NextGEM

Next Generation Integrated Sensing and Analytical System for Monitoring and Assessing Radiofrequency Electromagnetic Field Exposure and Health

D5.1: Definition methodology on umbrella reviews of epidemiological studies

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Glossary of terms and abbreviations used

Abbreviation / Term	Description
AMSTAR	A Measurement Tool for the Assessment of Multiple Systematic Reviews
COSTER	Recommendations for conduct of systematic reviews in toxicology and environmental health research
DECT	Digital Enhanced Cordless Communication
ELF	Extremely low-frequency
EMF	Electromagnetic field
GA	Grant Agreement
GSM	Global System for Mobile Communications
ICNIRP	International Commission on Non-Ionizing Radiation Protection
JBI	Joanna Briggs Institute
JEM	Job exposure matrix
LTE	Long Term Evolution
MECIR	Methodological Expectations of Cochrane Intervention Reviews
MeSH	Medical Subject Headings
NextGEM	Next-Generation Integrated Sensing and Analytical System for Monitoring and Assessing Radiofrequency Electromagnetic Field Exposure and Health
PECOS	Population, Exposure, Comparison, Outcome, Study type
PICO	Population, Intervention, Control, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols Statement
RF	Radiofrequency
RoB	Risk of Bias
SAR	Specific absorption rate
UR-A/B	Umbrella review A/B
UMTS	Universal Mobile Telecommunications System
WHO	World Health Organization

Executive Summary

The deliverable D5.1 "Definition methodology on umbrella reviews of epidemiological studies" defines the methodology for umbrella reviews of epidemiological studies as used in NextGEM to conduct two umbrella reviews in Work Package 5. Umbrella reviews are reviews of published systematic reviews and meta-analyses based on a-priori defined methods, comprising inclusion and exclusion criteria, and a comprehensive search strategy. Umbrella reviews can provide an overview of the current body of evidence on a topic that has already been addressed in many studies. Because umbrella reviews are conducted using an equally systematic approach as compared to systematic reviews, the results are considered more robust than those from overview articles that use a selective ad-hoc approach. In addition, rating tools (such as AMSTAR) can be used in umbrella reviews to assess the Risk of Bias (RoB) of included qualitative and/or quantitative reviews. There was a surge of systematic reviews and meta-analyses published on health effects of radiofrequency electromagnetic fields (RF-EMF) over the last two decades. However, there are concerns about potential bias in these overview articles. Furthermore, some of these evidence synthesis articles provide conflicting, redundant, and potentially misleading conclusions. Therefore, it can be difficult for decision makers and policy-makers to identify reliable overview articles of high methodological quality.

This deliverable includes a general rationale for conducting umbrella reviews in the context of hazard assessments relating to exposure to radiofrequency fields and cancer, based on human observational studies. In addition, the deliverable outlines the protocol of two separate but strictly connected umbrella reviews of the epidemiological evidence on cancer risks from exposure to RF-EMF. One umbrella review will be carried out on the association of cancer outcomes with RF-EMF exposure by near-field sources, and one umbrella review will assess the association of cancer outcomes with RF-EMF exposure by far-field sources. This deliverable also includes a discussion on the strengths and limitations of an umbrella review and a conclusion.

1 Introduction

While modern society heavily relies on emerging technologies utilizing radiofrequency electromagnetic fields (RF-EMF, 100 kHz-300 GHz), especially in telecommunication applications, there is concern about their potential negative impact on human health. This concern is amplified by the potential accumulation of various RF-EMF signal types. In particular, some citizen advocate groups have voiced concern that fifth-generation telecommunication systems (5G; 5G New Radio; 5G NR) may pose a more substantial risk to public health compared to earlier generation systems [1]. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the International Committee on Electromagnetic Safety of the Institution of Electrical and Electronic Engineers (ICES-IEEE) have issued exposure guidelines and standards to mitigate scientifically proven adverse effects [1]. According to experts, cancer is the most relevant potential hazard of EMF at exposure levels below current international guidelines [2]. Cancer is also the most investigated health outcome in studies investigating prolonged exposure to EMF from mobile communication. These studies account for about 40% of all related epidemiological studies currently indexed in the specialized literature database EMF-Portal (https://www.EMF-portal.org/en). In order to establish a solid scientific foundation for evidence-based risk assessment regarding potential carcinogenicity of RF-EMF exposure, NextGEM is slated to conduct two umbrella reviews of systematic reviews and meta-analyses of human observational studies on cancer risk associated with exposure to RF-EMF. Umbrella reviews, if executed and interpreted accurately, have the potential to yield the highest level of evidence. The published systematic reviews and meta-analyses will be subjected to a comparative evaluation of their methodological quality, taking into account factors such as transparency, adherence to predefined protocols, effectiveness in addressing the relevant scientific inquiries, and the reliability of their conclusions. This assessment will be based on reference benchmarks and expert evaluation.

1.1 Mapping NextGEM Outputs

The purpose of this section is to map NextGEM's Grant Agreement (GA) commitments, both within the formal Task description and Deliverable, against the project's respective outputs and work performed.

Table 1: Adherence to NextGEM's GA Tasks and Deliverables Descriptions

TASKS	
Task Number & Title	**Respective extract from formal Task Description**
Task 5.1 - Umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on RF-EMF exposure and cancer risk	The goal is to systematically summarize the evidence regarding near- and far-field exposure to RF-EMF and cancer risk in the general and working population provided by human observational studies, using the novel approach of the umbrella review. Umbrella reviews systematically compile evidence from multiple systematic reviews and meta-analyses into one document that is accessible and usable deliverable for public health policymaking. However, it is common that systematic reviews and meta-analyses on the same topic, even published in the same year, come to different conclusions. By systematically summarizing and comparing results of all relevant systematic reviews and meta-analyses on exposure to RF-EMF and cancer risk, Task 5.1 can provide the highest quality of evidence and complete overview of the literature body. The level of evidence from human observational studies will be integrated with those relating to experimental studies of carcinogenic effects of EMF in animal and cells models.
DELIVERABLE	
Deliverable: D5.1: Definition methodology on umbrella reviews of epidemiological studies This deliverable will define the methods and tools used to perform the umbrella reviews of systematic reviews and meta-analyses of epidemiological studies of potential human cancer hazards from exposure to RF-EMF.	

