X LITERATURE SEARCH STRATEGY AND STUDY EVALUATION FOR HEALTH RISK ASSESSMENT

This appendix describes criteria and procedures for literature search and for inclusion and assessment of papers used to develop the sections of the Monograph as published for the public consultation. The expert group that will finalize the Monograph will also review this appendix and make the final decisions about the criteria.

The process of identifying studies to be included in this Monograph as basis for the health risk assessment, started by defining criteria of relevant studies, such as type of exposure and year and language of publication. This was followed by the development and execution of strategies of searching for relevant studies for each topic and type of study. The papers resulting from the search were initially screened by title and when there was doubt about their relevance, the abstracts were read. Papers that were clearly not relevant were discarded. Additional papers were sometimes obtained by searching for related papers in the databases or by consulting reference lists of other papers, often reviews. Additional papers were also identified when searching for or when reading papers for other topics of this Monograph. This resulted in a list of possible relevant papers that all were obtained in order to consult the full text. The list of relevant papers was finalized when having discarded papers that were found not to be relevant based on the full text.

For each type of study, inclusion criteria (see X.3) were defined. Papers were discarded if they were found to be duplications (see X.3.1) or if they did not comply with the quality criteria for inclusion (see X.3.2.1). All papers that remained were included in the relevant section of the Monograph. Information from these papers was extracted and the papers were further assessed. In addition to papers that were in full compliance with inclusion criteria, categories specific for the different types of studies were defined based on a priori specified criteria (see X.3.2.2 and X.3.2.3). Epidemiological and volunteer studies used the category "Papers with uncertainties related to inclusion criteria" and animal and in vitro studies used the category "Studies not included in the analysis". Studies in these two last categories are described in subsections and are currently not included in the summary tables. The process from performing the search until the categorisation of papers is illustrated in Figure X1.

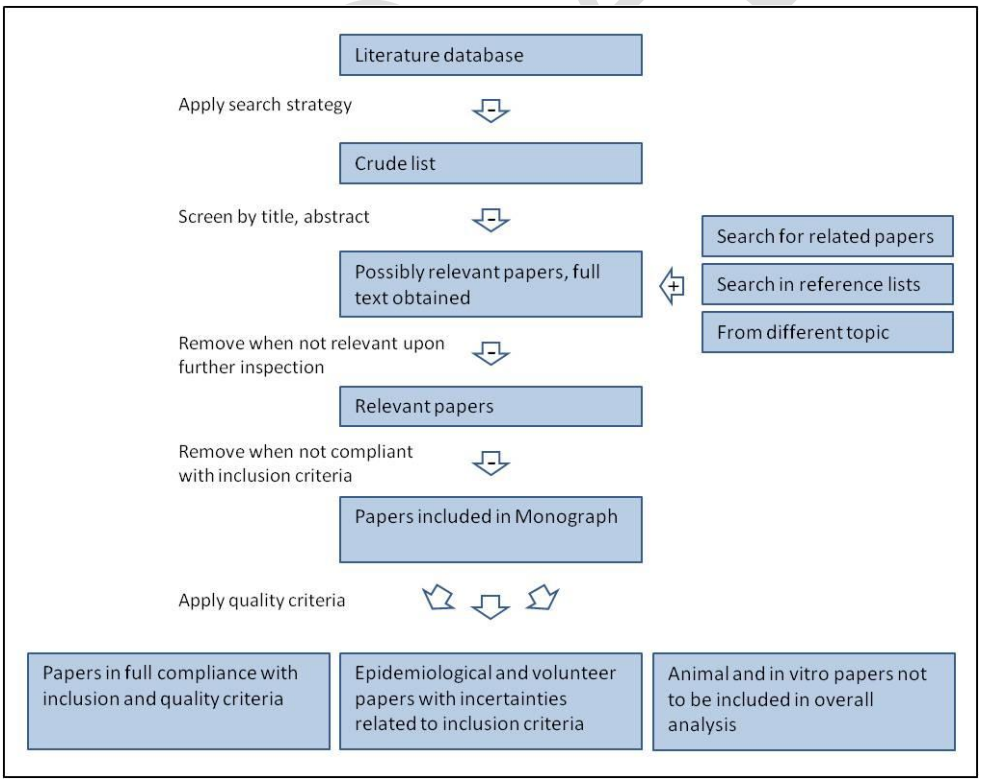

Figure X1. Main steps in search for, screening and assessment of papers.

