Protocol for a Systematic Review of the *in vivo* Studies on Radiofrequency (100 kHz – 300 GHz) Electromagnetic Field Exposure and Cancer

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Protocol

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Abstract

Background. An Italian project aims to review the scientific literature on the possible carcinogenicity of radiofrequency (100 kHz – 300 GHz) electromagnetic field (RF-EMF) exposure. The ENEA team has to carry out a systematic review of the *in vivo* studies on this topic.

Objectives. Development of a protocol for a systematic review (meta-analysis included) to investigate the potential carcinogenic risk following RF-EMF *in vivo* exposure to doses above or within legal limits. The aim of this review is

- to provide a descriptive and, if possible, a quantitative summaries of the results of the examined RF-EMF *in vivo* studies, together with an assessment of the consistency of observations and of the causes of heterogeneity.
- to assess the weight of evidence to support or refute the hypothesis of carcinogenic effects caused by RF-EMF exposure and to draw conclusions about the potential for carcinogenicity of RF-EMF exposure.

Methods: We will search for relevant studies in electronic academic databases and in the reference list of selected papers and reviews on the topic, including the descriptive reviews on RF-EMF carcinogenic effect carried out by international panels of experts since 2011. PECO's statements were defined: experimental studies on rodents of both sexes, all ages and species, all genetic background (Population) exposed to RF-EMF alone, or in combination with other physical or chemical agents (Exposure); only studies reporting outcome data in exposed and sham control groups (Comparison); all types of cancer with all tumor-related outcome measures (Outcome) will be included.

Only peer-reviewed articles written in English will be considered without limit in publication date.

Eligibility criteria were defined for screening of papers, moreover the risk of bias assessment will be performed using a specific risk of bias tool for animal studies. Only studies with "definitely low and/or probably low risk of bias" will be included in the analysis. A meta-analysis will be performed, if feasible, for all outcome measures: for subgroup analysis a minimum of 3 studies per subgroup will be required. If meta-analysis will not be possible, data will be reported through the descriptive summary.

Systematic review registration: PROSPERO CRD42020191105.

Highlights

- An Italian collaborative research agreement aims to review the scientific literature on the possible carcinogenicity of RF-EMF (100 kHz – 300 GHz).
- The ENEA team will systematically review and, if possible, meta-analyse estimates the effects of *in vivo* exposure to RF-EMF exposure on cancer.

- The ENEA group is a multidisciplinary team of researchers with a consolidated experience both in carcinogenicity experiments and radiofrequency dosimetric assessment.
- The proposed protocol uses the NTP OHAT Approach for Systematic Review as an organizing framework.
- The proposed protocol aims to lead to the first systematic review providing a strength of evidence assessment on this topic.

1. Background

The work-plan of the INAIL-ISS collaborative research agreement “BRiC 06/2018” Ref Y43 “*Scientific evidence on the carcinogenicity of radiofrequency electromagnetic fields*” aims to review the scientific literature on the possible carcinogenicity of RF-EMF (100 kHz – 300 GHz) provided by general population epidemiological studies, epidemiological studies on workers, *in vivo* animal experimental studies and experimental studies on cells *in vitro*. The institution leader of the project is the Italian National Institute of Health (ISS) and the ENEA team, as a partner, has to carry out a systematic review of the *in vivo* studies on radiofrequency RF-EMF exposure and cancer. The investigator team is constituted by CM, which is the head of the Division Health Protection Technologies of ENEA, she is a biologist and she is the chief scientific officer of the INAIL Project for ENEA, by PV and PG, biologists with a consolidate experience in experimental studies on carcinogenesis, by RP and LA, electronic engineers with a consolidate experience in dosimetry of electromagnetic fields.

In this paper, the protocol for a systematic review and, if possible, for a meta-analysis of data concerning *in vivo* experimental animal studies and cancer is presented. To our knowledge, it is the first systematic review protocol on this topic. The protocol is registered in PROSPERO with the following registration number: CRD42020191105.