1.2 Deliverable overview and report structure

Based on the objectives and work carried out under Task 5.1, with the aim to conduct two umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on RF-EMF exposure and cancer risk, the document starts with the Executive Summary followed by the Introduction in Section 1.

Section 2 focuses on the general motivation and rationale for conducting umbrella reviews with the research question of exposure to RF-EMF and associated risk of cancer in humans (Section 2.1). The section finishes with the objectives of the two umbrella reviews (Section 2.2) that will be carried out in NextGEM based on the protocol outlined in this document.

Section 3 of the deliverable document outlines the methods for conducting the two umbrella reviews, one on near-field RF-EMF exposure and cancer (UR-A) and one on far-field RF-EMF exposure and cancer (UR-B). This includes general information on the protocol development and the used methodologies (Section 3.1). Further described in detail are the eligibility criteria in the framework of the PECOS scheme to inform which studies are relevant and will be included in the umbrella reviews (Section 3.2). Particular emphasis is placed on the exposure component ("E" of PECOS), because this is where the two umbrella reviews differ from each other. One focuses on near-field RF-EMF exposure, (UR-A), and the other one on far-field RF-EMF exposure (UR-B), while all other components of the PECOS are similar (Section 3.2.2). We describe the relevant steps of a systematic umbrella review to come to the included studies, that is, the search strategy and the study screening and selection process (Section 3.3 and Section 3.4). These phases are followed by data extraction, and data synthesis (Section 3.5 and Section 3.6). We then describe the critical appraisal of the identified studies, which will include a Risk of Bias (RoB) assessment of all included systematic reviews and meta-analysis (Section 3.7). The RoB will be one of the main results of the umbrella reviews and will help to identify well conducted overviews. Then, we address general strengths and weaknesses of umbrella reviews (Section 3.8).

Section 4 summarizes the conclusions of the deliverable.

2 Umbrella reviews of near-field (UR-A) and far-field (UR-B) exposures to RF-EMF and cancer in humans

Exposure to radiofrequency electromagnetic fields (RF-EMF; frequencies 100 kHz to 300 GHz) is ubiquitous. The use of RF-EMF has grown steadily since the 1950s and includes various applications in medicine, industry, domestic appliances, security, military activity, navigation and especially telecommunications. In telecommunications, RF-EMF is employed for radio and TV broadcasting, and for mobile telephony [3].

Since the late 1990s and early 2000s, when mobile telephony became prevalent among the general public, there have been concerns among citizens, governments, and experts about potential health effects of this technology. With the advent of new technological developments in this field, including 5G mobile networks, and increasing wireless connectivity of devices via the internet, known as Internet of Things (IoT), these concerns remain relevant. Therefore, conducting an evidence-based health risk assessment regarding RF-EMF is crucial to inform and support decision-makers as well as address concerns among the general public.

The World Health Organization (WHO) is currently updating the assessment of potential health hazards from exposure to RF-EMF. As part of this activity, WHO conducted a comprehensive global survey in 2018, targeting leading experts in the field of RF-EMF health effect research to ascertain the most pressing health effects potentially associated with RF-EMF. Based on the survey findings, six key areas of concern were identified, and WHO commissioned a series of systematic reviews of observational and experimental studies on the following topics: cancer, adverse reproductive outcomes, cognitive impairment, human self-reported symptoms, oxidative stress, and heat-related effects, tinnitus, migraine and non-specific symptoms. Cancer was most frequently rated as critical by the respondents of the survey among these different areas of concern. The responding experts based their decision mainly on evidence from human studies and public concern [2].

To synthesize all available evidence from published systematic reviews and meta-analyses on RF-EMF and cancer, we will carry out two umbrella reviews of human observational studies, one on near-field and one on far-field exposures to RF-EMF and risk of neoplastic diseases.

2.1 Rationale for umbrella reviews on RF-EMF and cancer in humans

At exposure levels below limits defined by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) no mechanism for carcinogenicity of RF-EMF is established. Several hundred experimental studies investigated the capacity of RF radiation to induce genetic damage since genotoxicity is one of the key biological indicators of carcinogenicity and the most common characteristic of established carcinogens [4][5]. The results of these studies are inconsistent with experimental studies showing significant genotoxicity and others reporting absence of an effect from RF exposure. The effects, when present, are a function of frequency, amplitude, and modulation, and in most cases are not replicated in follow-up studies [6][8][9][10] with methodological quality of the studies being one of the main reasons [11].

To inform the general public and support policy makers and health-care professionals in making sound decisions, all relevant and available scientific evidence should be used. However, current evidence can consist of dozens or even hundreds of studies presenting complex, multifaceted and even conflicting evidence, posing challenges to deriving accurate conclusions. Systematic reviews provide a comprehensive overview based on a-priori defined methods regarding the inclusion and exclusion of primary studies and evaluate the quality of the body of evidence. As such, systematic reviews are a good evidence synthesis tool and crucial for evidence-based decision-making [12].

