from several Italian public research agencies. The project is supported by the Italian Workers' Compensation Authority (INAIL) in the framework of the CRA with the Istituto Superiore di Sanità "BRiC 2018/06 – Scientific evidence on the carcinogenicity of electromagnetic fields".

1. Introduction

1.1. Rationale

Exposure of the public to radiofrequency electromagnetic fields (RF-EMF, 100 kHz – 300 GHz) emitted by wireless communication technologies (including mobile phones, base stations, and WiFi) raises concern regarding possible health effects. The upcoming diffusion of 5G networks is expected to have a major impact on exposure scenarios, due to the use of very high carrier frequencies with massive bandwidths, and increased base station density, which will also increase risk perception.

The exposure limits established by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guarantee protection against the established effects of RF-EMF, *i.e.* the stimulation of excitable tissues in the intermediate frequency range (100 kHz–10 MHz), and temperature increase due to the absorption of electromagnetic energy by the body tissues (above 10 MHz) (ICNIRP 2020b). The induction of long-term effects, like cancer, due to prolonged exposures to RF-EMF below the limits is still a matter of scientific and public debate. Many epidemiological and experimental (*in vivo* and *in vitro*) studies have been performed over the last decades, but the results are still inconclusive and conflicting. The available scientific literature has been analyzed by several international panels of experts (ANSES 2013; ARPANSA 2014; IARC 2013; IEEE 2019; SCENIHR 2015; SCHEER 2023) and individual scientists (Verschaeve 2012; Vijayalaxmi and Scarfi 2014).

Among the experimental studies, *in vitro* mechanistic studies have recently received increased emphasis by the International Agency for Research on Cancer (IARC), which highlights their importance in corroborating evidence and providing biological plausibility to other types of studies, provided that the quality of the study design, exposure assessment methods and biological assay validity are assured (Samet et al. 2020). Genotoxicity, a key characteristic of human carcinogens (Smith et al. 2016), is one of the most investigated outcomes in experimental studies on the effects of RF-EMF (SCHEER 2023). However, none of the ten systematic reviews commissioned by the World Health Organization (WHO) in the framework of an updated RF-EMF hazard and risk assessment, deals with this topic (Verbeek et al. 2021). *In vitro* studies addressing genetic damage in mammalian cells exposed to RF-EMF were the subject of comprehensive reviews (Manna and Ghosh 2016; Meltz 2003) and *meta*-analyses (Halgamuge et al. 2020; Vijayalaxmi and Prihoda 2008; 2012; 2019), even though none of these literature syntheses met the requirements of a proper systematic review, due to the lack of transparently reported methods, pre-defined inclusion criteria, and formal assessment of susceptibility to bias.

1.2. Objective

To perform a systematic review of the scientific literature on genotoxic effects induced by RF-EMF in *in vitro* experimental models. The overall aim is to assess the confidence and level of evidence of the induced effects in mammalian cell cultures.

2. Methods

The systematic review was carried out following the guidelines developed by the National Toxicology Program-Office of Health Assessment and Translation (NTP-OHAT 2019), and according to the detailed procedures reported in a previously published protocol (Romeo et al. 2021), briefly summarized below.

The reporting of this systematic review, abstract included, conforms to the PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Page et al. 2021a; Page et al. 2021b).

We included experimental *in vitro* studies assessing the capability of RF-EMF (100 kHz to 300 GHz), to induce genotoxic effects in mammalian cells, with no restrictions on species (human or animal), biological model (freshly collected cells, or cell lines), cell nature (healthy or cancerous). The PECO (Population, Exposure, Comparator, Outcome) statement is reported in Table 1.

2.1. Amendments to the protocol

In the summary risk-of-bias (RoB) by evidence stream, or tiering, (Table 3 of the published protocol), we reported the "Selection bias" domain, but decided not to consider this item for the final RoB assessment, since all the included studies used homogeneous cell suspensions, and therefore, they were all considered at "definitely low" RoB for the "randomization of the exposure levels" and "allocation concealment" questions. Considering these items in the tiering would have biased towards the Tier 1 classification the whole quality assessment.

2.2. Inclusion and exclusion criteria

We included experimental *in vitro* studies assessing the capacity of RF-EMF to induce genotoxic effects in mammalian cells (Table 1), with no restrictions on species (humans or animal), biological model (freshly collected cells, or immortalized cells), cell nature (healthy or cancerous), or cell lineage. We did not include studies on genotoxic effects of RF-EMF in non-mammalian cells to reduce as much as possible the indirectness of the evidence stream. We did not apply restrictions on the frequency band in the range 100 kHz to 300 GHz, or on exposure duration. We excluded studies not providing information on the characteristics of the RF signal (continuous or pulsed waves, CW/PW), as well as those not reporting a quantitative measure of exposure level/dose expressed in the appropriate unit [induced electric field, E_{ind} in V/m (100 kHz–10 MHz); SAR in W/kg (10 MHz–6 GHz); or incident or

Table 1
PECO statement.

Population	*In vitro* models of healthy or cancerous mammalian cells (of human or animal origin), either immortalized or freshly collected via drawing/explantation.
Exposure	Controlled *in vitro* exposure to radiofrequency radiation (100 kHz-300 GHz), based on suitable exposure metrics. *Exposure details*: Frequency bands: 100 kHz to <10 MHz; 10 MHz to ≤6 GHz; >6 GHz to ≤300 GHz; Metrics: induced electric field (E_{ind}, V/m) in the 100 kHz-10 MHz range, Specific Absorption Rate (SAR, W/kg) in the 10 MHz – 6 GHz range, power density (PD) of the incident or absorbed field (W/m^2) in the 6 GHz – 300 GHz range; Signal characteristics: continuous wave (CW); pulsed wave (PW); Duration (hours).
Comparator	Either incubator (negative) or sham-exposed (sham) control samples.
Outcome	Genotoxicity, intended as a capability of inducing DNA damage, and/or mutations, assessed as: *Primary endpoints*: chromosomal aberrations, micronuclei, aneuploidy, spindle disturbances, sister chromatid exchanges, mutations. *Secondary endpoints*: Single and double DNA strand breaks, chromatin condensation, and 8-hydroxy-2′-deoxyguanosine adducts.

absorbed power density in W/m^2 (6 GHz–300 GHz)]. Studies in which the RF-EMF exposure of the sample was obtained using a commercial source (*e.g.*, a mobile telephone) in contact with or at a certain distance from the sample container, were excluded in absence of appropriate dosimetry analysis because, in such situation, the control of electromagnetic and environmental conditions cannot be assured, resulting in uninterpretable findings and irreplicable experimental conditions (Zeni and Scarfì 2012). With reference to the study design, admissibility was restricted to studies including unexposed samples, consisting of either incubator (negative) controls, or sham-exposed controls. The sham-control is a sample placed in an exposure system identical to that used to administer the treatment, except for the emission of RF-EMF, to guarantee the very same environmental conditions to all experimental groups. Based on the type of DNA damage (irreversible *vs.* repairable), we distinguished between genotoxicity-related endpoints of primary interest (*i.e.*, biomarkers of irreversible damage, including chromosomal aberrations, micronuclei, aneuploidy, spindle disturbances, sister chromatid exchanges, or mutations), and of secondary interest (*i.e.*, biomarkers of repairable damage (including single and double DNA strand breaks, chromatin condensation, and 8-hydroxy-2′-deoxyguanosine adducts) (Krewski et al. 2019). For studies that evaluated genotoxicity in relation to both RF-exposure alone, and to co-exposure to RF fields and other agents, only findings concerning RF-exposure alone were considered, in order to focus on potential genotoxic effects of RF-EMF themselves. We restricted inclusion to peer-reviewed journal articles reporting findings from primary studies and published in English. Letters, meeting abstracts, conference proceedings, and commentaries were excluded, whereas reviews were used to check for missing articles (Romeo et al. 2021).

2.3. Search strategy

The databases NCBI PubMed, Web of Science (WOS), and EMF-Portal were used as information sources, with bibliographic searches starting at the inception date of each database (e.g., 1946 for PubMed), and ending on 31st December 2022 (Romeo et al. 2021). For each database, we calculated the sensitivity (proportion of relevant records identified by the search) and precision [(number of relevant records divided by the total retrieved) x100] of the search strategy. The search strategies, reported in Annex 1 (Section 1) were calibrated against a library of "seed studies" investigating biological effects of RF-EMF on *in vitro* models, showing a good sensitivity (98 % and 95 % for PubMed and Web of Science, respectively), despite a low precision (6 % PubMed; 3.7 % Web of Science).

2.4. Screening for eligibility

Study selection was performed in duplicate by two reviewers (SR and MRS) and disagreements were discussed with a third assessor (OZ). The first screening was based on title and abstract, and then the full text of included studies was analyzed to verify compliance with the predefined inclusion criteria. Data extraction and recording of bibliographic information, experiment features and results, was performed by the same two reviewers, and disagreement discussed with the third one.

2.5. Data collection process and data items

Data extraction and recording of bibliographic information, experiment features and results, was performed by the same two reviewers as reported in detail below.

For each of the included studies, the following information was extracted and recorded by hand in an Excel file.

1. Bibliographic information: (paper ID, full reference, declared conflict of interest, source(s) of fundings, corresponding author).
2. Information on exposure conditions and experimental procedures:
   - o Cell model (primary cells or immortalized cell lines, of human or animal origin).
   - o Exposure conditions: RF frequency band, waveform (continuous wave or pulsed signal with indication of modulation type), level (below, around, or above the (ICNIRP 2020a) exposure limit, exposure duration (short, long, or chronic), and exposure mode (continuous or intermittent).
   - o Experimental design: presence of negative controls, sham controls, positive controls; temperature monitoring; dosimetry (appropriateness of the methods used, homogeneity of the field distribution in the samples and within samples), blindness at the step of exposure administration and sample analysis; type of endpoint (Table 1); bioassay (test type, elapsed time between exposure and sample analysis, appropriateness of the applied methods).
3. Results: number of independent experiments/ donors with replicates, statistics, qualitative (absence or presence of statistically significant alterations of the specific endpoint) results.

For each study, individual experiments were identified based on the combination of the exposure parameters (frequency, signal, level, or duration), cell type, endpoint analyzed, and elapsed time between exposure and sample analysis.

After data extraction, some descriptive statistics were derived to characterize the experiments with respect to i) year of publication; ii) cell type; iii) endpoint analyzed; and iv) exposure parameters. In relation to the latter, the following subgroups were considered:

- o Frequency: 100 kHz to <10 MHz (F1); 10 MHz to ≤6 GHz (F2); >6 GHz to ≤300 GHz (F3).
- o Duration of exposure: ≤1h (ED1, acute); >1h to ≤24 h (ED2, long); >24 h (ED3, chronic, including intermittent exposures lasting several days).
- o Exposure level: Specific Absorption Rate (SAR) ≤1 W/kg or Absorbed Power Density (S_{ab}) <20 W/m^2 or Incident Power Density (S_{inc}) <10 W/m^2 (EL1); 1 W/kg < SAR ≤ 2 W/kg or S_{ab} = 20 W/m^2 or S_{inc} = 10 W/m^2 (EL2); SAR > 2 W/kg or S_{ab} > 20 W/m^2 or S_{inc} > 10 W/m^2 (EL3).[2]

We considered the feasibility of a quantitative synthesis of results, concluding that the large methodological variation across experiments precluded a *meta*-analysis. The overall occurrence of statistically significant effects in the whole experimental dataset, and the proportion of "positive" experiments within exposure- and endpoint-specific data subsets, were also evaluated. We summarized the findings in endpoint-specific tables, displaying the presence and direction of effects across exposure parameters and studies.

2.6. Risk of bias assessment

The need of specific guidelines for systematic reviews of mechanistic studies *in vitro* is widely recognized, and efforts to develop standardized approaches are ongoing (De Vries et al. 2021).

To assess the study's internal validity, or risk of bias (RoB), we used the OHAT Risk of Bias Rating Tool for Human and Animal Studies (NTP-OHAT 2015b), following the methodological indications provided by the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration [(NTP-OHAT 2019), pp. 36–43]. Although the OHAT Handbook does not explicitly consider experimental studies *in vitro*, suggestions on how to adapt the procedures for experimental animal studies to studies on cellular models are available (Rooney 2015a).

We briefly summarize below the OHAT approach to the assessment

[2] It should be noted that the value of 20 W/m^2 for S_{ab} refers to the ICNIRP basic restriction, whereas the value of 10 W/m^2 for S_{inc} is a reference level.

of the internal validity for experimental animal studies, at the individual study level (§ 2.5.1), and as summary RoB (§ 2.5.2); then, we describe the customization of the OHAT RoB process to the line of evidence examined in our systematic review (Annex 2).

2.6.1. Assessment of the internal validity at the individual study level

Bias is defined as a systematic error (or deviation from the truth) in results or inferences (NTP-OHAT 2019). The OHAT RoB tool (NTP-OHAT 2015b) aims at assessing whether the design and conduct of a study compromised the credibility of the link between exposure and outcome. The OHAT RoB tool was designed to coherently assess RoB across various evidence streams (human studies, studies on animal models, and mechanistic studies). It consists of a common set of 11 questions relating to six bias domains. The questions relevant to experimental animal studies were used as the basis for development of our *in vitro* RoB tool (Table 2), in line with previous hazard assessments performed by OHAT ((National Toxicology 2019; NTP-OHAT 2016; Rooney 2015b).

We developed bias-answer forms customized to the subject of this review (Annex 2, Section 1) and used them to assign RoB ratings, according to the four options listed in Annex 2 (Table S2.1).