X.1 Relevant studies

Studies of relevance for the health risk assessment of this Monograph were defined by the scope stating that WHO "will deliver a critical, scientific review on the effects of radiofrequency fields on all studied outcomes of relevance to human health, but excluding usage for medical diagnostic and therapeutic purposes …". The frequencies to be covered were restricted to the range 100 kHz – 300 GHz, and further specifications were done for each type of study:

- **Epidemiological** studies include different categories of study design, but not case reports or case series.
- **Volunteer studies** include experimental studies with humans, that means laboratory studies and intervention studies.
- **Animal studies** include experimental studies with laboratory animals and observational studies with domestic animals.
- **In vitro studies** include laboratory studies carried out on cell cultures or isolated tissue samples.

Furthermore, for all types of studies, a study was defined as relevant for this review if it was published:

- after the time period covered by the previous EHC monograph assessing potential health effects of RF EMF (WHO 1993), that is between 01-01-1992 and 31-12-2012, and for some sections also later studies (this will be updated to include more recent studies for the final version of the Monograph);
- in a peer-reviewed scientific journal. Narrative reviews are not included. Meta-analyses are not included at this stage. Conference proceedings are not included. Withdrawn papers are not included.

It was agreed to include papers in the following official WHO languages: Chinese, English, French, Russian and Spanish, while due to restricted language competence of available experts and restricted options for translations, none of the identified Russian papers and only epidemiological Chinese papers have been included. Papers in German were systematically included, whereas papers in other languages were included if experts that could help with these were easily identified and available.

X.2 Search strategy

In the following, common features in the search strategies are described for all types of studies as well as separately for the epidemiological studies and the experimental (volunteer, animal and in vitro) studies. The detailed search strategies for each chapter will be provided in a separate Appendix.

X.2.1 All types of studies

Using the predefined search strategies, systematic searches were performed in PubMed for all types of studies, in ISI Web of Science for epidemiological and volunteer studies, and in Embase for epidemiological studies.

In addition, in some cases EMF literature databases, such as the EMF Portal (http://www.emf-portal.de/), ELMAR (http://elmar.swisstph.ch/), and private databases were screened.

X.2.2 Epidemiological studies

A general search strategy was constructed aiming for identification of *all* epidemiological studies of potential health effects of exposure in the frequency range included in this review, regardless of outcome or study design. The search strategy consisted of two parts; one with the aim of identifying publications studying relevant exposures, and the other to identify all types of epidemiological studies. The search identified articles that fulfilled both the exposure part and the design part of the search strategy. To identify literature addressing specific outcomes, search terms that identified the specific outcome were added to the general search. Thus, the general search strategy designed for epidemiological studies was used as the basis for the search for literature on all specific outcomes.

During elaboration of the search strategy, it became evident that occupational studies were not covered to the same degree as other exposure sources, mainly because many occupational studies, especially during the first part of the calendar period covered by the search, did not specifically study RF exposure or not even electromagnetic fields, but rather studied a large number of occupations of which some may have had a high prevalence of RF field exposure. It was not considered feasible to go through all available occupational studies regardless of studied exposure. Instead, an intensified search was performed of the reference lists of available reviews and original occupational studies of electromagnetic field exposure.

X.2.3 Experimental studies

For the experimental studies separate searches were performed for each section to identify papers relevant for the health related outcomes covered by that section. Hence, search terms related to the outcomes were specified for each section. Search terms related to exposure were identified across sections for each type of experimental studies. In addition, for some sections terms were used to restrict the number of hits.

X.3 Inclusion criteria

All papers that had been identified as relevant based on the criteria defined in section X.1 were screened. They were excluded from further assessment if they were duplication papers (see section X.3.1) or if they did not comply with the specified inclusion quality criteria (see section X.3.2). Excluded papers are listed at the end of the relevant section.

X.3.1 Duplication papers

Some epidemiological studies have been published in more than one paper. In such cases only the first original publication was included in this review and duplication reports were excluded, unless new additional results were presented. For duplication papers on human volunteer studies, the paper that provided the most complete coverage of the relevant outcomes of the study was included, and other reports of the same study were used only if they provided complementary relevant information.