A surge of systematic reviews published over the past two decades bears testament to the strong demand for this form of evidence synthesis [13] . However, concerns have been raised regarding the rapidly increasing number of systematic reviews and meta-analyses. These concerns include the potential susceptibility of bias in these studies, and the massive production of conflicted, redundant, low-quality and potentially misleading evidence synthesis articles [14]. These concerns also apply to the RF-EMF and cancer topic. J. Ioannidis [14] reports on 12 meta-analyses published between 2006 and 2014 on the potential association of mobile phone use and cancer. He highlights that these studies varied in eligibility criteria, time of the literature search, and number of included studies (between 2 and 47). In addition, the studies showed conflicting results, varying from some potentially increased risk for long-term use (≥10 years) and

ipsilateral gliomas, to the interpretation of the results as consistent with a null effect. However, Ioannidis does not delve further into differences between these papers.

It is not uncommon that some reviews conducted on the same research question within the same year come to different conclusions, confusing those who try to develop a coherent understanding of the current evidence, in particular for shaping policy [15] . This is where an umbrella review can come into play. In order to synthesize and evaluate the evidence, scientists have recently started to conduct overviews of systematic reviews and meta-analyses, called umbrella reviews [12][16]. Umbrella reviews can provide an overview of the complete body of evidence on a certain topic. Because umbrella reviews are conducted using an equally systematic approach as compared to systematic reviews, the results are based on a more solid foundation than common overview articles based on an ad-hoc elective approach. In addition, quantitative approaches, such as those used in the AMSTAR systematic review quality assessment tool, can be used in umbrella reviews to grade the reliability of evidence on a certain topic [17].

2.2 Objective of umbrella reviews on RF-EMF and cancer in humans

The aim of the two planned umbrella reviews is to collect and assess all available evidence from published systematic reviews and meta-analyses of human observational studies on a possible association between exposure to RF-EMF and risk of neoplastic diseases. The following specific objectives are included in this umbrella review:

- Identify relevant systematic reviews and meta-analyses of subject-relevant epidemiological studies;
- Extract and synthesize the evidence;
- Assess heterogeneity across systematic reviews and meta-analyses on the same exposure-outcome association;
- Appraise critical quality of included studies.

In order to account for different exposure conditions (near-field and far-field), two bodies of evidence will be reviewed separately to assess the neoplasia hazard in relation to RF-EMF:

- UR-A on RF-EMF exposure from near-field sources
- UR-B on RF-EMF exposure from far-field sources

Both umbrella reviews will include exposure to general and working population to give a comprehensive overview of the body of evidence. The scientific questions are expressed as a PECOS statement (see Table 2 below).

3 Protocol for umbrella reviews on exposure from near-field sources of RF-EMF (UR-A) and far-field sources of RF-EMF (UR-B) and cancer in humans

This section includes the definition of methods and tools that will be used to perform the umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on human cancer hazards associated with exposure to RF-EMF from near-field sources (UR-A) and far-field sources (UR-B). The described methods form the protocol which will be followed when carrying out the two umbrella reviews. It is a double branched protocol, which means that there is a single protocol including a priori defined methods of both the UR-A and UR-B.

3.1 Protocol development

This protocol mostly follows the Joanna Briggs Institute (JBI) methodology for umbrella reviews [18][13]. It deviates from the JBI approach regarding the critical appraisal of the included studies. In place of the critical appraisal checklist for systematic and research synthesis proposed by Aromataris et al. [18][13], we will use AMSTAR 2. The latter ("A MeaSurement Tool to Assess systematic Reviews - AMSTAR 2") is a popular instrument for critically appraising systematic reviews also for assessing non-randomized studies [19].

The protocol will also be aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement (PRISMA-P) [20].

One protocol for the two umbrella reviews will be registered in PROSPERO, which is an international prospective register for protocols for systematic reviews and also umbrella reviews (https://www.crd.york.ac.uk/prospero/). In case any amendments to this protocol are made during the review process, changes and related reasons will be reported in the deliverables and the final review paper.

3.2 Eligibility criteria

To define the scope and research question of the umbrella reviews, we used the structure of population (P), exposure (E), comparator (C), outcome (O), and study type (S) (Table 2).

Table 2: PECOS scheme for umbrella reviews on exposure from near-field sources of RF-EMF (UR-A) and far-field sources of RF-EMF (UR-B) and cancer in humans

UR-A. Umbrella review of evidence syntheses on near-field RF-EMF exposure and cancer in humans	
Population	Members of the general and working population, without restriction on sex, age, or other individual restrictions
Exposure	Near-field head-localized RF-EMF exposure from personal or occupational use of wireless devices (mobile phones, cordless phones, hand-held transceivers) or from medical devices such as cochlear implants occurring prior to the outcome event
Comparator	Never or non-regular exposure to near-field RF-EMF
Outcomes	• All neoplasms, e.g., tumours arising in the head region (including glioma/brain tumours in adults, paediatric brain tumours, meningioma, acoustic neuroma, pituitary gland tumours, salivary gland tumours) • Lymphomas • Leukaemia
Study type	Systematic reviews and meta-analyses of epidemiological studies informative for hazard assessment purposes: cohort studies, case-control studies (including variants thereof), and others (e.g., mobile phone-related simulation studies)

UR-B. Umbrella review of evidence syntheses on far-field RF-EMF exposure and cancer in humans	
Population	Members of the general and working population, without restriction on sex, age, or other individual characteristics
Exposure	Far-field whole body environmental or occupational RF-EMF exposure from radio-television transmitters, base stations or any other fixed-site transmitter, occurring prior to the outcome event
Comparator	Never or low-level of exposure to far-field RF-EMF
Outcomes	• All neoplasms, e.g., tumours arising in the head region (including glioma/brain tumours in adults, paediatric brain tumours, meningioma, acoustic neuroma, pituitary gland tumours, salivary gland tumours) • Lymphomas • Leukaemia
Study type	Systematic reviews and meta-analyses of epidemiological studies informative for hazard assessment purposes: cohort studies, and case-control studies (including variants thereof)

3.2.1 Population description

Both umbrella reviews will include members of the general population and occupationally active individuals. No restrictions on sex, age, or other individual characteristics will be applied.