2. Rationale

Exposure to electromagnetic fields (EMF) has grown steadily over the past decades and in 2011 the International Agency for Research on Cancer (IARC) classified radiofrequency electromagnetic fields (RF-EMF) as “possibly carcinogenic to humans”, thus allocating them to Group 2B of its classification system. The possible carcinogenic effects of RF-EMF have been investigated in laboratory animals since the early 1980s because *in vivo* studies have an important role in supporting the evidence derived from epidemiological studies investigating carcinogenic effects of RF exposure on the general population in daily life. After IARC monograph publication in 2013 several international panels of experts carried out descriptive literature reviews on this topic (ANSES 2013, ANSES 2016, ARPANSA 2014, RSC-EC 2014, WHO 2014, SCENIHR 2015, HCN 2016, CCars 2017, ICHENF 2018, SSM-SC 2013–2019, FDA 2020 (see the acronyms table). Nowadays, no systematic reviews on carcinogenic RF effects are available; this is the first attempt of a systematic review on radiofrequency carcinogenic effects *in vivo* studies. RF-EMF animal studies on carcinogenesis cover a wide range of experimental situations, in terms of exposure

modality, study design and biological endpoints. This peculiarity has ambivalent effects: on one hand, it is very difficult to make a univocal classification of the studies and, consequently, to compare the results for a comprehensive analysis, on the other hand, the diversity of studies manages to cover a wide range of experiments, providing a reasonably well insight into the effects of RF-EMF exposure on carcinogenesis in laboratory animals.

Regarding the exposure, different frequencies were used, from a few hundred MHz to some GHz, with different modulation schemes, e.g. continuous wave (CW), pulsed, Global System for Mobile Communication (GSM) like signals and Code Division Multiple Access (CDMA) like signals. The used signals are mainly those of mobile communications but the variety of signals and platforms, over the years and in different countries of the world, does not simplify the homogenization of work for a review. In telecommunications, unlike other applications, lies the greater diversification of signals. The other signals studied were mainly at the frequency of 2.45 GHz, used for Wireless Fidelity (WiFi) system and microwave ovens. One of the main critical issue in the RF-EMF experimental *in vivo* studies is the dosimetry (Paffi et al. 2013, Kuster et al. 2000, Chou et al. 1996), the assessment of the effective dose induced in the RF-EMF exposed object/subject provided in terms of Specific Absorption Rate (SAR, W/kg). Many differences can be observed both in terms of RF dose of treatment, from non-thermal SAR levels to high SAR levels associated with an increase in body temperatures and method of exposure (i.e. full-body vs localized exposure, restrained vs free animals moving within large cages), together with not always appropriate use of control groups. Finally, the effect of RF-EMF exposure was studied both using RF-EMF alone and in synergy with other physical and chemical agents as well known carcinogens.

In addition to this difficulty in standardizing the experimental results, it should be also considered that the literature experimental data on the carcinogenic effects of RF-EMF often report conflicting conclusions; even contradictory results are sometimes obtained in replicas of experiments.

3. Objective

Keeping the previous considerations in mind, all study designs and all tumor-related outcomes measure will be analyzed aiming:

- to revise and summarize, narratively and quantitatively (if feasible), findings from the available *in vivo* studies on RF-EMF (100 kHz – 300 GHz) exposure and cancer;
- to assess the confidence and level of evidence in support of the carcinogenicity of RF-EMF provided by experimental studies in animals to understand the potential carcinogenic risk following exposure to doses above or within legal limits.

4. Methods

The methodology for systematic reviews for *in vivo* studies, described in the 'Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence

Integration (https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019_508.pdf) edited by the National Toxicology Program (NTP) - Office of Health Assessment and Translation (NTP-OHAT, 2019), will be applied.

Experts from the Cochrane Collaboration (<https://www.cochrane.org/>),

Navigation Guide (<https://ehp.niehs.nih.gov/doi/10.1289/ehp.1307175>),

GRADE Working Group (<https://www.gradeworkinggroup.org/>),

CAMARADES (<http://www.dcn.ed.ac.uk/camarades/default.htm>),

SYRCLE 1 (<https://norecopa.no/3r-guide/systematic-review-centre-for-laboratory-animal-experimentation-syrcle>)

and others were consulted to write this guide, aimed to assess new methods for evidence-based evaluation of nonhuman toxicological studies, including mechanistic studies, starting from the aspects of existing methods for a systematic review. Other handbooks will be consulted to upgrade the methodology regarding specific aspects of experimental studies (Higgins and Green 2011; Hooijmans et al 2014).

This protocol adheres with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015).

4.1 Eligibility criteria

The eligibility criteria were defined using the Population, Exposure, Comparison, Outcome (PECO) strategy (NTP, 2015 a, b).

4.1.1.Types of populations

Only articles reporting experimental studies on rodents of both sexes, of all ages and species, of all genetic background (wild type, transgenic and tumor-prone animal models) will be included in this review.