In customizing the OHAT bias-answer forms (NTP-OHAT 2015a) we accounted for the specific features of the reviewed body of evidence, and the good experimental practices in the relevant research field. The rating instructions for each bias domain are detailed in Annex 2 (Section1) and are briefly recalled below.

- Under the *Selection bias* domain, there are two bias questions relevant for the included studies: "Randomization of the exposure levels" and "Allocation concealment". All studies using homogeneous cell suspensions may be considered at definitely low risk of bias for these questions. As a matter of fact, the majority of *in vitro* studies investigating the genotoxicity use homogeneous cell suspensions, even when the cells are extracted from tissues (e.g. blood or sperm). Experimental samples are prepared by taking predefined volumes of cell suspensions from a single batch, which are then randomly allocated to identical cell containers (Petri dishes, flasks, etc.).
- *Confounding bias*: according to OHAT, confounding bias is not a relevant key-item for experimental animal studies, whereas the influence of particular confounding or effect-modifying factors may be assessed under "other potential threats to internal validity" (NTP-OHAT 2015b). We considered these indications also applicable to experimental *in vitro* studies.
- *Performance bias*: under this bias domain, we addressed the presence of sham and/or incubator controls, and if they were handled in parallel to RF-exposed samples, as well as blinding of the research personnel to study groups during exposure assignment/administration.
- Attrition/Exclusion bias: for the *in vitro* experimental studies considered herein, we addressed under this bias domain loss of samples (proportion, and distribution across study groups).
- Confidence in exposure characterization: We considered the items related to adequate description of RF signal, exposure set-up, methods to monitor relevant electromagnetic and biological parameters, and appropriateness of methods for dosimetry analyses.
- Confidence in outcome characterization was assessed in relation to endpoint-specific "gold-standard" methods of determination, and their correct implementation as documented using positive controls, as the latter provide evidence of controlled experimental conditions, and assurance that the assay methodology is responding adequately to a well-known agent (Simko et al. 2016).
- Selective reporting: under this domain, as far as deductible from the information available in the study reports, we assessed whether reporting of all endpoints relative to the analyzed samples, and findings from the analyzed exposure conditions, was complete and independent of the magnitude and direction of the results.
- Other threats to internal validity: under this heading, we assessed the RoB related to temperature monitoring and control, as well as the appropriateness of statistical analysis.

Table 2
Bias questions relevant for the studies eligible for inclusion in the current systematic review (key elements considered for the tier classification are highlighted in bold).

Bias Domains	Bias questions	Relevance
Selection bias	*Was administered dose or exposure level adequately randomized?*	Yes
	Was allocation to study groups adequately concealed?	Yes
	Did selection of study participants result in appropriate comparison groups?	No
Confounding	*Did the study design or analysis account for important confounding and modifying variables?*	No
Performance bias	***Were experimental conditions identical across study groups?***	Yes
	Were the research personnel blinded to the study group during the study?	Yes
Attrition bias	*Were endpoint data complete without attrition or exclusion from analysis?*	Yes
Detection bias	***Can we be confident in the exposure characterization?***	Yes
	Can we be confident in the outcome assessment?	Yes
Selective reporting	*Were all measured endpoint conditions reported?*	Yes
Other bias	*Were statistical methods appropriate?*	Yes
	Did the study design or analysis account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	Yes

2.6.2. Summary RoB assessment

We applied the optional OHAT's 3-level tiering of the quality of individual studies, based on summary assessments of RoB for the domains most relevant to the specific systematic review (NTP-OHAT 2019) (Annex 2, Table S2.2). This tiering differs from scaling and is consistent with the Cochrane's overall risk-of-bias judgement (Higgins et al. 2023; Sterne et al. 2023).

In line with the OHAT procedure, we selected the bias items more relevant to our research topic, *i.e.*, (1) Identity of experimental conditions across study groups; (2) Confidence in exposure assessment; (3) Confidence in outcome assessment; (4) Temperature monitoring and control. To classify each study by bias-tier, we followed the OHAT criteria (NTP-OHAT 2019).

2.7. Synthesis of the evidence

We followed the guidance and tools provided by (Campbell et al. 2020; Popay et al. 2006) to conduct narrative syntheses in systematic reviews. We performed a preliminary synthesis by using the "Groupings and clusters" and "Tabulation" tools. Specifically, we grouped the included studies by endpoint, and tabulated the data reporting, for each experimental condition (cell type, exposure level, frequency, or duration), the related effect in terms of absence or presence of statistically significant changes (increased or decreased occurrence) of the specific endpoint in the exposed samples compared to the unexposed ones.

We carried out further syntheses by considering subgroups related to the exposure conditions (frequency, level, and duration), and to the summary RoB bias (−tiers) classification.

2.8. Certainty of evidence assessment

To assess the confidence in evidence (also called certainty or quality of the evidence), we followed the OHAT guidelines for animal studies (NTP-OHAT 2019), based on the GRADE approach, adapting them to *in vitro* mechanistic studies.

Table 3
Study characteristics table.

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
1	(Franzellitti et al. 2010)	1800 MHz (CW, GSM217 Hz, GSM talk); 2 W/kg; 4 h/16 h/24 h (5 min ON/10 min OFF)	HTR-8/Svneo, human trophoblast	DNA SB (Alkaline Comet assay)	Data reported in graphics
2	(Belyaev et al. 2009)	905/915 MHz (GSM), 1947.4 MHz (UMTS); 37 or 40 mW/kg; 1 h	Human peripheral blood lymphocytes	DNA SB (53BP1 and γ-H2AX foci formation); Chromatin condensation (anomalous viscosity time dependencies assay)	NO: blind exposure, concurrent sham. Data reported in graphics
3	(Campisi et al. 2010)	900 MHz (PW); 0.26 W/m^2; 20 min	Astrocytes from albino rat brain	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis, positive control, appropriate dosimetry. Data reported in graphics
4	(De Iuliis et al. 2009)	1800 MHz (CW); [0.4, 1, 2.8, 5, 10, 27.5] W/kg; 16 h	Human spermatozoa	8-OH-dG adducts (FITC-conjugated anti-8-OH-dG antibody)	NO: blind exposure and analysis, temp monitoring, appropriate dosimetry. Data reported in graphics
5	(Luukkonen et al. 2010)	872 MHz (CW, GSM); 5 W/kg, 3 h	Human SH-SY5Y Neuroblastoma Cells	DNA SB (Alkaline Comet assay)	NO: blind exposure
6	(Al-Serori et al. 2017)	1950 MHz (UMTS); 0.25; 0.5, 1 W/kg; 16 h (5 min OFF − 10 min ON)	human derived glioma cell line U251	MN (CBMN assay)	NO: blind exposure and analysis, positive control; NR: dosimetry Data reported in graphics
7	(Angeluts et al. 2014)	(0.1–2.0) x10^{6}MHz (PW); 125 and 200 μW/cm^2; 20 min	Whole blood leukocytes	DNA SB (Alkaline Comet assay)	Data reported in graphics
8	(Antonopoulos et al. 1997)	380 (TETRA25), 900 (DCS), 1800 (GSM) MHz; 80, 208, 1700 mW/kg; 56 h	Human peripheral blood lymphocytes	SCE (BRDU)	NO: sham, blind exposure and analysis, positive control; NR: field homogeneity. Data reported in graphics
9	(Avendaño et al. 2012)	2450 MHz (WiFi); 0.4–1.2 μW/cm^2; 4 h	Spermatozoa from human sperm	DNA SB (TUNEL Assay)	NO: sham, blind exposure and analysis, appropriate dosimetry Data reported in graphics
10	(Ballardin et al. 2011)	2450 MHz (CW); 5 and 10 mW/cm^2; 15 min	Chinese hamster V79	Spindle disturbances (Immunostaining)	NO: sham, blind exposure and analysis; NR: field homogeneity. Data reported in graphics
11	(Baohong et al. 2005)	1800 MHz (GSM); 3 W/kg; 2 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	–
12	(Baohong et al. 2007)	1800 MHz (GSM); 3 W/kg; 1.4 and 4 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	–
13	(Belyaev et al. 2005)	915 and 916 MHz (GSM); 37–38 mW/kg; 2 h	Human peripheral blood lymphocytes	Chromatin condensation (anomalous viscosity time dependencies); DNA SB (53BP1 foci formation)	NO: blind exposure, field homogeneity, concurrent sham Data reported in graphics
14	(Belyaev and Kravchenko 1994)	(41.5–41.7) x 10^3 (CW); 1 mW/cm^2; 10 min	Rat thymocytes	Chromatin condensation (anomalous viscosity time dependencies)	NO: blind exposure and analysis; NR: sham, temp monitoring, field homogeneity. Data reported in graphics
15	(Bisht et al. 2002)	835.62 (FDMA) and 847.74 (CDMA) MHz; 3.2, 5.1, 4.8 W/kg; 3, 8, 16, 24 h	C3H 10 T½ mouse embryo fibroblasts	MN (CBMN assay)	NO: blind exposure, field homogeneity
16	(Bisht et al. 2001)	847.74 MHz (CW); 5.5 and 4.9 W/kg; 24 h	Human blood lymphocytes	CA (FPG); MN (CBMN assay)	NO: blind exposure, field homogeneity
17	(Bourthoumieu et al. 2010)	900 MHz (GSM); 0.25 W/kg; 24 h	Human amniotic cells (fibroblastic lineage)	Aneuploidy (FISH analysis)	NO: blind exposure and analysis; NR: field homogeneity
18	(Bourthoumieu et al. 2011)	900 MHz (GSM); 0.25, 1, 2, 4 W/kg; 24 h	Human amniotic cells (fibroblastic lineage)	Aneuploidy (FISH analysis)	NO: blind exposure and analysis, positive control; NR: field homogeneity
19	(Brech et al. 2019)	123.90 x 10^{-3}, 250.80x10^{-3}, 250.80x10^{-3} MHz (CW); 0.38—–5.75 V/m; 1, 2, 3, 4, 5, 20, 24 h	Canine blood leukocytes; Human blood leukocytes	DNA SB (Alkaline Comet assay)	NO: sham, blind exposure Data reported in graphics
20	(Chemeris et al. 2006)	8800 MHz (PW); 1.6 kW/kg; 40 min	Human whole blood leukocytes; Human isolated lymphocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure; NR: field homogeneity
21	(Ciaravino et al. 1987)	2450 MHz (PW); 33.8 W/kg; 2 h	Chinese hamster ovary	SCE (BRDU)	NR: dosimetry
22	(Ciaravino et al. 1991)	2450 MHz (PW); 33.8 W/kg; 2 h	Chinese hamster ovary	SCE (BRDU)	NR: dosimetry

(*continued on next page*)

Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
23	(d'Ambrosio et al. 1995)	9000 MHz (CW and PW); 90 mW/g; 10 min	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: sham, blind exposure, positive control; NR: field homogeneity
24	(d'Ambrosio et al. 2002)	1748 MHz (CW and GSMK); 2.25 W/kg; 15 min	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: sham, blind exposure, positive control
25	(De Amicis et al. 2015)	(0.12) x10^6 MHz (PW); 0.4 mW/cm^2; 20 min	Human Caucasian Foetal Foreskin Fibroblasts HFFF2	DNA SB (Neutral and Alkaline Comet assay, γ-H2AX foci); MN (CBMN and CREST assays); CA (Non-disjunction FISH and telomere length analysis)	NO: blind exposure and analysis, positive control; NR: field homogeneity Data reported in graphics
26	(Duan et al. 2015)	1800 MHz (GSM); 1, 2, 4 W/kg; 24 h	mouse spermatocyte-derived cell line (GC-2)	DNA SB (Alkaline and FPG modified Comet assay, γ-H2AX foci formation)	Data reported in graphics
27	(Durdik et al. 2019)	915 (GSM), 1947.4 (UMTS) MHz; 4 and 40 mW/kg; 1–17 h	Mononuclear cells isolated from umbilical cord blood	DNA SB (Alkaline and Neutral Comet assay, γ-H2AX and 53BP1 foci formation)	NO: blind exposure and analysis, field homogeneity Data reported in graphics
28	(Esmekaya et al. 2011)	1800 MHz (GSM); 0.21 W/kg; 6, 8, 24, 48 h	Human peripheral blood lymphocytes	SCE (Hoescht staining)	NO: positive control, blind analysis; NR: field homogeneity. Data reported in graphics
29	(Falone et al. 2018)	1950 MHz (UMTS); 0.3 and 1.25 W/kg; 20 h	SHSY-5Y human neuroblastoma	DNA SB (Alkaline Comet assay)	NO: blind exposure. Data reported in graphics
30	(Falzone et al. 2010)	900 MHz (GSM); 2 and 5.7 W/kg: 1 h	Human spermatozoa	DNA SB (TUNEL assay)	NO: sham, positive control, blind exposure and analysis; NR: field homogeneity. Data reported in graphics
31	(Franchini et al. 2018a)	0.10–0.15 x10^6 MHz (PW); 0.4 mW/cm^2; 20 min	Human dermal fibroblasts	MN (CREST); CA (Telomere length analysis); DNA SB (γ-H2AX and 53BP1 foci formation)	NO: blind exposure and analysis, positive control (three cases). Data reported in graphics
32	(Franchini et al. 2018b)	25000 MHz (CW); 0.8 mW/cm^2; 20 min	Human Caucasian fetal foreskin fibroblasts (HFFF2); Human dermal fibroblasts	DNA SB (Alkaline Comet assay and γ-H2AX foci formation); MN (CREST); CA (Non-disjunction FISH and telomere length analysis)	NO: blind exposure and analysis, positive control; NR: field homogeneity. Data reported in graphics
33	(Gajski and Garaj-Vrhovac 2009)	915 MHz (GSM); 0.6 W/kg; 20 min	Human peripheral blood lymphocytes	DNA SB (Alkaline and FPG-modified Comet assay)	NO: sham, positive control, blind exposure and analysis; NR: field homogeneity
34	(Gapeyev et al. 2014)	42200 MHz (CW and PW); 0.1 mW/cm^2; 20 min	mouse whole blood leukocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure, temp monitoring; NR: field homogeneity. Data reported in graphics
35	(Gapeyev and Lukyanova 2015)	42200 MHz (CW and PW); 0.1 mW/cm^2; 20 min	mouse whole blood leukocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure, temp monitoring; NR: field homogeneity
36	(Garaj-Vrhovac et al. 1992)	7700 MHz (CW); 0.5, 10, 30 mW/cm^2; 0.5 and 1 h	Human peripheral blood lymphocytes	MN (CBMN assay); CA (Giemsa staining)	NO: sham, positive control, temp monitoring, blind exposure and analysis; NR: dosimetry, field homogeneity, donors' number. Data reported in graphics
37	(Garaj-Vrhovac et al. 1990)	7700 MHz (CW); 30 mW/cm^2; 15, 30, 60 min	V79 Chinese hamster cells	CA (Giemsa staining)	NO: sham, positive control, blind exposure and analysis; NR: dosimetry, field homogeneity, donors' number
38	(Garaj-Vrhovac et al. 1991)	7700 MHz (CW); 30 mW/cm^2; 15, 30, 60 min	V79 Chinese hamster cells	MN (CBMN assay); CA (Giemsa staining)	NO: sham, positive control, blind exposure/analysis, temp monitoring; NR: dosimetry, field homogeneity, number of experiments
39	(Glaser et al. 2016)	900 (GSM), 1950 (UMTS), 2535 (LTE) MHz; 0.5, 1, 2, 4 W/kg; 4, 20, 66 h	human promyelocytic leukemia cells HL-60; Human hematopoietic stem cells (HSC)	DNA SB (Alkaline Comet assay)	NO: field homogeneity. Data reported in graphics
40	(Gulati et al. 2020)	1923, 1947.47, 1977 MHz (UMTS); 40 mW/kg; 1 and 3 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis, temp monitoring, field homogeneity
41	(Hansteen et al. 2009a)	2300 MHz (CW and PW); 10 W/m^2; 53 h	Human peripheral blood lymphocytes	CA (Giemsa staining)	NO: blind exposure, appropriate dosimetry; NR: field homogeneity