3.2.2 Exposure description

The relevant exposure included in this umbrella review is human exposure to RF-EMF in the range of 100 kHz to 300 GHz. RF-EMF belongs to the non-ionizing region of the electromagnetic spectrum and therefore does not have sufficient energy in a single quantum of RF energy to ionize an atom or molecule [22]. This exposure originates from various applications in different frequency bands in the above stated range. An overview of the main applications and the corresponding frequency bands is provided in Table 3 [3].

Table 3: Radiofrequency spectrum allocation and main applications [3]

Radiofrequency band	**Main applications**
100-3000 kHz	Amplitude Modulated (AM) radio broadcast, radionavigation, 160 m amateur radio, induction heaters, electrosurgical units
3-30 MHz	International broadcast, amateur and Citizen Band (CB) radio, dielectric heaters, shortwave diathermy
30-300 MHz	Frequency modulated (FM) radio broadcast, Very High Frequency (VHF) television broadcast, mobile and handheld transmitters, cordless phones
300-3000 MHz	UHF television broadcast, 1G-5G mobile (cellular) phones and base stations, Digital Enhanced Cordless Telephones (DECT), Terrestrial Trunked Radio (TETRA), walkie-talkie, microwave ovens, microwave diathermy, air traffic radars, WiFi
3-30 GHz	Microwave relays, satellite uplinks, aircraft on-board radar, police radar, 5G mobile telephony, WiFi
30-300 GHz	Radio-astronomy, space-research, satellite, radionavigation

RF-EMF sources can be classified into near-field or far-field exposure devices, depending on the proximity of the device to the body. In far-field conditions, which occur at a distance of approximately two wavelengths from the emitting source, compliance with exposure limits can be accessed via measurements of RF environmental levels. These RF environmental levels are defined as Electric field strength (E), measured outside the body in Volt per meter (V/m) or as incident power density (S_{inc}), measured, also outside the body, in Watt per square meter (W/m2). When necessary, it is possible to sum up the incidence power density of RF signals at different frequencies. In near-field conditions, the RF energy interacts with the human body, and the appropriate metric is the Specific energy Absorption Rate (SAR, W/kg), or the absorbed power density (S_{ab}), in watt per square meter (W/m2), which accounts for different features of the absorbing tissues. In near-field conditions the SAR and absorbed power density is either calculated or measured in phantoms.

3.2.2.1 Near-field exposure in UR-A

UR-A will investigate the association between near-field RF-EMF exposure and cancer risk. For UR-A, wireless phones will be the main exposure source investigated by the included study reviews/meta-analyses. Of all types of wireless phones, mobile phones are the most common one. Other types of wireless phones were bag-phones or car-phones, introduced in the 1980s, and not used anymore. Furthermore, cordless phones using Digital Enhanced Cordless Communication (DECT) technology were introduced in the 1990s. RF exposure to the head from bag-phones or car-phones was very low and negligible to the aim of a hazard assessment [3]. Handheld mobile phones (analogue; frequency bands 450 MHz or 800/900 MHz), were introduced in the United States in 1984 and in 1987 in the Nordic countries. Later generations of handheld mobile phones were introduced approximately every decade: 2G in the early 1990s (Global System for Mobile Communications (GSM) 900/1800 MHz); 3G in 2000 (Universal Mobile Telecommunications System (UMTS), 1900 MHz); and 4G in early 2010s (Long Term Evolution (LTE), 800/2600 MHz). The latest generation (5G) also involves RF-EMF exposure in frequency bands above 6 GHz. Due to the short time since the introduction of this technology, no systematic reviews or meta-analyses of epidemiological studies on exposure RF-EMF from 5G technology and risk of cancer are expected to be identified in UR-A [3]. However, there have been studies on RF-EMF exposure >6 GHz on radar workers [8] which could be included in UR-B if there are systematic reviews or meta-analyses on this topic.

When held to the ear, mobile phones are typical sources of near-field exposure to RF-EMF, and therefore the main source of exposure considered in UR-A. The RF energy emitted by the mobile phone during voice calls, when the device is held to the ear, is absorbed by the surrounding tissues at a maximum depth of about 5 cm. The SAR to the brain depends on several factors, such as the user's physical characteristics, the phone's position relative towards the ear or the use of hands-free devices, and factors that affect the device transmission power (Lagorio et al., 2021). However, all these parameters are difficult to measure over a long exposure time window, which is needed for epidemiological studies on cancer, making it difficult (or rather impossible) to estimate the individual exposure in terms of SAR. Actually, almost all epidemiological studies of mobile phone use and cancer published to date relied on indirect measures of exposure (surrogate or proxy variables). These indirect measures take into account e.g., time spent talking and may be based on mobile phone carrier subscriber data or on self-reported mobile phone use. The umbrella review depends on the exposure variables and metrics most commonly used in the published systematic reviews and meta-analyses (i.e., mainly: ever use of mobile phones, time since start of mobile phone use, cumulative hours of mobile phone use, and cumulative number of calls). Self-reported laterality will not be considered as an eligible exposure indicator. Even though self-reported preferred side of the head for mobile phone use could be a meaningful determinant of the exposure to the brain, assessing laterality retrospectively via self-reports implies a relevant exposure misclassification [3], as shown in numerous validation studies [21] [23][24].

Besides mobile phone use, cordless phones will also be considered as a source of near-field exposure to RF-EMF. DECT is the most common technology in terms of cordless phones. They have a peak power of 250 mW and an average output power of 10 mW. Compared to 1G-2G mobile phones, the transmission power of cordless phones is 1-2 orders of magnitude lower [25][3]. Furthermore, we will include studies that included occupational exposure to handheld RF-transmitters (e.g., professional use of wireless devices such as walkie-talkies or radio sets, TETRA (Terrestrial Trunked Radio), assessed e.g., via a Job Exposure Matrix (JEM), job titles or personal exposure measurements.