4.1.2. Types of exposures

We will include studies where experimental animals were exposed to electromagnetic fields (100 kHz-300 GHz) alone, or in combination with other physical or chemical agents. The exposure systems details, exposure modality and dosimetric assessment should be reported. Studies regarding exposure to extremely low frequency (ELF), infrared, visible and ultraviolet (UV) radiations, as well as theranostic applications, will be excluded from this review. Papers with lack of dosimetric information or with the use of inappropriate sources for the generation of the incident field will be considered not eligible.

4.1.3. Types of comparators

To be eligible for inclusion, studies should report outcome data in the exposed groups and sham control group (a control group simulating all environmental conditions and stress factors of exposed animals, but in absence of RF-EMF exposure).

4.1.4. Types of outcomes

All types of cancer will be considered as well as all tumor-related outcome measures (e.g. incidence, tumor multiplicity, tumor volume, progression), while articles concerning genotoxicity and oxidative stress only will be excluded.

4.1.5. Types of studies.

Only peer-reviewed articles written in English will be considered; all publication dates will be included. Reviews will be excluded but retained as a check of the bibliographic research.

4.2. Information sources and search strategy

4.2.1. Electronic academic databases.

The following databases will be used for the search:

PubMed: www.pubmed.ncbi.nlm.nih.gov;

EMF-Portal: www.emf-portal.org/en.

Only English language peer-review papers, without restrictions on the year of publication, will be included in the review.

The search strategy (query) will be composed of seven distinct elements, separated by appropriate logical operators:

1. RF-EMF (identifying exposure);
2. *In-vivo* studies, animal studies, rodents, mice, rats (identifying population);
3. Carcinogenicity, cancer/tumor/neoplasia, neoplastic and non-neoplastic lesions, tumor induction/co-promotion (identifying outcome);
4. Body organs and tissues (identifying biological target);
5. Elements intended to exclude sources different from RF-EMF emissions: static and ELF electric and/or magnetic fields, UV radiations alone, infrared and visible radiation, ionizing radiation (identifying exclusion criteria for exposure item);
6. Elements intended to exclude theranostic applications: RF and microwave (MW) ablation, hyperthermia and MW imaging (identifying exclusion criteria for study type);

7. Elements intended to exclude other studies (i.e. observational).

4.2.2. Hand-searching.

The reference lists of the selected papers and reviews on the topic, including descriptive reviews carried out by international panels of experts since 2011, will be screened for potentially relevant papers that may have escaped the first search.

The NTP-OHAT Handbook (March 2019) specifies that it is possible to identify relevant publications that are not commercially published or are not readily available to the public yet. These publications (e.g. technical reports from government agencies or scientific research groups, working papers from research groups or committees) may include or summarize unpublished data. If present, their bibliographies will be scanned to identify other references escaped from database searches too.

All references coming from these last sources will be marked as “provided from other sources” in the study selection flow diagram.

4.3. Selection process

All potentially relevant articles will be screened for eligibility in two stages: a first stage in which the articles will be selected, on the basis of title and abstract, by three authors (RP, PV, PG), a second stage, in which the full text of the remaining papers will be independently reviewed by two groups of investigators, each composed by one biologist and one expert in EMF dosimetry (RP, PG group 1 and LA, PV group 2). Disagreements and technical uncertainties will be discussed and resolved between review authors.

The exclusion criteria will be prioritized according to the following items:

1. Not an original full research paper (e.g. review, editorial, letters);
2. No English paper;
3. Not animal (rodents) studies;
4. No cancer endpoints;
5. Exposure out 100 kHz – 300 GHz range;
6. Lack of dosimetric information;
7. No sham/control group;
8. Theranostic application.

4.4. Data collection process

4.4.1 Data extraction

The data extraction form will be defined and agreed upon before the start of papers analysis. The eligible papers will be equally divided between group 1 and group 2 to independently extract numerical data from text, tables, or figures of each article. In case of missing data of the outcome measures, if possible, the reviewer team will contact the authors at least once by mail.

4.4.2. Data items

The extracted data will include:

- i. study design (number of experimental groups, control group(s), number of animals per group, randomization and blind),
- ii. study type (e.g. cancer induction, co-carcinogenesis studies),
- iii. animal model, species, strain, sex, type of animal (wild type, transgenic),
- iv. timing of treatment (i.e. hours for days, days for weeks and total period; age or life stage at the start of dosing),
- v. exposure details i.e. frequency, modulation, dose and type of exposure (whole body vs localized exposure, restrained vs freely moving animals), exposure system,
- vi. primary outcome(s): all tumor-related outcome measures as incidence, tumor multiplicity, tumor volume, progression, latency, survival,
- vii. secondary outcome(s): all parameters related to animal health conditions evaluated at the end of life/experiment,
- viii. method to assess the endpoints,
- ix. data analysis and statistic evaluation,
- x. authors, year of publication, title, journal.