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Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
42	(Hansteen et al. 2009b)	18,000 (CW), 16,500 (PW) MHz; 1 and 10 W/m^2; 53 h	Human peripheral blood lymphocytes	CA (Giemsa staining)	NO: blind exposure, appropriate dosimetry; NR: field homogeneity
43	(He et al. 2017)	900 MHz (CW); 0.00025 W/kg; 3 h/day x 5 days	Bone marrow stromal cells	DNA SB (Alkaline Comet assay)	NO: blind exposure, appropriate dosimetry; NR: field homogeneity. Data reported in graphics
44	(Herrala et al. 2018)	872 MHz (CW and GSM); 0.6 and 6 W/kg; 24 h	Rat primary astrocytes	DNA SB (Alkaline Comet assay); MN (Flow-cytometry)	NO: blind exposure
45	(Hintzsche et al. 2012)	106000 MHz (CW); 0.04, 0.39, 0.88, 2 mW/cm^2; 2, 8, 24 h	HaCaT (human keratinocytes); Human dermal fibroblasts; Human-hamster hybrid cells (A_L)	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind analysis. NR: field homogeneity Data reported in graphics
46	(Hintzsche et al. 2011)	106000 MHz (CW); 0.043, 0.43, 4.3 mW/cm^2; 30 min	Human-hamster hybrid cells (A_L)	Spindle disturbances (acetic orcein staining)	NO: sham, blind exposure. Data reported in graphics
47	(Hook et al. 2004)	847.74 (CDMA), 835.62 (FDMA), 813.56 (iDEN), 836.55 (TDMA) MHz; 2.4, 2.6, 3.2, 24, 26 mW/kg; 2, 3, 21 h	Human lymphoblastic leukemia cells (Molt4)	DNA SB (Alkaline Comet assay)	NO: blind exposure; NR field homogeneity. Data reported in graphics
48	(Hou et al. 2015)	1800 MHz (GSM), 2 W/kg; 0.5, 1, 2, 4, 6, 8 h	Mouse embryonic fibroblasts NIH/3T3	DNA SB (γ-H2AX foci formation)	~~NO: blind exposure; NR: field homogeneity.~~ Data reported in graphics
49	(Houston et al. 2018)	1800 MHz (CW); 0.15 W/kg; 1, 2, 3, 4, 6 h	Mouse spermatogonial GC1 cells; Spermatocyte GC2 cells; Mouse cauda epididymal spermatozoa	DNA SB (Alkaline Comet assay); 8-OH-dG adducts (spectrophotometric assay); CA (HALO assay)	NO: sham, positive control (8 cases), blind exposure and analysis, appropriate dosimetry; NR: field homogeneity. Data reported in graphics
50	(Huang et al. 2008a)	1762.5 MHz (CDMA); 10 W/kg; 24 h	Jurkat T cells	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis; NR: field homogeneity
51	(Huang et al. 2008b)	1763 MHz (CDMA); 20 W/kg; 6, 24, 48 h	HEI-OC1 mouse auditory hair cells	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis; NR: field homogeneity
52	(Jooyan et al. 2019)	900 MHz (GSM); 0.3 W/kg; 4, 12, 24 h	Chinese hamster ovary (CHO)	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: sham, blind exposure and analysis, appropriate dosimetry. Data reported in graphics
53	(Karaca et al. 2012)	10715 MHz (CW); 0.84 mW/cm^2; 18 h (6 h/day x 3 days)	Mouse brain cells	MN (CBMN assay)	NO: sham, blind exposure, positive control, appropriate dosimetry; NR: field homogeneity
54	(Kerbacher et al. 1990)	2450 MHz (PW); 33.8 W/kg; 2 h	Chinese hamster ovary (CHO)	CA (Giemsa staining)	NO: blind exposure; NR: dosimetry, field homogeneity
55	(Kim et al. 2008)	835 MHz (CDMA); 4 W/kg; 6 and 48 h	L5178Y Tk+/- mouse lymphoma; Chinese hamster lung (CHL)	DNA SB (Alkaline Comet assay); CA (Giemsa staining)	NO: blind exposure and analysis, dosimetry. NR: field homogeneity. Data reported in graphics
56	(Komatsubara et al. 2005)	2450 MHz (CW); 5, 10, 20, 50, 100 W/kg; 2 h	Mouse m5S embryonic skin cells	CA (Giemsa staining)	NO: sham, dosimetry, blind exposure, temperature monitoring
57	(Korenstein-Ilan et al. 2008)	100000 MHz (CW); 0.031 mW/cm^2; 1, 2, 24 h	Human peripheral blood lymphocytes	Aneuploidy (FISH analysis)	NO: blind exposure and analysis, positive control
58	(Koyama et al. 2004)	2450 MHz (CW); 5, 10, 20, 50, 100, 200 W/kg; 2 h	Chinese hamster ovary (CHO)-K1 cells	MN (CBMN assay)	NO: sham, blind exposure, field homogeneity
59	(Koyama et al. 2003)	2450 MHz (CW);13, 39, 25, 50, 78, 100 W/kg; 18 h	Chinese hamster ovary (CHO)-K1 cells	MN (CBMN assay)	NO: blind exposure; NR: field homogeneity
60	(Koyama et al. 2016a)	120000 MHz (CW); 5 mW/cm^2; 24 h	HCE-T human corneal epithelial cell line	MN (CBMN assay)	NO: blind exposure and analysis. Data reported in graphics
61	(Koyama et al. 2016b)	60000 MHz (CW); 1 mW/cm^2; 24 h	Human corneal epithelial (HCE-T); human lens epithelial (SRA01/04)	MN (CBMN assay); DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis. Data reported in graphics
62	(Koyama et al. 2019)	40000 MHz (CW); 1 mW/cm^2; 24 h	Human corneal epithelial (HCE-T); human lens epithelial (SRA01/04)	MN (CBMN assay); DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis. Data reported in graphics
63	(Kumar et al. 2015)	900 (CW), 1800 (GSM) MHz; 2, 2.5, 10, 12.4 W/kg; 1.5 and 2 h	Lymphoblasts from rat bones	DNA SB (Alkaline Comet assay)	NO: sham; NR: blind analysis
64	(Kumar et al. 2011)	900 MHz (CW); 2 W/kg; 30 min	Rat lymphocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure

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Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
65	(Lagroye et al. 2004)	2450 MHZ (CW); 1.9 W/kg; 2 h	C3H 10 T/2 mouse fibroblasts	DNA SB (Alkaline Comet assay)	NO: blind exposure, field homogeneity. Data reported in graphics
66	(Li et al. 2001)	847.74 (CDMA), 835.62 (FDMA) MHZ; 3.2, 4.9, 5.1 W/kg; 2, 4, 24 h	C3H 10 T/2 mouse fibroblasts	DNA SB (Alkaline Comet assay)	NO: blind exposure; NR: dosimetry, field homogeneity
67	(Gurbuz et al. 2018)	1800 MHz (GSM); 1, 2, 4 W/kg; 24 h (5 min ON/10 min OFF)	Mouse spermatocyte-derived cells (GC-2)	DNA SB (Alkaline and Neutral Comet assay and γ-H2AX foci formation)	NO: positive control. Data reported in graphics
68	(Liu et al. 2013)	1800 MHz (GSM); 1, 2, 4 W/kg; 24 h (5 min ON/10 min OFF)	Mouse spermatocyte-derived cells (GC-2)	DNA SB (Alkaline Comet assay with and without FPG modification); 8-OH-dG adducts (flow-cytometry analysis)	Data reported in graphics
69	(Lixia et al. 2006)	1800 MHz (GSM); 1, 2, 3 W/kg; 2 h	Human lens epithelial cells line SRA01/04	DNA SB (Alkaline Comet assay)	NR: number of independent experiments. Data reported in graphics
70	(Lloyd et al. 1984)	2450 MHz (CW); 104 and 193 W/kg; 20 min	Human peripheral blood lymphocytes	CA (FPG) SCE (FPG)	NO: blind exposure and analysis, field homogeneity
71	(Lloyd et al. 1986)	2450 MHZ (CW); 4, 40, 100, 200 W/kg; 20 min	Human peripheral blood lymphocytes	CA (FPG) SCE (FPG)	NO: blind exposure and analysis, field homogeneity, positive control
72	(Luukkonen et al. 2009)	872 MHz (CW, GSM); 5 W/kg; 1 h	Human neuroblastoma SHSY-5Y cells	DNA SB (Alkaline Comet assay)	NO: blind exposure
73	(Maes et al. 1995)	954 MHz (GSM); 1.5 W/kg; 2 h	Human peripheral blood lymphocytes	CA (Giemsa staining)	NO: blind exposure, temp monitoring, appropriate dosimetry, positive control; NR: field homogeneity
74	(Maes et al. 1996)	954 MHz (GSM); 1.5 W/kg; 2 h	Human peripheral blood lymphocytes	SCE (BRDU)	NO: blind exposure, temp monitoring, appropriate dosimetry; NR: field homogeneity. Data reported in graphics
75	(Maes et al. 1997)	935.2 MHz (CDMA); 0.3–0.4 W/kg; 2 h	Human peripheral blood lymphocytes	CA (Giemsa staining); SCE (BRDU)	NO: sham, blind exposure and analysis, temp monitoring, positive control; NR: dosimetry, field homogeneity. Data reported in graphics
76	(Maes et al. 2000)	455.7 MHz (PW); 6.5 W/kg; 2 h	Human peripheral blood lymphocytes	CA (Giemsa staining); SCE (BRDU)	NO: sham, blind exposure and analysis, temp monitoring, positive control; appropriate dosimetry, field homogeneity
77	(Maes et al. 2001)	900 MHz (CW, GSM); 0.4, 2, 3.5, 5.5, 10 W/kg; 2 h	Human peripheral blood lymphocytes	CA (Giemsa staining); SCE (BRDU)	NO: sham, blind exposure, temp monitoring; NR: dosimetry, field homogeneity
78	(Maes et al. 1993)	2450 MHZ (PW); 75 W/kg; 0.5, 2 h	Human peripheral blood lymphocytes	CA (Giemsa staining); SCE (BRDU); MN (CBMN assay)	NO: sham, blind exposure, appropriate dosimetry, field homogeneity, positive control
79	(Malyapa et al. 1997a)	2450 MHz (CW); 0.7, 1.9 W/kg; 2, 4, 24 h	Human glioblastoma U87MG; C3H 10 T/2 mouse fibroblasts	DNA SB (Alkaline Comet assay)	NO: blind exposure, field homogeneity. Data reported in graphics
80	(Malyapa et al. 1997b)	835.62 (FMCW), 847.74 (CDMA), 0.6 W/kg; 2, 4, 24 h	Human glioblastoma U87MG; C3H 10 T/2 mouse fibroblasts	DNA SB (Alkaline Comet assay)	NO: blind exposure, field homogeneity. Data reported in graphics
81	(Manti et al. 2008)	1950 MHz (UMTS); 0.5, 2 W/kg; 24 h	Human peripheral blood lymphocytes	CA (FISH analysis)	NO: blind exposure. Data reported in graphics
82	(Markova et al. 2005)	905, 915 MHz (GSM); 37 mW/kg; 1 h	Human peripheral blood lymphocytes	DNA SB (53BP1/γ-H2AX foci formation); Chromatin condensation (anomalous viscosity time dependencies assay)	NO: field homogeneity
83	(Markova et al. 2010)	905, 915 (GSM), 1947.4 (UMTS) MHz; 37, 39 mW/kg; 1, 2, 3 h, 10 days (1 h/day, 5 days/week)	Human diploid VH-10 fibroblasts; Human adipose mesenchimal stem cells	DNA SB (53BP1 foci formation)	NO: blind exposure; NR: dosimetry, field homogeneity. Data reported in graphics
84	(Mashevich et al. 2003)	830 MHz (CW); 2, 2.9, 4.3, 8.2 W/kg; 72 h	Human peripheral blood lymphocytes	CA (FISH analysis)	NO: sham, blind exposure, field homogeneity, positive control. Data reported in graphics
85	(Mazor et al. 2008)	800 MHz (CW); 2.9, 4.1 W/kg; 72 h	Human peripheral blood lymphocytes	CA (FISH analysis)	NO: sham, blind exposure and analysis, positive control, appropriate dosimetry, field homogeneity. Data reported in graphics