3.2.2.2 Far-field exposure in UR-B

In UR-B a potential association between far-field RF-EMF exposure and cancer risk will be investigated. We will include studies with exposure from radio and television masts, mobile phone base stations, or any other fixed-site transmitter. In principle, the average or cumulative whole-body SAR (absorbed) power density are the relevant dosimetry quantities. However, SAR cannot be directly measured. Therefore, in epidemiological studies measurements or modelled levels of electric fields, magnetics fields or (incident) power density e.g., at the subject's residence are used. As a cruder proxy for the actual exposure, also distance to exposure sources has been used [3]. In general, the electric field strength decreases in the beam with 1/distance from the source for a transmitter. If the distance to e.g., the subject's home is objectively recorded from geocodes, the distance from a fixed-site RF exposure source is informative for antennas with a roughly isotropic transmission pattern. Large broadcast transmitter fulfils these criteria. For base stations this is usually not the case. Distance from a base-station is considered a poor indicator for exposure to RF-EMF indoors [3]. Furthermore, actual exposure also depends on factors such as shielding effects and multiple reflections from house walls or other buildings which are not captured by a distance-based metric [26][3].

Studies with objective and subjective exposure indicators such as measurements, modelling or geocoded-distances will also be considered. While geocoded-distances have the aforementioned limitations for mobile phone base stations, studies based on this metric will be included for both, broadcast transmitters, and mobile phone base stations. If published systematic reviews or meta-analysis included this measure, we will also include these studies in our umbrella review to strive for an overview of the literature which is as complete as possible. The same reasoning applies to studies based on self-reported distances. Even though these measures strongly correlate with risk perception [27], and their reliability as an exposure indicator is questionable [3]; we will however include them in our umbrella review to ensure a complete overview of the literature, as it is possible that authors of systematic reviews or meta-analysis included this exposure indicator. Furthermore, we will also include studies that included occupational RF exposure assessed e.g., via a JEM, job titles or personal exposure measurements.

3.2.3 Comparator description

The eligible systematic reviews or meta-analyses must include a group of unexposed or less exposed individuals to compare them with exposed or highly exposed individuals. The exposure contrast originates from differences in exposure frequency, intensity, duration, time since first exposure, average or cumulative exposure, distance to radio and television masts, and mobile phone base stations [3]. As described for the exposure component of PECOS, we again rely on the decisions of the authors of published systematic reviews and meta-analyses, and therefore include a wide range of potential comparators.

3.2.4 Outcome description

Neoplasia is characterized by uncontrolled growth and cell division [28] and can be classified into benign and malignant neoplasms based on their behaviour. In contrast to the benign neoplasms, malignant neoplasms, referred to as cancer, usually have a higher degree of anaplasia and have the properties of invasion and metastasis [3]. In oncology, neoplasms are further classified in tumour/types and subtypes because of the heterogeneity of the tumours. We will include all types of neoplasms that are reported in published systematic reviews and meta-analyses on exposure to RF-EMF, including e.g. tumours arising in the head region (including glioma/brain tumours in adults, paediatric brain tumours, meningioma, acoustic neuroma, pituitary gland tumours, salivary gland tumours), lymphomas and leukaemia as outcomes in our umbrella review. As there are no guiding biological hypotheses on which we could base a selection of neoplasms to include in our umbrella review and to assess the whole body of evidence, we will not restrict the outcome on a selective set of neoplasms. We will also include combined analyses in relevant systematic reviews or meta-analyses on the artificial summary category "all cancer". However, combining different neoplasms together could be problematic. When combining risk estimates for neoplasms with very different incidences, e.g., combining a more common neoplasm with a very rare neoplasms, the combined effect measure is difficult to interpret. This issue needs to be addressed in the report of the results of the umbrella reviews.

Regarding the diagnostic methods and measures of disease occurrence, we will include systematic reviews of studies that used either histologically-confirmed cases or were based on unequivocal diagnostic imaging, ascertainment through cancer registries, hospitals, or any other source that has a sufficient coverage of the study base during the time of the study. We will also include self-reported outcomes if they are included in the systematic review or meta-analyses identified in our umbrella review. Incident cases and mortality (with neoplasms as cause of death) as a measure of disease will be included as well. It is essential to rely on the included studies in the systematic reviews and meta-analyses

and therefore not to be restrictive in the inclusion criteria, to make sure that all relevant literature is included in our umbrella review.

3.2.5 Study type description

Systematic reviews and meta-analyses of epidemiological studies will be eligible for inclusion if they are informative for hazard assessment purposes, i.e., based on cohort studies, and case-control studies (including variants thereof) published in peer-reviewed journals. We consider a review as systematic if it includes a-priori defined methods on how the review is carried out, including the key sections of the PRISMA checklist [29]. This includes e.g., specific inclusion and exclusion criteria for the selection of original studies based on a PECOS scheme, a search strategy including a predefined selection of specific databases for the systematic search and a clear description of the study selection and data collection process. Systematic reviews or meta-analyses of interventional studies, or studies that use case series or expert opinions as their source of evidence, will not be included. Furthermore, all other types of reviews such as narrative reviews or scoping reviews will not be included. We will also not include any primary level studies such as ecological studies (time-trend analyses and geographical correlation), cross-sectional studies, case-case analyses, case-control studies, cohort studies and nested case-control studies.