We will also extract data on potential conflict of interest in included studies.

4.5. Risk of bias assessment

The internal validity and the quality of eligible studies will be evaluated using the approach recommended by NTP-OHAT (2019) for animal studies. It provides detailed instructions for assessing how potential sources of distortion may have affected the reliability of the results.

The nine included risk of bias criteria are:

1. Randomized exposure level;
2. Allocation concealment of study groups;
3. Evaluation in the study design or analysis of possible important confounding and modifying variables;
4. Blinding of research personnel;
5. Confidence in the exposure conditions;

6. Confidence in the outcomes assessment;
7. All measured outcomes reported;
8. Attrition/exclusion rate;
9. Possible conflicts of interest.

Regarding item 3, possible important confounding factors are, for example, uncontrolled temperature increases in the exposed animals or any other difference in the experimental conditions between exposed and comparison groups. It is worth bearing in mind that the presence of sham group is mandatory for the inclusion in the analysis and, for this reason, it is useless to remark the importance of identical exposure conditions as reported in NTP-OHAT (2019). Two groups of authors (RP, PG and LA, PV) will independently assess these criteria on the individual study level and they will classify the studies according to the following ratings: “++” definitely low risk of bias; “+” probably low risk of bias; “-” probably high risk of bias, or “--” definitely high risk of bias. Disagreements in the assessment will be discussed between the authors and resolved by consensus. Furthermore, using the OHAT approach, individual studies will be placed into three quality category based on the risk-of-bias ratings. The key criteria for determining the highest weight in the quality of the study are: (1) Confidence in the exposure characterization, (2) Confidence in the outcome assessment and (3) Evaluation in the study design or analysis of possible important confounding and modifying variables. The remaining criteria will be given less weight in determining the quality of the study.

4.6. Data synthesis criteria

4.6.1. Strategy

Structured descriptive summary of eligible studies will include the following items:

- experimental design (e.g. induction/promotion, co-promotion);
- outcome(s) reported;
- the animal model used;
- age of animals at the start of treatment;
- the developmental stage of animals at treatment and outcome assessment (e.g. mating and/or pregnancy status);
- exposure type and level;
- type of data (e.g. continuous or discrete), statistics presented in the paper, ability to access raw data;
- variation in the degree of risk of bias at the individual study level.

A meta-analysis, if feasible, will proceed according to the following main sequence (Vesterinen et al. 2013):

1. calculating an effect size for each comparison,

2. weighting the effect sizes according to the effect model adopted,
3. calculating the summary effect size
4. calculating the heterogeneity and the extent to which the predefined study design characteristics explain this heterogeneity,
5. evaluating the subgroups analysis;
6. checking the presence of meta-bias (e.g. attrition bias, publication/duplicate bias, detection bias).

If necessary, measures of absolute effect will be converted into relative effect measures, to ensure comparability of effect estimate and facilitate the meta-analysis that will be performed for all outcome measures: a minimum of 3 studies per group/subgroup will be required (Moya et al. 2014, Hooijmans et al. 2014)

4.6.2. Additional analysis

Heterogeneity in the results of the meta-analysis may be observed. Variations in the effect size across sub-sets of studies are expected, for instance, if there are differences between species or between exposure levels and exposure modalities. Thus, subgroup analysis or meta-regression may give insight into the relation between study characteristics and the effect size, to find an explanation.

If meta-analysis is not possible, data will be reported through the descriptive summary.

4.6.3. Effect models

Because of the exploratory nature of animal studies, random effect and fixed-effect models will be used to calculate the cumulative mean difference of studies with significant heterogeneity ($60\% < I^2 < 75\%$) and without significant heterogeneity ($I^2 < 60\%$), respectively. Extracted data will be analyzed using appropriate software for meta-analysis. Forest plots will be constructed for each useful parameter and the mean difference value, standard error and p-values will be determined (Borenstein et al. 2009 a, b).

4.6.4. Heterogeneity

Heterogeneity among studies will be assessed with Cochran Q test and further quantified by I^2 statistics. If studies will be affected by high ($I^2 = 75\%$ or greater) heterogeneity, a narrative synthesis will be done.