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Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
86	(McNamee et al. 2002a)	1900 MHz (CW); 0.1, 0.26, 0.92, 2.4, 10 W/kg; 2 h	Human peripheral leukocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind exposure and analysis Data reported in graphics
87	(McNamee et al. 2003)	1900 MHz (CW, PW); 0.1, 0.26, 0.92, 2.4, 10 W/kg; 24 h	Human peripheral Leukocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind exposure.
88	(McNamee et al. 2002b)	1900 MHz (TDMA); 0.1, 0.26, 0.92, 2.4, 10 W/kg; 2 h	Human peripheral leukocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind exposure and analysis
89	(Meltz et al. 1989)	2450 MHz (PW); 30 W/kg; 4 h	L5178Y mouse leukemia	Mutations (trifluorothymidine mutation assay)	NO: blind exposure and analysis
90	(Meltz et al. 1990)	2450 MHz (PW); 40 W/kg; 4 h	L5178Y mouse leukemia	Mutations (trifluorothymidine mutation assay)	NO: blind exposure and analysis; NR: field homogeneity
91	(Miyakoshi et al. 2019)	5800 MHz (CW); 1 mW/cm^2; 24 h	Human corneal epithelial (HCE-T)	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind exposure and analysis; NR: dosimetry, field homogeneity. Data reported in graphics
92	(Miyakoshi et al. 2002)	2450 MHz (CW); 13, 25, 39, 50, 78, 100 W/kg; 2 h	human brain tumor derived MO54	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis; NR: field homogeneity. Data reported in graphics
93	(Mizuno et al. 2015)	12.5 MHz (CW); 21.3 W/kg; 2, 24 h	Human embryo lung-derived SV40 virus transformed WI38VA13 subcloned 2RA cells	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: sham, blind exposure and analysis, field homogeneity. Data reported in graphics
94	(Nakatani-Enomoto et al. 2016)	1950 MHz (UMTS); 2 and 6 W/kg; 1 h	Human spermatozoa	8-OH-dG adducts (flow-cytometry analysis)	Data reported in graphics
95	(Phillips et al. 1998)	813.56 (iDEN), 836.55 (TDMA) MHz; 2.4, 2.6, 24, 26 μW/g; 2, 3, 21 h	Molt-4 T-lymphoblastoid cells	DNA SB (Alkaline Comet assay)	NO: blind exposure and analysis, positive control
96	(Regalbuto et al. 2020)	2450 MHz (CW, Wifi); 0.7 W/kg; 2 h	Human adult fibroblasts	DNA SB (γ-H2AX/53BP1 foci formation); MN (CREST assay)	NO: blind exposure, positive control. Data reported in graphics
97	(Romeo et al. 2020)	1950 MHz (CW, WCDMA, AWGN); 0.15, 0.3, 0.6, 1.25 W/kg; 20 h	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure. Data reported in graphics
98	(Sakuma et al. 2006)	2142.5 MHz (CW, WCDMA); 80, 250, 800 mW/kg; 2 and 24 h	Human glioblastoma A172; Human IMR-90 lung fibroblasts	DNA SB (Alkaline Comet assay)	NO: appropriate analysis, field homogeneity. Data reported in graphics
99	(Sannino et al. 2006)	1950 −MHz (UMTS); 0.5 and 2 W/kg; 24 h	Human peripheral blood leukocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure
100	(Sannino et al. 2009a)	900 MHz (GSM); 1 W/kg; 1 and 24 h	Human dermal healthy fibroblasts; Turner's syndrome fibroblasts	DNA SB (Alkaline Comet assay); MN (CBMN assay)	Data reported in graphics
101	(Sannino et al. 2009b)	900 MHz (GSM); 1.25 W/kg; 20 h	Human peripheral blood lymphocytes	MN (CBMN assay)	–
102	(Sannino et al. 2019)	1950 −MHz (UMTS); 0.3 and 1.25 W/kg; 20 h	Human peripheral blood lymphocytes; V79 Chinese hamster fibroblasts	MN (CBMN assay)	NO: blind exposure Data reported in graphics
103	(Sannino et al. 2014)	1950 −MHz (UMTS); 0.3 W/kg; 20 h	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure
104	(Sannino et al. 2017)	1950 −MHz (UMTS); 0.15, 0.3, 0.6, 1.25 W/kg; 20 h	Chinese hamster fibroblasts V79	MN (CBMN assay)	NO: blind exposure
105	(Sannino et al. 2011)	900 MHz (GSM); 1.25 W/kg; 20 h	Human peripheral blood lymphocytes	MN (CBMN assay)	–
106	(Sarimov et al. 2004)	895, 900, 905, 915 MHz (GSM); 5.4 mW/kg; 0.5 and 1 h	Human peripheral blood lymphocytes	Chromatin condensation (anomalous viscosity time dependencies assay)	NO: blind exposure and analysis, field homogeneity. Data reported in graphics
107	(Scarfi et al. 2006)	900 MHz (GSM); 1, 5, 10 W/kg; 24 h	Human peripheral blood lymphocytes	MN (CBMN assay)	–
108	(Scarfi et al. 2009)	9000 MHz (CW); 70 mW/g; 10 min	Bovine peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure; NR: field homogeneity
109	(Scarfi et al. 2003)	120,000 and 130000 MHz (PW); 0.06 and 0.035 mW/cm^2;20 min	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure, temp monitoring; NR: field homogeneity. Data reported in graphics
110	(Schrader et al. 2011)	835 MHz (CW); 60 mW/kg; 0.17, 0.5, 1, 2 h	Human-hamster hybrid (AL) FC2 cells	Spindle disturbances (acetic orcein staining)	NO: blind exposure and analysis. Data reported in graphics

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Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
111	(Schrader et al. 2008)	900 (CW, GSM); 10.7 and 17.2 mW/kg; 0.5 h	Human-hamster hybrid (AL)	Spindle disturbances (acetic orcein staining)	NO: positive control, temp monitoring; NR: field homogeneity
112	(Schuermann et al. 2020)	1800 (CW, GSM), 1950 (UMTS, GSM), 2450 (Wifi), 866 (RFid) MHz; 0.5, 2, 4.9 W/kg; 1, 4, 24 h	Human MRC-5 lung fibroblast; human trophoblast HTR-8/SVneo; ES-1 human skin fibroblast	DNA SB (Alkaline and FPG modified Comet Assay)	Data reported in graphics
113	(Schwarz et al. 2008)	1950 MHz (UMTS); 0.05, 0.1, 0.5, 1, 2 W/kg, 24 h; 0.1 W/kg, 4, 8, 12, 16, 20, 24, 48 h; 0.1 W/kg 16 h (5 min ON, 10 min OFF)	Human fibroblasts ES-1; Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay)	Data reported in graphics
114	(Shckorbatov et al. 1998)	42220 MHz (CW); 0.2 mW/cm^2; 1, 5, 15, 30, 60 s	Human buccal epithelium	Chromatin condensation (heterochromatin granule quantity)	NO: sham, dosimetry, blind exposure and analysis, positive control, field homogeneity
115	(Shckorbatov et al. 2010)	36650 MHz (CW); 1, 10, 30, 100 μW/cm^2; 10 s	Human fibroblasts	Chromatin condensation (heterochromatin granule quantity)	NO: sham, dosimetry, blind exposure and analysis, positive control, field homogeneity. Data reported in graphics
116	(Shckorbatov et al. 2009)	35000 MHz (CW); 30 μW/cm^2; 10 s	Human buccal cells	Chromatin condensation (heterochromatin granule quantity)	NO: sham, dosimetry, blind exposure and analysis, positive control, temp monitoring, field homogeneity
117	(Silva et al. 2016)	900 MHz (CW); 0.082 W/kg; 16 h	Primary thyroid cells	Aneuploidy (Flow-cytometry assay)	NO: appropriate dosimetry, blind exposure and analysis, positive control, temp monitoring, field homogeneity. Data reported in graphics
118	(Speit et al. 2013)	1800 MHz (CW); 1.3 W/kg; 24 h	human lymphoblastoid cells HL-60	DNA SB (Alkaline Comet assay); MN (CBMN assay)	Data reported in graphics
119	(Speit et al. 2007)	1800 MHz (CW); 1 and 2 W/kg; 1, 4, 18, 22, 24 h	Human diploid fibroblasts ES1; Chinese hamster fibroblasts V79	DNA SB (Alkaline Comet assay); MN (CBMN assay)	Data reported in graphics
120	(Stronati et al. 2006)	935 MHz (GSM); 1 and 2 W/kg; 24 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay); SCE (BRDU); CA (BRDU)	Data reported in graphics
121	(Su et al. 2017)	1800 MHz (GSM); 4 W/kg, 1, 6, 24 h	Human glioblastoma U-251; Human glioblastoma A172; Human neuroblastoma SHSY-5Y	DNA SB (γ-H2AX foci formation)	Data reported in graphics
122	(Su et al. 2018)	1800 MHz (GSM); 4 W/kg, 1, 6, 24 h	Primary rat astrocytes; Rat Microglia; Rat Cortical neurons	DNA SB (γ-H2AX foci formation)	Data reported in graphics
123	(Sun et al. 2016)	1800 MHz (CW); 4 W/kg, 1, 12, 24, 36 h	Atm + Mouse embryonic fibroblasts	DNA SB (Alkaline and Neutral Comet assay)	Data reported in graphics
124	(Tice et al. 2002)	837 (VM, CDMA, TDMA, PCS), 1909.8 (PCS) MHz; 1, 1.6, 2.5, 2.9, 5, 10 W/kg; 3 and 24 h	Human blood leukocytes; Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay); MN (CBMN assay)	NO: blind analysis; NR: field homogeneity
125	(Valbonesi et al. 2008)	1817 MHz (GSM); 2 W/kg; 1 h	human trophoblast HTR-8/SVneo	DNA SB (Alkaline Comet assay)	Data reported in graphics
126	(Vijayalaxmi 2006)	2450 and 8200 MHz (PW); 2.13 and 20.71 W/kg; 2 h	Human peripheral blood lymphocytes	CA (BRDU); MN (CBMN assay)	NO: blind exposure and analysis, field homogeneity
127	(Vijayalaxmi et al. 2001a)	847.74 MHz (CDMA); 4.9 and 5.5 W/kg; 24 h	Human peripheral blood lymphocytes	CA (BRDU); MN (CBMN assay)	NO: blind exposure; NR: dosimetry, field homogeneity
128	(Vijayalaxmi et al. 2001b)	835.62 MHz (FDMA); 4.4 and 5 W/kg; 24 h	Human peripheral blood lymphocytes	CA (BRDU); MN (CBMN assay)	NO: blind exposure, field homogeneity
129	(Vijayalaxmi et al. 2000)	2450 MHz (PW); 2.135 W/kg; 2 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	NO: blind exposure, field homogeneity
130	(Vijayalaxmi et al. 1997)	2450 MHz (CW); 12.46 W/kg; 1.5 h (continuous and 3x 30 min ON/30 min OFF	Human peripheral blood lymphocytes	CA (BRDU); MN (CBMN assay)	NO: blind exposure and analysis, temp monitoring, field homogeneity
131	(Vijayalaxmi et al. 2013)	2450 MHz (CW, WCDMA); 10.9 W/kg; 2 h	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure, temp monitoring, field homogeneity
132	(Waldmann et al. 2013)	1800 MHz (GSM); 0.2, 2, 10 W/kg; 28 h	Human peripheral blood lymphocytes	MN (CBMN assay); CA (BRDU); DNA SB (Alkaline Comet assay); SCE (BRDU)	Data reported in graphics
133	(Wang et al. 2015)	900 MHz (GSM); 0.5, 1, 2 W/kg; 24 h	Mouse neuroblastoma Neuro-2a	DNA SB (Alkaline and FPG-modified Comet assay)	Data reported in graphics