3.3 Search strategy

Eligible studies will be searched in the following databases: Medline via PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://www.webofscience.com), and EMF-Portal (https://www.emf-portal.org/). EMF-Portal is a dedicated database of scientific literature on the health effects of exposure to electromagnetic fields with high coverage of the topic [31]. The search timeframe (online first) will extend from the database inception dates to December 2023 or the date of the actual literature search, whichever comes later. In order to adhere to the MECIR (Methodological Expectations of Cochrane Intervention Reviews) guidelines and COSTER (Recommendations for the conduct of systematic reviews in toxicology and environmental health research) recommendation we will update the search within 12 months before publication of the umbrella review if needed [32][33]. We will develop a search strategy using keywords, Medical Subject Headings (MeSH) terms and free text, which will be combined for the Search in Medline via PubMed and Web of Science. As to EMF-Portal, we will take advantage of the in-built facilities to calibrate our search, including the following predefined criteria for topics "Epidemiological studies" or "Reviews, surveys, summaries". The following criteria for frequency ranges will be selected in EMF-Portal "Radio frequency (≥10 MHz)" or "Mobile communications". These criteria will be combined with "cancer" or "tumour" as keywords.

Additionally, we will manually search all reference lists of the included studies to identify additional reviews of relevance. In general, we will only include peer-reviewed journal articles. We will consider indexing in Medline as evidence of peer-review status. With regards to publication language, we expect the majority of articles in English. However, we will not exclude any article based on other language, but the search queries will include English terms only. We will not include publications of the following type: editorials, letters to the editor, or comments.

3.4 Study screening

The EndNote software will be used for assembling results of the literature search, to remove duplicates and to manage data throughout the study selection process. EndNote was ranked highest for usability and acceptability in a recent comparative study of systematic review automation software packages [30].

The records identified will be evaluated by their coherence with the subject matter of the systematic review and other relevant features to determine their compliance with the predetermined inclusion/exclusion criteria. This evaluation will be conducted at either the title/abstract or full-text levels of the review, as appropriate.

To assess the eligibility of identified articles for inclusion, two reviewers will independently evaluate their relevance. The two reviewers will take part in a pilot testing of the study selection, with written instructions on the categorization scheme, variable coding, and handling of multiple publications per study on a small subset of references retrieved. Disagreements between reviewers will be resolved by consensus. If no consensus can be achieved, a third reviewer will be included. The outline of the study selection procedure will be shown in a flow chart in the report of the findings of the two umbrella reviews in one of the next deliverables, similar to the example displayed in Figure 1.

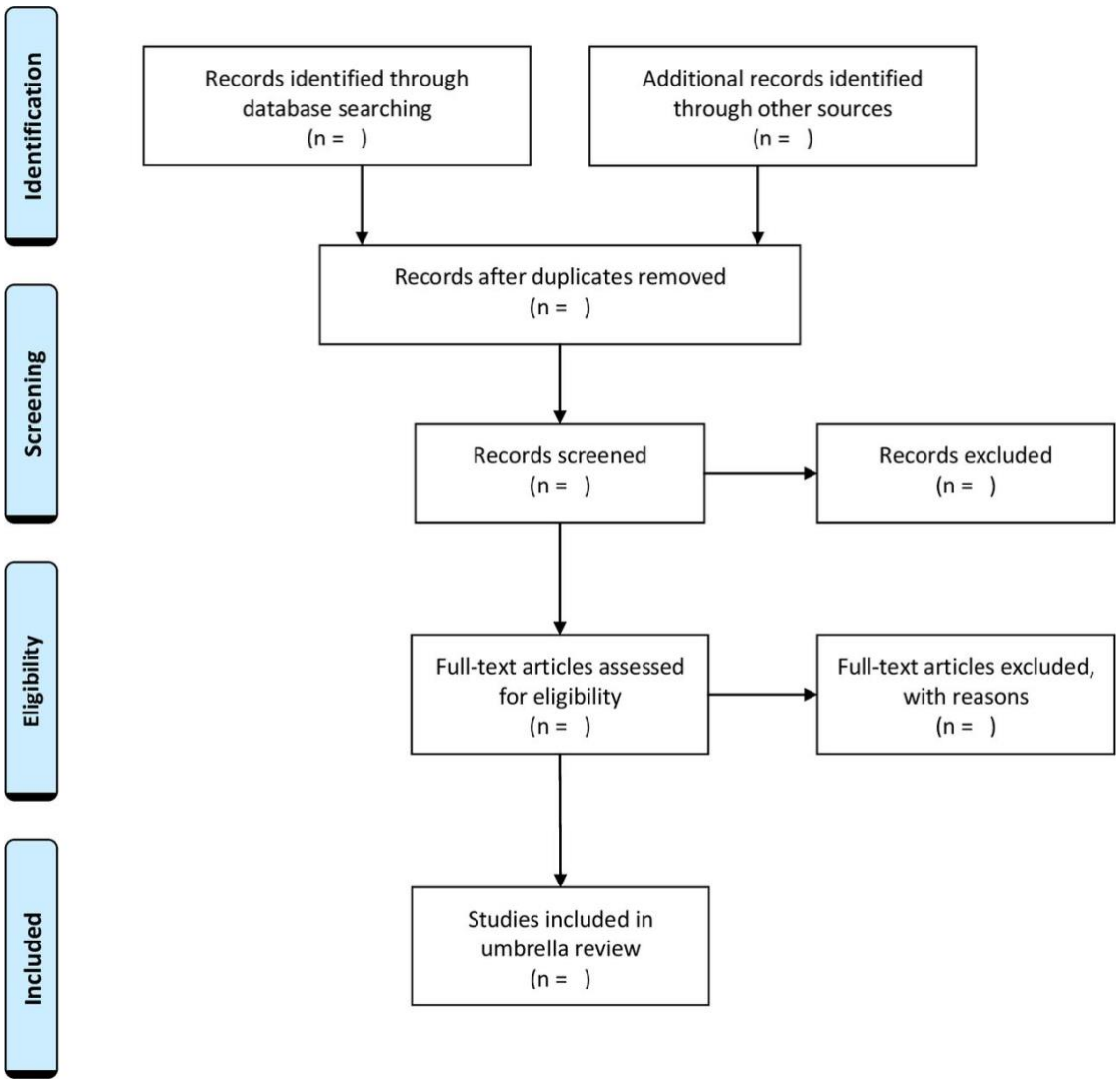

Figure 1: PRISMA flow diagram [20]

For title/abstract screening, all records will be classified in one of three categories (0 = Irrelevant; 1 = Relevant; 9 = Unclear relevance). Examples of records that can be excluded at this stage are those where the title/abstract/keywords indicate that the publication pertains to topics other than the adverse health effects of RF-EMF (e.g., RF ablation or telemedicine/mobile-health applications), experimental animal studies, epidemiological studies on cancer and exposure to Extremely Low-Frequency (ELF) fields, or on RF-EMF exposure and non-neoplastic diseases.