X.3.2 Design and methodology criteria

X.3.2.1 Quality criteria for inclusion of papers in the Monograph

In order to be able to draw conclusions from a study, it is imperative that it complies with certain requirements regarding design and methodology. Inclusion criteria based on such quality requirements were specified a priori for the different types of studies:

Epidemiological studies

- The study base was identified (i.e. the population intended for inclusion was identified, eligible participants were either the whole population or a randomly selected sample, either through sampling from the whole study base, or through a method that allowed assessment of the representativity of the participants. Cross-sectional or case-control studies with self-selection of participants from an unidentified study base, e.g. through advertisement, were excluded).
- Use of proper denominators for calculations of prevalence/incidence in a descriptive or incidence study.
- At least two levels of exposure was considered (except in incidence time trend studies)
- Relevant statistical analysis.

Volunteer studies

- The exposure conditions were blinded to the participants.
- The study included at least two exposure levels, whereof one could be a sham exposure, under otherwise similar conditions. Standby mode of a mobile phone is not regarded as RF exposure, so any study that used a mobile phone in standby mode as the only source of exposure is excluded (Hansson Mild, Bach Andersen & Pedersen, 2012).

Animal studies and in vitro studies

- The study included at least two exposure levels, one of which being sham exposure, with otherwise similar conditions. Standby mode of a mobile phone is not regarded as RF exposure, so any study that used a mobile phone in standby mode as the only source of exposure is excluded. (NB: the current version of the sections for in vitro studies include studies using phones in standby mode; these will be deleted upon revision.)

X.3.2.2 Papers with uncertainties related to inclusion criteria – epidemiological and volunteer studies

For epidemiological and volunteer studies, criteria were formulated a priori based on uncertainties related to inclusion criteria. These studies are given little or no weight in the final analysis, with the weight determined based on the total assessment of the paper, and of all the available scientific evidence, as further described in Section X.4. The papers with such uncertainties are described in separate sections in the text, and the reason for the categorisation of them is provided. Such papers are not listed in the tables.

The criteria are specified in the following for each type of studies.

Epidemiological studies

- There is insufficient information provided for an appropriate judgment of all items specified for inclusion, e.g. the paper provides no information about the source of study subjects (study base), or procdedures used to select subjects for inclusion.

Volunteer studies

- There is insufficient information to decide whether the participants were blinded.
- The exposure levels were not sufficiently controlled and documented (e.g. a mobile phone in talk mode without level control).
- There is no relevant statistical analysis when this is needed to conclude on statistical significance.
- Exposures were given in fixed order.

The last three of these criteria are related to the inclusion criterion specifying that the study should include at least two exposure levels, whereof one could be a sham exposure, under otherwise similar conditions. When the exposure level cannot be determined, conclusions about potential effect of RF exposure will have limited value. Without relevant statistical analysis, assessment of effect of RF exposure compared to sham may be difficult or impossible. With fixed order of exposure, it is uncertain whether the exposure conditions were similar, since there could be an effect of order and/or of time.

X.3.2.3 Papers included in the Monograph but not to be used in the analysis – animal and in vitro studies

Additional criteria were formulated a priori for animal and in vitro studies to be included in the overall analysis of a particular topic (and thus ultimately in the health risk assessment). The papers that did not comply with those criteria are briefly described in separate sections in the text, and the reason for not including them in the analysis is provided. Such papers are not listed in the tables.

The following criteria for not being included in the analysis were specified for both animal and in vitro studies:

- There is no relevant statistical analysis when this is needed to conclude on statistical significance.
- The exposure levels were not sufficiently controlled and documented (e.g. a mobile phone in talk mode without level control).

In addition for *animal studies:*

- Exposures were given in fixed order.

In addition for *in vitro studies*:

- The biological assay was not properly carried out.
- The number of independent experiments was insufficient (less than 3).

X.4 Quality assessment of papers included in the Monograph

All papers included in the Monograph were fully assessed. Assessment criteria were developed mainly based on recognised recommendations and checklists for what to include in the reports of the respective study types. For all study types, the following main issues should be assessed for each individual study:

- statistical precision/statistical power (width of confidence intervals when provided, primarily study size);
- potential bias;
- consistency and plausibility of results and, when relevant, dose-respons relation;
- indirectness (reduced validity in relation to such as study population, exposure, time lag between exposure and outcome assessment, and endpoints).

For each of the study types more specific assessment criteria were specified.