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Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
134	(Xu et al. 2013)	1800 MHz (GSM); 3 W/kg; 1 and 24 h (5 min ON/10 min OFF)	Chinese Hamster Lung CHL; Primary rat astrocytes; Human amniotic epithelial FL; Human lens epithelial HLEC; Human skin fibroblasts; Human umbilical vein endothelial (HUVEC)	DNA SB (γ-H2AX foci formation, Alkaline and Neutral Comet assay)	NO: blind exposure Data reported in graphics
135	(Yao et al. 2008)	1800 MHz (GSM); 1, 2, 3, 4 W/kg; 2 h	Human lens epithelial SRA01/04	DNA SB (γ-H2AX foci formation, Alkaline Comet assay);	NR: blind exposure and analysis Data reported in graphics
136	(Zeni et al. 2003)	925 MHz (CW, GSM); 0.2 and 1.6 W/kg; 44 h (14x6min ON/3h OFF) and 3 days (1 h/day)	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: sham, blind exposure, positive control; NR: blind analysis
137	(Zeni et al. 2007)	120,000 and 130000 MHz (PW); 0.4, 0.24, 1.4, 2 mW/g; 20 min	Human peripheral blood lymphocytes	MN (CBMN assay); DNA SB (Alkaline Comet assay);	NO: blind exposure, positive control; NR: blind analysis
138	(Zeni et al. 2005)	900 MHz (GSM); 0.3 and 1 W/kg; 2 h	Human peripheral blood lymphocytes	MN (CBMN assay); SCE (BRDU); CA (Giemsa staining)	NO: blind exposure Data reported in graphics
139	(Zeni et al. 2012a)	1950 MHz (UMTS); 0.15, 0.3, 0.6, 1.25 W/kg; 20 h	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: blind exposure
140	(Zeni et al. 2012b)	1950 MHz (UMTS); 10 W/kg; 24 h	Rat pheochromocytoma (PC12)	DNA SB (Alkaline Comet assay)	NO: blind exposure
141	(Zeni et al. 2008)	1950 MHz (UMTS); 2.2 W/kg; 24, 44, 68 h	Human peripheral blood lymphocytes	MN (CBMN assay); DNA SB (Alkaline Comet assay)	NO: blind exposure
142	(Zhang et al. 2002)	2450 MHz (CW); 5 mW/cm^2; 2 h	Human peripheral blood lymphocytes	MN (CBMN assay); DNA SB (Alkaline Comet assay)	NO: sham, blind exposure and analysis, dosimetry; NR: field homogeneity
143	(Zhijian et al. 2009)	1800 MHz (GSM); 2 W/kg; 24 h	Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	NR: blind exposure and analysis
144	(Zhijian et al. 2010)	1800 MHz (GSM); 2 W/kg; 2 h	human B-cell lymphoblastoid HMy2.CIR	DNA SB (Alkaline Comet assay)	NR: blind exposure and analysis. Data reported in graphics
145	(Zotti-Martelli et al. 2005)	1800 MHz (CW); 5, 10, 20 mW/cm^2; 1, 2, 3 h	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: sham, dosimetry, temp monitoring, blind exposure, positive control; NR: field homogeneity. Data reported in graphics
146	(Zotti-Martelli et al. 2000)	2450 and 7700 MHz (CW); 10, 20, 30 mW/cm^2; 15, 30, 60 min	Human peripheral blood lymphocytes	MN (CBMN assay)	NO: sham, dosimetry, blind exposure, positive control; NR: field homogeneity
147	(Zuo et al. 2015)	1800 MHz (GSM); 2 and 4 W/kg; 24 h	Rat spiral ganglion neurons (SGN)	DNA SB (Alkaline Comet assay)	NR: number of independent experiments Data reported in graphics
148	(Nikolova et al. 2005)	1710 MHz (GSM); 1.5 W/kg; 6 and 48 h	Mouse embryonic stem cells ES	DNA SB (Alkaline and Neutral Comet assay); CA (Giemsa staining) SCE (BRDU)	NO: positive control Data reported in graphics
149	(Ozgur et al. 2014)	900 and 1800 MHz (GSM); 2 W/kg; 1, 2, 3, 4 h	Hepatocarcinoma cells HEP-G2	DNA SB (Tunel Assay)	NO: blind exposure and analysis, positive control; NR: dosimetry, field homogeneity Data reported in graphics
150	(Khalil and Alshamali 2010)	900 and 1800 MHz (GSM); 1 and 1.2 W/kg; 1 h	Human peripheral blood lymphocytes	SCE (BRDU)	NO: sham, blind exposure, temp monitoring, appropriate dosimetry
151	(Koyama et al. 2007)	2450 MHz (CW); 5, 10, 20, 50, 100, 200 W/kg; 2 h	Chinese Hamster Ovary (CHO)-K1	Mutations (HPRT)	NO: sham, blind exposure and analysis, field homogeneity. Data reported in graphics
152	(Jin et al. 2021)	1762 MHz (LTE); 8 W/kg; 24 and 48 h	Murine melanoma cells B16; Human keratinocytes – HaCaT	DNA SB (γ-H2AX foci formation, Neutral Comet assay)	NO: sham, blind exposure and analysis Data reported in graphics
153	(Kim et al. 2021)	1760 MHz (LTE); 4 W/kg; 4 days (4 h/day)	Human neuroblastoma SHSY-5Y cells	DNA SB (γ-H2AX foci formation)	NO: sham, blind exposure and analysis, positive control Data reported in graphics
154	(Zeni et al. 2021)	1950 MHz (UMTS); 0.3 W/kg; 20 h	Human neuroblastoma SHSY-5Y cells	DNA SB (Alkaline Comet assay)	NO: blind exposure Data reported in graphics
155	(Lawler et al. 2022)	60000 MHz (PW); 2.6 mW/cm^2; 4 and 2 days (5 h/day)	Human dermal fibroblasts	DNA SB (γ-H2AX foci formation)	NO: blind exposure and analysis, positive control; NR: field homogeneity; NR:

(*continued on next page*)

Table 3 (*continued*)

ID	Article	Exposure conditions (frequency, signal type, level, duration)	Cell type	Endpoint (assay)	Notes
					number of independent experiments
156	(Sannino et al. 2022)	1950 MHz (UMTS); 0.3 W/kg; 20 h	Human neuroblastoma SHSY-5Y cells	DNA SB (Alkaline Comet assay)	Data reported in graphics NO: blind exposure
157	(Choi et al. 2020)	1700 MHz (LTE); 1 and 2 W/kg; 72 h	Human adipose tissue-derived stem cells (ASCs); Huh7 liver cancer stem cells	DNA SB (γ-H2AX foci formation)	Data reported in graphics NO: sham, blind exposure and analysis.
158	(Suzuki et al. 2017)	1950 MHz (UMTS); 2 W/kg; 1 h	Mouse spermatozoa: Mouse oocytes	CA (Giemsa staining)	Data reported in graphics NO: positive control
159	(Al-Serori et al. 2018)	1950 MHz (UMTS); 0.25, 0.5, 1 W/kg; 16 h	Human derived glioma lines U87; Human derived glioma lines U251; Human neuroblastoma cells SH-SY5Y; Glioblastoma stem-like cells NCH421k; human diploid fibroblast cells ES-1; Human buccal cells TR-146; Human liver derived cells HepG2; Normal human primary astrocytes; Human peripheral blood lymphocytes	DNA SB (Alkaline Comet assay)	NO: negative control Data reported in graphics

(8-OH-dG: adducts of 8-hydroxy-2′-deosiguanosine; AWGN: Average White Gaussian Noise; BRDU: bromodeoxyuridine staining; CA: Chromosomal Aberrations; CBMN: Cytokinesis-block micronucleus; CW: Continuous Wave; CDMA: Code-Division Multiple Access; CREST: antikinetochore antibody staining; DNA SB: DNA Strand Breaks; DCS: Digital Communication System; FDMA: Frequency-division Multiple Access; FISH: Fluorescence In Situ Hybridization; FMCW: Frequency-Modulated Continuous Wave; FPG: Fluorescence Plus Giemsa; GSM: Global System for Mobile Communication; GSMK: Gaussian Minimum Shift Keying; HPRT: Hypoxanthine phosphoribosyl transferase; iDEN: Integrated Digital Enhanced Network; LTE: Long Term Evolution; MN: Micronuclei; NR: Not Reported; PW: Pulsed Wave; PCS: Personal Communication System; RFid: Radiofrequency Identification; SCE: Sister Chromatid Exchange; TDMA: Time-Division Multiple Access; TETRA25: Trans European Truncated Radio; UMTS: Universal Mobile Communication System; VM: Voice Modulated; WiFi: Wireless Fidelity).

We assessed the confidence in evidence for each endpoint–related body of evidence. We assigned to each stream of evidence a rating, reflecting the confidence with which the study findings accurately reflect a true association between exposure to RF-EMF and the endpoint.

In the OHAT approach, four descriptors are used to indicate the degree of confidence in the body of evidence:

- High Confidence (++++) – The true effect is highly likely to be reflected in the apparent relationship.
- Moderate Confidence (+++) – The true effect may be reflected in the apparent relationship.
- Low Confidence (++) – The true effect may be different from the apparent relationship.
- Very Low Confidence (+) – The true effect is highly likely to be different from the apparent relationship.

First, we assigned to each body of evidence an initial confidence rating based on the capacity of the study design to evaluate the exposure-outcome association (NTP-OHAT 2019). This ability depends on the presence or absence of four key features: (1) the exposure to the substance is experimentally controlled; (2) the exposure occurred prior to the outcome; (3) the outcome is assessed at the individual level (*i.e.*, not through population aggregate data); and (4) an appropriate comparison group is included in the study.

The initial confidence rating was then upgraded or downgraded depending on several factors, assessed across studies. Factors for downgrading included the summary risk-of-bias (tiering), inconsistency, indirectness, imprecision, and publication bias. Factors for upgrading included the magnitude of the average effect, dose–response, and consistency of results across species/models.

For each body of evidence, we considered only the studies reporting a statistically significant effect of RF exposure, and tabulated the study distribution by cell model, exposure categories and summary RoB. Then, we summarized the results of the appraisal in an "Evidence profile" table. In line with our systematic review protocol (Romeo et al. 2021), we applied the decision rules described below.

- *Summary risk-of bias*. We downgraded the certainty of evidence one-level when most information was from "Tier 2" or "Tier 3", and would apply a two-level downgrade when the proportion of "Tier 3" studies was sufficient to affect the interpretation of results.
- *Indirectness*. Extrapolation of findings from isolated biological systems to living organisms is challenging, and *in vitro* mechanistic studies can only provide supportive evidence on potential cancer effects in humans (Guyatt et al. 2011). This inherent limitation of the evidence bodies examined in current review was considered under the domains of indirectness, applying the following rules:
  (a) Relevance of the cell model to humans: studies of genotoxic effects in primary cells were assigned greater confidence than in immortalized cells, and exposure induced genotoxic effects in human cells was assigned greater confidence than studies on non-human cells. We applied a one-level downgrade when, in a given body of evidence, most studies were conducted on non-human cells.
  (b) Endpoint's predictivity of long-term DNA damage: studies investigating biomarkers of irreversible DNA damage were assigned greater confidence than studies of reparable damage biomarkers (Krewski et al. 2019).

Indirectness was rated as "Serious" when most of the effects were observed in human (primary) cells, and as "Very serious" when most of the effects were observed in animal (immortalized) cells. We applied a one-level or two-level downgrading for "Serious" or "Very Serious" indirectness, respectively.

- *Dose-response*. We applied one-level upgrade in the presence of dose–response gradients consistently reported by studies investigating primary endpoints.
- *Consistency across different cell models/exposure conditions*. Within and across endpoint-specific studies, we applied a one-level upgrade in case of coherence of results across species/models, and exposure types (frequency range, SAR range, continuous/pulsed waveforms, continuous/intermittent exposure).

3. Results

3.1. Study selection

The output of the literature search and study selection process are shown in a PRISMA flow-diagram (Fig. 1). We retrieved a total of 9859 records from the literature searched through three databases. The sensitivity and precision of search strategies resulted were, respectively, 95% and 3.4% for EMF-Portal; 90% and 5.1% for PubMed NCBI; 84% and 2.8% for WOS. After duplicates removal, 7750 records were screened based on title and abstract, leading to the identification of 247 potentially relevant articles. Among these, the full-text of 244 records was assessed for eligibility (three full-text could not be retrieved), leading to the inclusion of 159 articles, and the exclusion of the remaining 85. The list of excluded reports with exclusion reasons is provided in the online Annex 1 (Section 2). Most of the reports were excluded for lack of compliance with criteria defined in the PECO statement (RF exposure (n = 15), *in vitro* exposure (n = 10), genotoxicity outcome (n = 19), use of cell cultures (n = 2)), or because they were not primary source of data (review papers, or letters). A non-negligible number of studies (n = 24) was excluded because they lacked a quantitative measure of exposure level/dose expressed in the appropriate unit, and/or because RF-EMF exposure was obtained using a commercial source (e.g., a mobile telephone) in the lack of an appropriate dosimetry (Romeo et al. 2021). One article by (Diem et al. 2005) was excluded from the analysis due to the controversy about truthfulness of data (Tuffs 2008).

3.2. Study characteristics

The 159 included study-reports are listed in Table 3, along with the main experimental characteristics (exposure frequency, signal, level and duration, cell type(s), endpoint(s) analyzed). Notes about the lack of crucial features in the experimental design (sham-exposure, dosimetry, blind procedures, temperature monitoring, positive control, field homogeneity) are provided in the last column. Note that when there was direct evidence that some the above features were not considered, we used "NO", whereas we used "NR" (Not Reported) when such information was not clearly stated in the study.