Full-text articles will be retrieved for records classified as relevant or as having unclear relevance (codes 1 and 9) and will be examined to confirm or modify their relevance classification. Confirmed codes 1 or 9 articles will be classified by setting/source of RF-EMF exposure (UR-A or UR-B), and investigated neoplasm(s).

Eligibility for inclusion will then be assessed based on compliance with the predefined inclusion/exclusion criteria. At the completion of this stage, all identified articles will be divided into three non-overlapping groups: (i) irrelevant; (ii) relevant but ineligible for inclusion, with reason(s) for exclusion specified; (iii) relevant and eligible for inclusion in one of the two umbrella reviews (or in more than one, if multiple types of RF-EMF exposure are investigated). The list of studies excluded at full text (group ii) will be provided in the completed review paper. If a systematic review or meta-analysis addresses risk of multiple tumours and/or multiple exposure types, we will consider the syntheses related to each specific exposure-neoplasm pair as separate studies. For example, one systematic review or meta-analyses could include the outcomes meningioma and glioma. In our umbrella review both outcomes will be included separately, if the systematic review or meta-analysis reported the results adequately stratified by outcome.

3.5 Data extraction

Data will be extracted independently by two reviewers into pre-designed and pre-piloted forms. These standardized abstraction forms will be established in Microsoft Excel. Ambiguities related to data extraction will be resolved by discussion or by a third reviewer if the two primary reviewers are unable to achieve consensus. When necessary, data is not provided in the article, we will contact the corresponding authors to provide the missing data. The following data will be extracted:

(1) Citation details
(2) Objectives of the included systematic review or meta-analysis
(3) Type of review
(4) Participant details
(5) Setting and context
(6) Number of databases sourced and searched
(7) Date range of database searching (the search timeframe, e.g., from the database inception date to a specific predefined date or the date of the actual literature search)
(8) Publication date range of studies included in the systematic review or meta-analyses that inform each outcome of interest
(9) Number of studies, types of studies and country of origin of studies included in each review
(10) Instrument(s) used to appraise the primary studies and rating of their quality
(11) Outcomes reported that are relevant to the umbrella review research question
(12) Method of synthesis/analysis employed to summarize the evidence, e.g., qualitative vs. quantitative summary or fixed-effects vs. random-effects meta-analyses and
(13) Comments or notes the umbrella review authors may have regarding any included study

As proposed by the JBI approach [18][13], the majority of this information will appear in the "Table of included review characteristics" that will be part of the deliverables of the umbrella reviews.

3.6 Data synthesis

The data from the included studies will be synthesized as a narrative review including a qualitative synthesis of the findings using text and tables describing study characteristics and the overall results of the umbrella review. The results will be presented separately for UR-A and UR-B. We will also present the studies in each umbrella review (UR-A and UR-B) stratified by exposure to the general population and occupational exposure if the included systematic reviews and meta-analyses allow for this. The presentation of results will be limited to those studies presented in the selected systematic reviews, meta-analyses. Primary research study level data will not be presented in the umbrella review, which is in line with the JBI approach [18].

A clear indication of overlap between primary studies in each of the included systematic reviews and meta-analyses will be presented in the umbrella review. If one study is included multiple times, this will be pointed out. This can occur e.g., if a cohort is analysed several times and results are reported in different articles including different lengths of follow-up.

3.7 Critical appraisal of identified studies

Systematic reviews and meta-analyses are important resources for evidence based decision making and for supporting policy makers and health-care professionals, because they can summarize the body of evidence on a certain topic based on a-priori defined methods [34]. Furthermore, systematic reviews and meta-analyses help health-care professionals, policy makers, and researchers to deal with extracting key information from a rapidly increasing number of published articles. Particularly meta-analyses are considered to be the highest level of scientific evidence. However, the uncritical use of results and conclusions of systematic reviews is risky [19], as not all systematic reviews are necessarily of high quality [35], and this is a particular concern. Systematic reviews or meta-analyses with suboptimal quality can be harmful. Ioannidis criticizes the "massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses" [35]. Ioannidis analysed meta-analyses of occupational and environmental health and medicine, regarding the issue of massive, low quality production [14]. He identified and included 12 overlapping meta-analyses published between 2006 and 2014 on the use of mobile phones and brain cancer risk They reported conflicting findings. He pointed out that these studies differed substantially in eligibility criteria, number of studies included and

conclusion. Those meta-analyses included between 2 and 47 studies based on different criteria such as different types of included tumours, design/quality criteria, and minimum required follow-up for latency. Finally, this also leads to differences in the interpretation and conclusions in the studies. Some studies reported an increased risk, especially with long-term use (≥10 years) and for the outcome of ipsilateral gliomas, while others were keen to interpreter the results as consistent with a null effect [14]. Furthermore, systematic reviews are subject to a range of potential biases [19], e.g. publication bias. It is important that users of systematic reviews and meta-analyses can identify high quality reviews and separate those from suboptimal quality reviews, especially if the findings and conclusions are used for decision making and shaping policy. To assess the quality of systematic reviews and meta-analyses different tools are available [19].