Epidemiological studies

The quality criteria for epidemiological studies were elaborated mainly based on recommendations in STROBE, which is an initiative to strengthening the reporting of observational studies in epidemiology (www.strobe-statement.org). STROBE does not make quality assessments, but provides a checklist with items that are important to include in reports of observational studies. Important items for adequate reporting are also of importance for assessment of study quality and evaluation of the findings. Other quality assessment scales were also discussed and taken into consideration when elaborating the quality criteria, e.g. GRADE (http://www.gradeworkinggroup.org/) and the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). These scales were, however, judged to be too superficial and technical and would miss essential quality aspects if applied on their own. For the GRADE system the main limitation was that it has been developed to assess clinical trials and interventions, and is therefore less suitable for observational studies of potential risk factors for disease.

Potential biases from the following sources was assessed:

- selection bias (likelihood of inclusion of eligible cases and controls (state source of control selection), successful follow-up in cohort studies (should not be related to exposure) (NB: selection bias can also occur as internal missing data);
- outcome misclassification (detection bias, nocebo);
- exposure assessment and categorization (choice of cut-points);
- non-differential exposure misclassification;
- differential exposure misclassification (recall bias) – can also occur as differential completeness of reporting, observer bias;
- reverse causation (incl. also prodromal effects);
- confounding;

- statistical methods;
- internal consistency, external consistency/validity, dose-response.

Volunteer studies

For volunteer studies the CONSORT statement and checklist for trials (Schulz et al., 2010) was the main source for developing quality assessment criteria and in addition the Gold Standard Publication Checklist (Hooijmans et al., 2011) was used, which is targeted at experimental animal studies. Some adjustments, mostly by adding criteria, were done to adapt to the specific conditions of volunteer studies with RF EMF exposure.

Potential biases from the following sources were assessed:

- study design (randomization, counterbalance, habituation sessions);
- design of exposure sessions (adaptaion periods, time between exposures);
- blinding;
- background exposure (particularly important with low exposure levels and in studies including participants with IEI-EMF);
- artefacts (e.g. RF EMF signals interference with recording equipment, heat generated by exposure equipment);
- effects of other factors (exposures and conditions before and during sessions);
- confounding factors in between-group analyses;
- statistical methods;
- dropouts or exclusion of participants or of individual outcomes;
- deviations from predefined protocol.

Concerning indirectness, the following was assessed:

- the characteristics of exposure used in studies with IEI-EMF participants deviated from that reported by the particpants to cause symptoms.

Animal studies

The criteria for the quality assessment of animal studies were based on the Gold Standard Publication Checklist (Hooijmans et al., 2011):

- proper dosimetry;
- proper statistical analysis;
- sufficient group size;
- blinding of exposure and analysis.

In vitro studies

The quality assessment of *in vitro* studies has primarily applied criteria suggested for toxicological investigations. Some adjustments were done to take into account the issues related to RF EMF exposure (Samaras, Kuster & Negovetic, 2006; Zeni & Scarfi, 2012).

- Proper dosimetry;
- Proper temperature control;
- Sufficient number of independent experiments;
- Appropriateness of cell types *vs.* the endpoint investigated;
- Proper statistical analysis.

REFERENCES

Hansson Mild K, Bach Andersen J, Pedersen GF (2012). Is there any exposure from a mobile phone in stand-by mode? Electromagn Biol Med, 31(1):52-56.

Hooijmans C et al. (2011). The Gold Standard Publication Checklist (GSPC) for improved design, reporting and scientific quality of animal studies GSPC versus ARRIVE guidelines. Lab Anim, 45(1):61.

Samaras T, Kuster N, Negovetic S (2006). Deliverable D36: Recommendations on engineering requirements/aspects for experimental research in Bioelectromagnetics; Deliverable D37: Recommendations on quality assurance in Bioelectromagnetics research EMF-NET (http://ihcp.jrc.ec.europa.eu/our_activities/public-health/exposure_health_impact_met/emf-net/docs/reports/Report%20on%20Reccomendation%20in%20Bioelectromagnetcs%20Aug2006.pdf, accessed 26 September 2014).

Schulz KF et al. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ, 340:c332.

Zeni O, Scarfi MR. Experimental requirements for in vitro studies aimed to evaluate the biological effects of radiofrequency radiation. In: Costanzo S, ed. *Microwave Materials Characterization*. InTech, 2012. (Available from: www.intechopen.com/books/microwave-materials-characterization/experimental-requirements-for-in-vitro-studies-aimed-to-evaluate-the-biological-effects-of-radiofreq; accessed 26 September 2014).