The following figures provide a graphical synthesis of the information extracted from the included papers.

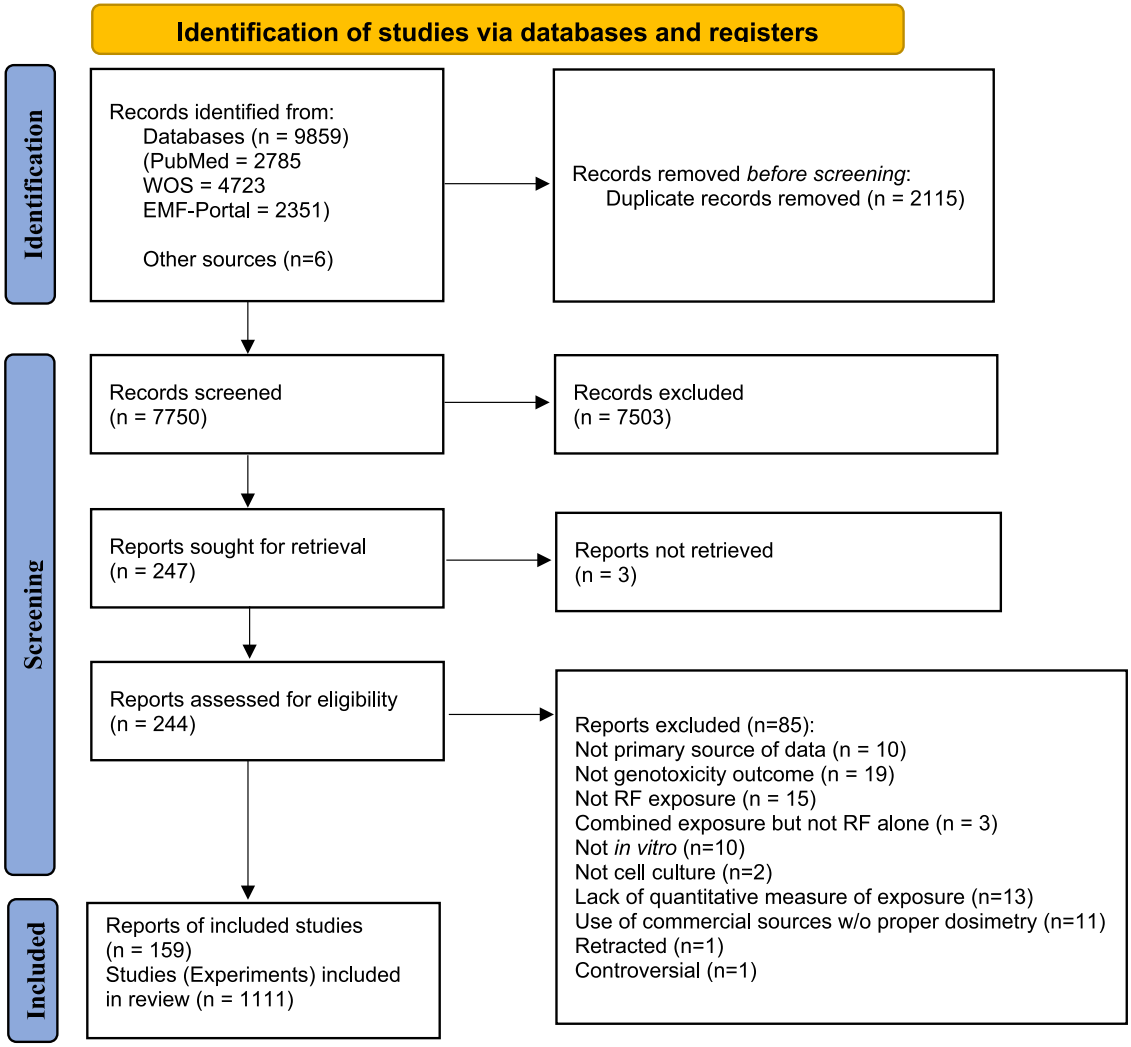


Fig. 1. PRISMA flow-chart of the studies selection process.

Fig. 2(a) reports the temporal trend of publication, from 1968 (year of the first published paper from our bibliographic search) to December 31st, 2022, of both included and excluded studies. Starting from the 2000 s there has been a significant increase in the number of publications, probably due to greater funding to research in this sector by national and international organizations. However, this was accompanied by a proportional increase in the excluded works, suggesting that, despite the increase in research funding, there were no substantial improvements in the methodological quality.

From the 159 included studies we extracted 1,111 experiments, which are tabulated by endpoint in the "Summary of findings" tables (S3.1-S3.9) reported in Annex 3. A descriptive summary of the experiments in relation to the primary factors of interest is reported in three graphics (Fig. 2, b-d). Fig. 2(b) shows the types of cells used in the experiments. The studies investigating cells of human origin (838, mainly peripheral blood lymphocytes) far outweighed those based on animal cells (273, mainly from rodents), while the use of primary cells compared to cell lines was quite balanced (609 *vs*. 502).

Fig. 2(c) displays the relative occurrence of the genotoxicity endpoints eligible for inclusion in the current systematic review. Most of the experiments (58.4%) evaluated the effect of RF exposure on single and/or double DNA breaks, mainly using the Comet test (alkaline and/or neutral) but also based on the formation of foci (in particular, γH2AX and/or 53-BP1), which are considered as an early marker of DNA double strand breaks (Kuo and Yang 2008). In 23.9% of studies the endpoint was the formation of micronuclei was mainly, which was mainly determined through the cytokinesis block micronucleus assay. Less frequently investigated endpoints included chromosomal aberrations (7.7%, mainly by Giemsa or BRDU staining), sister chromatid exchange (3.2%, mainly by BRDU staining), chromatin condensation (3.0%, mainly by anomalous viscosity time dependencies assay), 8-hydroxy-2′-deoxyguanosine adducts (1.3%, mainly by flow-cytometry analysis), spindle disturbances (1.1%, mainly by immunostaining), mutations (0.9%, mainly by HPRT assay) and aneuploidy (0.7%, mainly by FISH analysis).

Fig. 2(d) shows the percentage of experiments by subgroups of the three exposure parameters (frequency, level, and duration). Most of the experiments (85%) were performed applying RF-EMF at frequencies assigned to the F2 subgroup (from 10 MHz to ≤6 GHz, but mostly around the frequencies associated to wireless technologies), 12.3 % at frequencies above 6 GHz (F3, from > 6 GHz to ≤300 GHz) and only 2.7% below 10 MHz (F1). Regarding exposure levels, the 48.1% of the experiments were performed applying values below the ICNIRP exposure limits for the general population (EL1), 34.1% above (EL3), and 17.7% around them (EL2). Finally, as regards the exposure duration, there was a larger prevalence of long exposures (ED2, from >1 h to ≤24 h; 71.5%) than acute exposures (ED1, ≤1h; 21.9%,), or chronic exposures (ED3, >24 h; 6.6%).

3.3. Risk of bias in individual studies and summary risk of bias

The results of RoB assessment for the 159 considered studies are reported in the Annex 2 (Section 2), whereas the rationale behind the assessment is reported in Annex 4 ("RoB_assessment with rationale"), for each study and for each bias domain. Fig. 3(a) shows, for each bias domain, the percentages of studies that were classified at "definitely low" (++), "probably low" (+), "probably high" (−) or "definitely high" (–) RoB.

All the included studies used homogeneous cell suspensions, even when the cells were extracted from tissues (e.g., blood or sperm). Therefore, they were all considered at "definitely low" RoB for the "randomization of the exposure levels" and "allocation concealment" domains (Romeo et al. 2021; Rooney 2015a). Under the performance bias domain, we assessed whether there were identical experimental

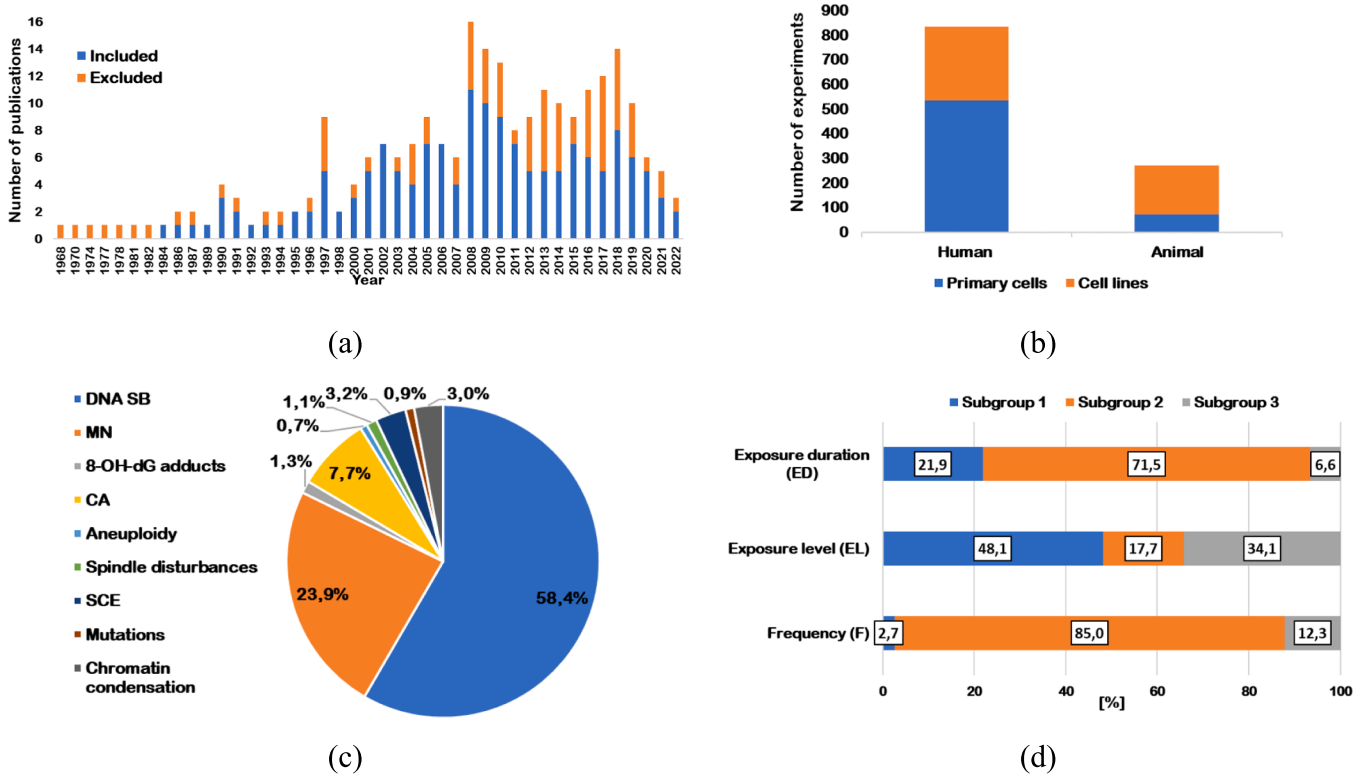
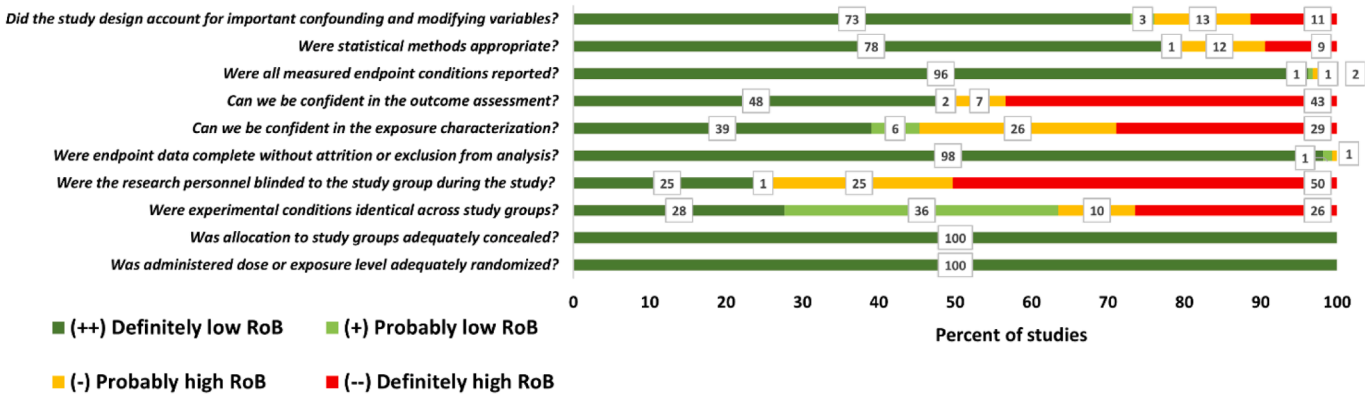


Fig. 2. (a) Temporal trend of publication of included and excluded studies; (b) Number of experiments performed with primary cells or with cell lines, of human or animal origin; (c) Proportion of the genotoxicity endpoints analyzed in the experiments (DNA SB: DNA strand breaks; MN: micronuclei; 8-OH-dG adducts: 8-hydroxy-2′-deosiguanosine adducts; CA: chromosomal aberrations; SCE: sister chromatid exchange). (d) Percentages of experiments in the three exposure parameter subgroups (ED1/ED2/ED3; EL1/EL2/EL3; F1/F2/F3, according to definitions provided in section 2.4).