4.7. Quality of evidence assessment

We will apply the confidence rating approach based primarily on guidance from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (Balsheim et al. 2011, Guyatt et al. 2011). The GRADE framework is often applied to evaluate the quality of evidence and the strength of recommendations for outcomes reported in systematic reviews (Higgins and Green 2011) on human and animal studies. We will assess the quality of evidence for the entire body of evidence by each outcome, with any disagreements resolved by a third review author. We will downgrade

the quality of evidence for the following five GRADE reasons: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias.

We will grade the evidence, according to the three Navigation Guide standard quality of evidence ratings: "high", "moderate" and "low". Within each of the relevant domains, we will rate the concern for the quality of evidence, using the ratings "none", "serious" and "very serious". We will start at "high" for randomized studies: quality will be downgraded for no concern by nil grades (0), for a serious concern by one grade (– 1) and a very serious concern by two grades (– 2). We will upgrade the quality of evidence for the following other reasons: large effect, dose-response and plausible residual confounding and bias.

4.8. Strength of evidence assessment

We will apply a modified version of the Navigation Guide methods (Woodruff and Sutton, 2014) for the nonhuman evidence (Koustas et al. 2014). The rating will be based on a combination of four criteria (I) sufficient evidence of toxicity; (II) limited evidence of toxicity; (III) inadequate evidence of toxicity; or (IV) evidence of lack of toxicity, which in turn are based on the criteria used by the International Agency for Research on Cancer (IARC 2013).

5. Discussion

This systematic review of *in vivo* studies of carcinogenesis from exposure to RF EMF will respond to the need for clarity emerged in the scientific community following the publication of several studies with contradictory results. In our opinion, this systematic review will help to establish the extent of the epidemiological evidence on this topic, in a reproducible and rigorous way.

We are not aware of published systematic reviews and meta-analysis addressing this issue. The World Health Organization's (WHO) Radiation Program has an ongoing project to assess potential health effects, included carcinogenesis, of exposure to radiofrequency electromagnetic fields, in the general and working population, throughout systematic reviews.

Any changes made to this protocol will be outlined in PROSPERO and reported in the final manuscript.

The results of this systematic review will complement the results of the main project "BRiC 06/2018" Ref Y43 "Scientific evidence on the carcinogenicity of radiofrequency electromagnetic fields" aiming to carry out a systematic review of scientific evidence on the carcinogenicity of RF-EMF (100 kHz – 300 GHz) exposure, using methods useful to minimize biases in the identification-selection-synthesis of studies and in the formulation of conclusions.

These results and meta-analysis will be presented at conferences and published in a peer-reviewed journal. Moreover, the main project scheduled a final public event to present all the results.

Abbreviations

AGNIR = Advisory Group on Non-Ionising Radiation (UK);

ANSES = Agence Nationale de Sécurité Sanitaire de l'Alimentation de l'Environnement et du Travail (France);

ARPANSA = Australian Radiation Protection and Nuclear Safety Agency;

CCARS = Comité Científico Asesor en Radiofrecuencias y Salud (Spain);

ELF = Extremely Low Frequency

FDA = Food and Drug Administration; HCN = Health Council of the Netherlands;

GRADE = The Grading of Recommendations Assessment, Development and Evaluation

IARC = International Agency for Research on Cancer;

ICHENF = Interagency Committee on the Health Effects of Non-Ionizing Fields (New Zealand);

ICNIRP = International Commission for Non-Ionizing Radiation Protection; NTP = National Toxicology Program

ISS = Italian National Institute of Health

MW = Micro Wave

OHAT = Office of Health Assessment and Translation

RF-EMF = Radio Frequency Electro Magnetic field

RSC-EC = Royal Society of Canada Expert Committee;

SAR = Specific Absorption Rate

SSM-SC = Scientific Council on Electromagnetic Fields (Sweden);

SCENIHR = Scientific Committee on Emerging and Newly Identified Health Risks;

SSM = Swedish Radiation Safety Authority;

WHO = World Health Organization.

Declarations

Ethical Approval and Consent to participate

This study will not require ethics consideration as it based on published studies.

Consent for publication

The publication of the protocol on PROSPERO and, if possible on a peer reviewed journal is one of the objectives of the funded project.

Availability of supporting data

Authors have the access to all scientific databases, in order to collect all relevant papers for the systematic review.

Competing interests

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.

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Authors' contributions

CM: Conceptualization, Supervision, Project administration, Funding acquisition; RP: Conceptualization, Methodology, Writing - Review & Editing, Visualization; PV: Methodology, Writing - Original Draft; LA and PG: Methodology, Writing - Review & Editing. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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