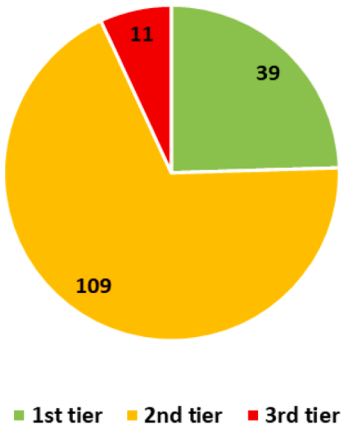
conditions across study groups, and if the research personnel were blinded to the study group. We evaluated if the study design included sham and/or negative (incubator) controls, and if they were handled in parallel to RF-exposed samples. Studies were considered at "definitely low" RoB when there was direct evidence that both negative and sham controls were included and handled in parallel to RF-exposed samples, or at "probably low" RoB when there was indirect evidence that sham control was included. Example of indirect evidence is when, based on description and images of the exposure set up, it could be argued that the control samples did comply with the characteristics of a sham control, even though it was not explicitly termed "sham" in the report, or when sham controls were not included, but multiple exposure levels (e.g. multiple SAR values) were administered, since it could be assumed that the environmental conditions were homogeneous across study groups. Studies were classified as "probably high" RoB when there was indirect evidence that only incubator controls were used, or that sham controls were not handled in parallel to RF-exposed samples, or if there was insufficient information on whether study groups were handled in parallel. Studies were classified as "definitely high" RoB when there was direct evidence of the abovementioned conditions. Most included studies were classified at probably (36 %) or definitely (28 %) low RoB, whereas the 26 % of studies were classified at definitely high RoB mainly for the absence of a proper sham control, and 10 % of studies at probably high RoB. The 50 % of all included studies were at "definitely high" RoB because the research personnel were not blinded to the exposed groups during RF exposures.

Under the "Attrition bias" domain, we assessed whether outcome data was complete, or if loss of samples was adequately addressed, and reasons were documented when samples were removed from a study, or if missing data had been imputed using appropriate methods. The 98 % of included studies was at "definitely low" RoB for this domain.

Under the "Detection bias" domain, we assessed, for each study, the confidence in exposure characterization and in the outcome assessment. Regarding the exposure characterization, we carefully analyzed dosimetry methods, to assess whether they were appropriate and clearly described. For example, we considered estimates of SAR from measurements of the electric field in absence of the sample as inappropriate dosimetry method, because such procedure does not take into account that the sample significantly perturbs the electric field. On the other hand, we considered appropriate, estimates of SAR from computation of electric field in the sample or by calorimetric measurements. A further quality factor was the homogeneity of field distribution in the samples. We considered a nonuniformity degree of the electric field distribution within the sample around 30 % as a good quality standard in terms of exposure characterization. Among the included studies, 26 % was at "probably high" RoB, and the 29 % at "definitely high" RoB (mainly due to inappropriate dosimetry methods, or lack of indications regarding field homogeneity), whereas 6 % and 39 % of studies were at "probably



(a)



(b)

Fig. 3. (a) Risk of bias at the individual study level. Ratings are expressed as percentages (out of 159 total studies); (b) Assignment of the included papers to quality categories based on the results of the summary risk of bias ("1st tier", high quality; "2nd tier", moderate quality; "3rd tier", low quality).

low" and "definitely low" RoB, respectively. With respect to outcome assessment, we evaluated whether the biological assays applied were suitable to the endpoint analyzed, carried out by using standard methods, adequately sensitive, (as tested by using positive controls), and if the research personnel were blinded to the exposure status of the samples during the endpoint determination. Out of all included studies, 7 % was at "probably high" RoB and 43 % at "definitely high" RoB, mainly because the research personnel were not blinded to the study group during the outcome analysis, and/or for the absence of positive controls in the experiment, whereas 2 % and 48 % of studies were at "probably low" and "definitely low" RoB, respectively.

Under the "Selective reporting" domain, we assessed whether all the study's measured endpoints outlined in the methods, abstract, and/or introduction, were reported. Almost all included studies (96 %) were at "definitely low" risk for "selective reporting" bias.

Under the "Other bias" domain, we assessed the appropriateness of statistical methods applied to test the significance of results, and the presence of uncontrolled confounding from temperature increases. Regarding the appropriateness of statistical analysis, 78 % of included studies were at "definitely low" RoB (one study was at "probably low" RoB), whereas 12 % and 9 % were at "probably" and "definitely high" RoB, respectively, mainly due to the lack of indication of the number of independent experiments performed, or because less than three independent experiments were carried out. A temperature increase during exposure was considered as the most relevant confounding factor in the study design. Therefore, for each study, we assessed whether temperature inside the samples was monitored continuously during treatment (or, at least, in preliminary experiments aimed at characterizing the temperature profile), by using adequate instruments (e.g., fiber optic thermometers, infrared cameras, or other tools that do not perturb the field). If heating of the sample during RF exposure was likely to occur (e.g., when using SAR values above the exposure limits), we checked if specific measures to counteract such heating were adopted (e.g., circulation of cooling water) or if the study design included a temperature control (*i.e.* a sample subjected to the same temperature increase induced by different methods, such as thermostatic water/oil-bath, or DC current). Most of the included studies monitored temperature during exposure with adequate methods (73 % at "definitely low" and 3 % at "probably low" RoB), whereas the 13 % and 11 % were at "probably" and "definitely high" RoB respectively, mainly for the absence of temperature control.

Fig. 3(b) shows the distribution of the 159 studies by summary RoB category ("tier"): 109 studies (68.6 %) were classified as of moderate quality (tier 2), 39 (24.5 %) of high quality (tier 1), and 11 studies (6.9 %) of low quality (tier 3). It is worth nothing that, of the 109 studies of moderate quality, 37 received an evaluation of probably or definitely high RoB in at least three of the four key domains, mainly in relation to performance bias, due to the absence of sham samples, or to detection bias, due to inadequate dosimetry, or to exposure to a non-uniformly distributed electromagnetic field, or to the inappropriateness of the biological methods (absence of positive control and/or lack of blinding to exposure during the endpoint determination).

3.4. Synthesis of findings

Tables S3.1 through S3.9 in Annex 3 summarize the findings from the 1111 experiments extracted from the 159 included studies, sorted by endpoint. The reviewed body of evidence is characterized by a large variability of the parameters considered. In fact, just considering the biological model adopted, cells of human origin were used in 838 experiments, and cells of animal origin (mainly rodents) in 273; primary cells were used in 609 experiments and cell lines in 502 experiments. Among the cells of primary origin, most experiments were conducted on human lymphocytes (but lymphocytes from cattle, canids and rodents were also used), along with spermatozoa, astrocytes, thymocytes, amniotic cells, and cells from brain, adipose, dermal, pulmonary, or epithelial tissues. Similarly variable was the type of healthy cell lines (fibroblasts, trophoblasts, spermatocytes, keratinocytes, stem cells, ovarian, epithelial, umbilical, corneal, etc.), and cancer cells (neuroblastoma, glioma, other types of brain tumor, leukemia cells, and others). A considerable variability was also evident in the endpoints analyzed, and in the exposure conditions. Indeed, even though most of the studies applied RF-EMF in the frequency range used for information and communication technologies (mobile phone, wi-fi), the other exposure parameters (continuous or pulsed wave, signal characteristics, SAR values, exposure duration and modality) varied over broad ranges.

In 80% of experiments, RF exposure did not induce statistically significant alterations of the analyzed biological parameter in the exposed *vs* the unexposed samples. A graphical synthesis of these data is reported in Fig. 4, which shows the proportion of experiments that observed statistically significant effects of RF exposure by subgroups of exposure parameters (Fig. 4a), and by endpoint (Fig. 4b). Among the experiments in which statistically significant effects were reported, there was no clear pattern of exposure-outcome associations, neither in relation to the exposure parameters (Fig. 4a), nor with respect to the endpoints considered (Fig. 4b). Regarding the exposure parameters, the percentage of experiments reporting significant effects is always less than 35% (34.7% in the case of exposures lasting $\leq$1 h, ED1), and it is worth noting that statistically significant effects were mainly observed at the lowest exposure levels and for the shortest durations, suggesting the absence of a dose–response relationship. As far as the endpoints are concerned, in some instances the percentage of experiments reporting significant effects was higher than 50%. This occurred in the case of spindle disturbances (90%, Annex 3, Table 3.7), chromatin condensation (62.9%, in Annex 3, Table 3.5), and 8-hydroxy-2′-deoxyguanosine adducts (57.1%, in Annex 3, Table S3.6). However, in all these instances, the number of experiments carried out was small (10, 35 and 14, respectively), and obtained by 13 studies performed by 8 research groups, which suggest a possible bias in the results.

Fig. 5 describes the results obtained in terms of absence or presence of significant effects considering the outcome of the experimental quality assessment. In this case, the assessment was not made at the level of the single experiment, but at the level of single paper, considering the outcome of the RoB analysis and the assignment to quality categories (Annex 2, Section 2). The "Effect" category included all those studies in which a statistically significant effect was observed for at least one of the extracted experiments, whereas the "No effect" category included only the studies in which significant effects were not observed at all. Although in both categories most of the studies are of moderate quality (tier 2), the absence of significant effects prevails among the studies classified in tier-1 and tier-2 categories, while for the tier-3 studies the trend is reversed.

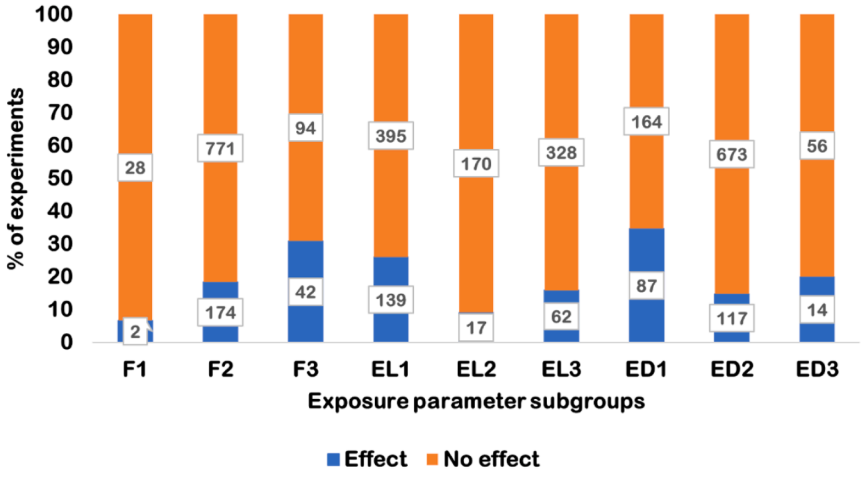
3.5. Certainty of evidence

The certainty of evidence was assessed at the endpoint level, and then integrated across endpoints.

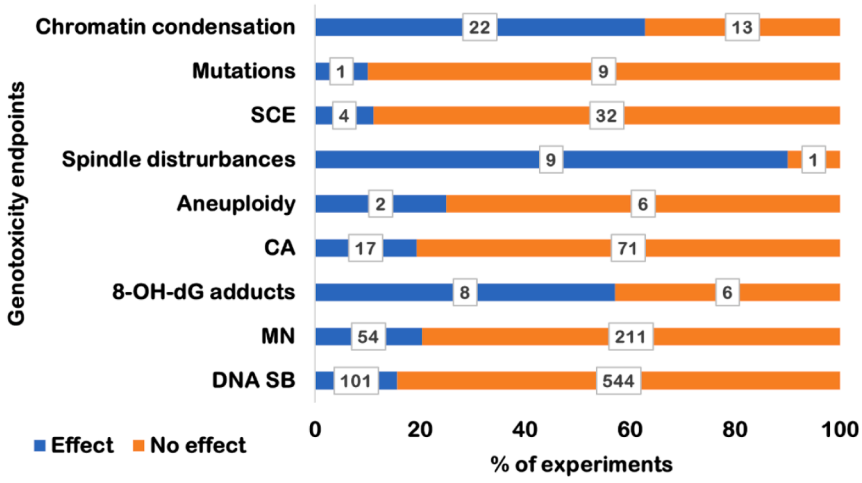
The initial confidence rating was set to "high" for all endpoint-specific bodies of evidence (Annex 5, Table S5.2), because experimental *in vitro* studies fulfill design features described in section 2.8.

We then assessed the certainty of evidence for each endpoint-specific set of studies. We restricted the assessment to studies reporting statistically significant effects of RF exposure (Annex 5, Table S5.3). Table S5.1 in Annex 5 provides, for each endpoint, a synopsis of the cell models, exposure conditions, and summary RoB for this subset of "positive" studies.

The "Evidence profile table" (Annex 5, Table S5.2) summarizes the results of the appraisal. The dataset of studies investigating DNA strand breaks (18 out of 24 studies in Tier 2), micronuclei (11 out of 15 studies in Tier 2), aneuploidy (1 out of 1 study in Tier 2), 8-OH-dG adducts (2 out of 3 studies in Tier 2), mutations (1 out of 1 study in Tier 2), sister chromatid exchanges (1 out of 1 study in Tier 2), and spindle



(a)



(b)

Fig. 4. (a) relative incidence (and absolute numbers in the labels) of experiments reporting significant effects and no effects with respect to the exposure parameter subgroups (F1/F2/F3; ED1/ED2/ED3; EL1/EL2/EL3, according to definitions provided in section 2.4; (b) relative incidence (and absolute numbers in the labels) of experiments reporting significant effects and no effects with respect to the genotoxicity endpoints considered (DNA SB: DNA strand breaks; MN: micronuclei; 8-OH-dG adducts: adducts of 8-hydroxy-2′-deosiguanosine; CA: chromosomal aberrations; SCE: sister chromatid exchange).

disturbances (4 out of 4 studies in Tier 2) were classified at "Serious" summary RoB, and the related confidence in evidence was downgraded one-level; the summary RoB rating was considered "Very serious" for the studies investigating chromosomal aberrations (3 out of 7 studies in Tier 2 and 3 out of 7 studies in Tier 3) and chromatin condensation (4 out of 8 studies in Tier 2 and 4 out of 8 studies in Tier 3), and a two-level downgrade was applied. The indirectness was considered "Serious" for the studies investigating DNA strand breaks (human cells in 16 out of 24 studies), micronuclei (human cells in 10 out of 15 studies), chromosomal aberrations (human cells in 5 out of 7 studies), chromatin condensation (human cells in 7 out of 8 studies), aneuploidy (human cells in 1 out of 1 study), and sister chromatid exchanges (human cells in 1 out of 1 study), resulting in a one-level downgrade of the quality of evidence (Annex 5, Table S5.1 and S5.2). The indirectness was considered "Very serious" for the study dataset of 8-OH-dG adducts (animal cells in 2 out of 3 studies), mutations (animal cells in 1 out of 1 study) and spindle disturbances (animal cells in 3 out of 4 studies), resulting in a two-level downgrade of the quality of evidence (Annex 5, Table S5.1 and S5.2).

There was no evidence of dose–response relationship (Fig. 4a) and no upgrade was applied.

Due to the large heterogeneity of cell species/model and exposure types (Fig. 4b), we did not upgrade any body of evidence for consistency.

The final rating of the certainty of evidence at the endpoint level, restricted to "positive" studies, is reported in Annex 5, Table S5.2 There is "Low" certainty of evidence of an effect of the exposure on DNA strand breaks, micronuclei, aneuploidy and sister chromatid exchange, and "Very Low" evidence of an effect of the exposure on any other endpoints.

It is worth noting that, except for the "positive" studies of DNA strand breaks and micronuclei, there wer few studies of other endpoints: only one study of aneuploidy, mutations and sister chromatid exchanges; three, four, seven and eight studies for 8-OH-dG adducts, spindle disturbances, chromosomal aberrations and chromatin condensation, respectively (Annex 5, Table S5.1).

Overall, the experimental *in vitro* studies considered in this qualitative review provide "Low" certainty evidence of genotoxic effects from exposure to RF-EMF.

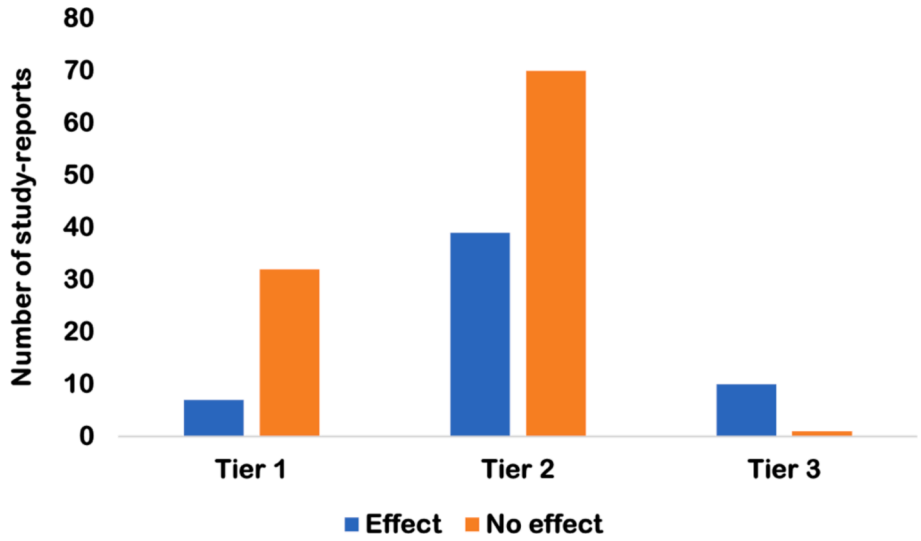


Fig. 5. Representation of the number of study-reports in terms of absence or presence of significant effects with reference to the evaluation of the experimental quality ("Tier 1", high quality; "Tier 2", moderate quality, "Tier 3" low quality).

4. Discussion

Several comprehensive reviews (Karipidis et al. 2021; Manna and Ghosh 2016; Meltz 2003) and *meta*-analyses (Halgamuge et al. 2020; Vijayalaxmi and Prihoda 2008; 2012; 2019) of studies addressing genetic damage in mammalian cells exposed to RF-EMF have been carried out. However, although those papers considered a large set of studies, they were non-compliant with the structured approach of systematic reviews (Whaley et al. 2020). Therefore, to the best of our knowledge, this is the first systematic review of the scientific literature on genotoxic effects in mammalian cell cultures in relation to RF-EMF exposure, based on transparently reported methods, pre-defined inclusion criteria, and formal assessment of susceptibility to bias. In the reports by (Vijayalaxmi and Prihoda 2008; 2012; 2019) the authors performed *meta*-analyses of data from papers addressing genetic damage in human cells exposed to RF-EMF, to determine whether a significant increase in genetic damage provides a potential mechanism for carcinogenicity of RF-EMF. The authors concluded that the difference between RF-exposed and sham-/unexposed controls was small with a few exceptions, in which there was a statistically significant increase in genotoxicity assessed from some endpoints. However, the effect was observed in studies with small sample size and was largely attributable to low quality of the experimental methods employed. The evidence was also considered weak in other review papers (Halgamuge et al. 2020; Manna and Ghosh 2016; Meltz 2003) in which genotoxicity was one of the outcomes (cell transformation, metabolism, apoptosis, etc.) considered. The findings from our systematic review are in line with the above-mentioned conclusions but are strengthened by the structured approach adopted.

Our systematic review presents some limitations regarding both the review process and the included evidence.

Regarding the limitations of the review process, we must mention that the bibliographic search only considered peer-reviewed papers published in English language, therefore we may have missed potentially relevant articles published in other languages. Moreover, even though we demonstrated that the search queries were characterized by high sensitivity, it is also possible that relevant search terms for the identification of articles could not be found in the title, abstract, or MeSH terms of some articles, so that the searches did not return all potentially relevant articles. The literature search was conducted only on three databases; however one of them was EMF-Portal, which is a thematically specialized literature database on biological and health-related effects of EMF and, due to its content specificity and documented high coverage of the research topic (Bodewein et al. 2019; Driessen et al. 2017), is expected to have a larger precision on the topic of this systematic review compared to other information sources.

In a large number of papers included in this systematic review it proved difficult to extract, in a complete and accurate way, quantitative data from each experiment. In 88 out of 159 studies, data were reported in graphical form (bars, dispersion lines) only, and our attempts to estimate data points by using digital rulers turned out to be very inaccurate. This was the main reason which precluded the possibility of carrying out a quantitative synthesis (*meta*-analysis) of the data. Therefore, a narrative synthesis was deemed as the most appropriate way to provide a transparent synthesis of the evidence, and to highlight possible subgroups of data and exposure-endpoint combinations that might be amenable to *meta*-analyses in a future work.

From the analysis of the experiments reporting effects, it emerged that most "positive" studies are of moderate quality (tier 2), but many of them received a negative rating in at least three of the four key RoB domains. Furthermore, for a reliable assessment of health risks following exposures to chemical and physical agents, the replication of the experiments by independent research groups is required. Some of the experiments reporting genotoxic effects from RF exposures, when repeated, did not confirm the original results. For example, the results of experiments by (Phillips et al. 1998) were not confirmed by another research team (Hook et al. 2004). Similarly, the results reported by (Diem et al. 2005) were not observed in the studies by (Schuermann et al. 2020; Speit et al. 2007). Furthermore, the findings from (Malyapa et al. 1997a) were not confirmed (Lagroye et al. 2004). Other experiments reporting effects have not been replicated by independent research groups.

An additional consideration concerns the endpoints examined. The onset of chromatin condensation, mitotic spindle disturbances, and the formation of 8-hydroxy-2′-deosiguanosine adducts were apparently more sensitive to RF-EMF exposure. On the other hand, from an analysis of the characteristics of the experiments described in Annex 3, Tables S3.1–S3.9, it is evident that these experiments were performed in a few studies, generally carried out by the same research groups.

Regarding the exposure conditions, it is interesting to note that most of the experiments were carried out at exposure levels below or around the ICNIRP exposure limits for the general public (Fig. 2d), which suggests attempts to avoid or control heat generation during RF exposure.

In this systematic review we analyzed only a part of the huge amount of data gathered from the included papers. To give the readers a synopsis of the current state of the available literature, we considered the main

exposure (frequency, level, duration) and biological (endpoint) parameters, and left out others like waveform type (continuous or pulses wave), modulation, exposure modality (continuous or intermittent). Moreover, for the studies addressing more than one genotoxicity endpoint, we assessed the results at the single endpoint level and did not consider their combination. We are currently analyzing these additional data, which will be the subject of future publications.

Another methodological limitation lies in the absence of guidelines specifically devoted to the systematic analysis of the scientific evidence provided by mechanistic studies (including *in vitro* studies). OHAT is currently developing a more structured approach for considering mechanistic data (NTP-OHAT 2019). Mechanistic data are generally not required to reach hazard identification conclusions. Rather, they may be used to raise (or lower) the category of the hazard assessment. Therefore, we had to borrow and adapt methods and criteria developed for animal studies (NTP-OHAT 2019). This was particularly challenging when performing the RoB assessment and the rating of the certainty of evidence and may rise concerns about the result of these assessments. However, our approach may provide useful indications for the development of specific guidelines.

In the assessment of certainty of evidence, we only considered studies (54 out of 159) reporting significant effects of RF exposure in at least one of the experimental conditions considered. We acknowledge that this is not a standard method, which provides only a partial assessment of the evidence analyzed. However, we thought it might be worth assessing the robustness of findings from these studies, and verifying whether any patterns of effects with respect to the biological or electromagnetic parameters could be detected. These "positive" studies were characterized by a large variability in the cellular models adopted, and there was no clear pattern of exposure-outcome association, neither in relation to the exposure parameters, nor with respect to the endpoints considered. Statistically significant effects were mainly observed at the lowest exposure levels and for the shortest durations, suggesting the absence of a dose–response relationship. It must be noted that the number of experiments per exposure subgroup is largely variable (as reported in Fig. 4a), and that only amongst the studies classified as "Tier-3" (based on summary assessments of RoB) did the number of studies reporting effects exceed the number of studies reporting no effect (Fig. 5). On the other hand, 80% of experiments reviewed showed no effect of RF exposure on the large majority of endpoints, especially the irreversible ones, independently of the exposure features, level, and duration (moderate evidence of no effect). Therefore, we conclude that, in the whole, RF exposure probably does not increase the occurrence of genotoxic effects *in vitro* (Santesso et al. 2020).

5. Conclusions

The main conclusion of our systematic analysis is that the certainty of evidence for genotoxic effects of RF-EMF in mammalian cell cultures is weak. No genotoxic effects of RF exposure were observed in most experiments, especially those concerning irreversible endpoints, independently of the exposure features, level, and duration (moderate certainty evidence of no effect). In the whole, we conclude that the analysis of the papers included in this review, although only qualitative, suggests that RF exposure likely does not increase the occurrence of genotoxic effects *in vitro*, also considering that the absence of significant effects prevails among the studies classified in tier-1 and tier-2 categories, whereas for the tier-3 studies the trend is reversed, highlighting how methodological quality affects the studies outcome (Simko et al. 2016).

This systematic review may provide support to panels of experts involved in policy making regarding safety of exposure to RF-EMF.

Furthermore, it is possible to state that, although the number of publications on this topic has considerably increased in recent years, this has not translated into an improvement of the experimental quality. Only a small number of the reviewed studies qualified for inclusion in the tier 1 category, while most of them, including those of moderate quality, still present considerable criticalities in key experimental features (use of sham samples, adequate dosimetry, exposure to a uniformly distributed electromagnetic field, appropriateness of biological methods, presence of positive control and outcome analysis blind to the exposure). It is evident that methodological quality is demanded for future research into this field, which will aim at producing sufficiently similar and unbiased data to be aggregated in meaningful categories.

Registration and protocol

Romeo, S.; Zeni, O.; Sannino, A.; Lagorio, S.; Biffoni, M.; Scarfi, M.R. Genotoxicity of radiofrequency electromagnetic fields: Protocol for a systematic review of *in vitro* studies. Environ Int 2021;148:106386.

Support

This work was supported by the Italian Workers' Compensation Authority (INAIL), a public, no-profit entity, and performed in the framework of the CRA with the Istituto Superiore di Sanità (ISS) "BRiC 2018/06–Scientific evidence on the carcinogenicity of radiofrequency electromagnetic fields" (ISS PI Mauro Biffoni; INAIL representative Carlo Grandi); grant code I85B19000120005. INAIL had no role in the systematic review. SL withdrew from the BRiC 2018/06 project on 1 April 2020.

CRediT authorship contribution statement

Stefania Romeo: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Anna Sannino:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Maria Rosaria Scarfi:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Susanna Lagorio:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Olga Zeni:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors greatfully acknowledge the Editor and the three anonymous reviewers that, with their comments and suggestions, helped improving the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109104.

Data availability

Data will be made available on request.

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