To assess the methodological quality of the included studies in this umbrella review, we will use AMSTAR 2 [19]. AMSTAR 2 is updated to allow for the critical appraisal of systematic reviews or meta-analyses of observational studies. Furthermore, AMSTAR 2 provides the tools to identify critical weaknesses that reduce the confidence in the findings of a review and the robustness of the results. The authors of AMSTAR 2 also point out that this tool is developed to assist decision makers in identifying high quality systematic reviews. AMSTAR was first published in 2007 as a practical critical appraisal tool for policy makers and health professionals to enable them to assess the quality of systematic reviews of randomized controlled trials of interventions, without having an advanced training in epidemiology. The development of AMSTAR was based on the results of a scoping review of available rating tools. From this review the authors set up a list of items that are relevant to assess the risk of bias and quality of a systematic review. The list was pilot tested, revised and its usability and reliability were assessed. A revised version was then externally validated by a panel of content experts, which then finally resulted in the AMSTAR tool [36][37].

In the meantime, several critiques on the original AMSTAR tool have been published, and the authors developed an updated and revised version of AMSTAR including also feedback received at a workshop. One of the most important additions of AMSTAR 2 was the implementation of assessing observational studies, which have different key issues in terms of bias compared to randomized intervention studies. An expert group of authors of the original instrument and additional members with expertise in the conduct of observational studies, development of appraisal tools, biostatistics and study design was set up to develop AMSTAR 2. The following changes to the initial version were agreed on by the panel:

- Simplify the response categories
- Align the definition of research questions with the PICO (population, intervention, control group, outcome) framework
- Seek justification for the review authors' selection of different study designs (randomised and non-randomised) for inclusion in systematic reviews
- Seek more details on reasons for exclusion of studies from the review
- Determine whether the review authors had made a sufficiently detailed assessment of risk of bias for the included studies (whether randomised or non-randomised)
- Determine whether risk of bias with included studies was considered adequately during statistical pooling of results (if this was performed)
- Determine whether risk of bias with included studies was considered adequately when interpreting and discussing the review findings [19]

Overall AMSTAR 2 consists of 16 items with the options to respond with yes, partial yes and no. The following items are cited from the original publication [19] and are included in the AMSTAR 2 tool:

1) Did the research questions and inclusion criteria for the review include the components of PICO?
2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3) Did the review authors explain their selection of the study designs for inclusion in the review?
4) Did the review authors use a comprehensive literature search strategy?
5) Did the review authors perform study selection in duplicate?
6) Did the review authors perform data extraction in duplicate?
7) Did the review authors provide a list of excluded studies and justify the exclusions?
8) Did the review authors describe the included studies in adequate detail?

9) Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?
10) Did the review authors report on the sources of funding for the studies included in the review?
11) If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12) If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13) Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?
14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15) If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

The original publication on AMSTAR 2 by Shea et al. [19] includes additional explanations regarding the rationale for every item. As an example, item 2 is about using a a-priori defined methods to carry out the systematic review. The authors explain that systematic reviews are observational research, and methods should be agreed on before the review starts. Furthermore, they explain that the use of a protocol reduces the risk for bias in the review. Additionally, the original publication contains supplementary material with even more detailed description of the single items and there is a form of that includes the 16 items and tick boxes. However, the authors of AMSTAR 2 explain that not all items apply all the time. For example, if a systematic review does not contain a meta-analysis, then the items covering the aspects of the appropriateness of the meta-analytical methods will not apply. Figure 2 shows an excerpt of the form.

AMSTAR 2

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:	Optional (recommended)	
☐ Population	☐ Timeframe for follow-up	☐ Yes
☐ Intervention		☐ No
☐ Comparator group		
☐ Outcome		

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:	For Yes:	
The authors state that they had a written protocol or guide that included ALL the following:	As for partial yes, plus the protocol should be registered and should also have specified:	☐ Yes
☐ review question(s)	☐ a meta-analysis/synthesis plan, if appropriate, *and*	☐ Partial Yes
☐ a search strategy	☐ a plan for investigating causes of heterogeneity	☐ No
☐ inclusion/exclusion criteria	☐ justification for any deviations from the protocol	
☐ a risk of bias assessment		

Figure 2: Excerpt of AMSTAR 2 form [19]

From the 16 items, the authors of AMSTAR 2 consider 7 items as critical domains that have significant impact on the validity and conclusion of a review:

- "Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)

- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)" (Shea et al., 2017)

Based on the 16 items, and especially the seven critical domains, a critical quality assessment, of all included systematic reviews in the two umbrella reviews, will be done. In this process, each included review will be categorized in one of the following rankings: high, moderate, low, critically low as suggested by the authors of AMSTAR 2. The rating will reflect the overall confidence in the results of a review. A review that is rated high is supposed to have no or one non-critical weakness and therefore provides a comprehensive and accurate summary on the topic. The rating will be moderate if there is more than one non-critical weakness. Moderate confidence in the results mean that there are no critical flaws in the review and it provides an accurate summary of the results. Still multiple non-critical weaknesses may reduce the confidence in the review and can lead to a downgrade from moderate to low confidence. A low rating will be selected if one critical flaw with or without non-critical weaknesses is present, resulting in a review that may not provide a comprehensive and accurate summary of available and relevant studies. A review is judged as critically low in terms of the overall confidence in the results if there is more than one critical flaw with or without non-critical weaknesses. The authors of AMSTAR 2 suggest that reviews rated critically low should not be relied on to provide a comprehensive and accurate summary of available studies.

The overall results of the critical appraisal including all systematic reviews identified in the two umbrella reviews will be displayed in a heat map to provide an intuitive graphical overview. An example for such a heat map is shown in Figure 3.

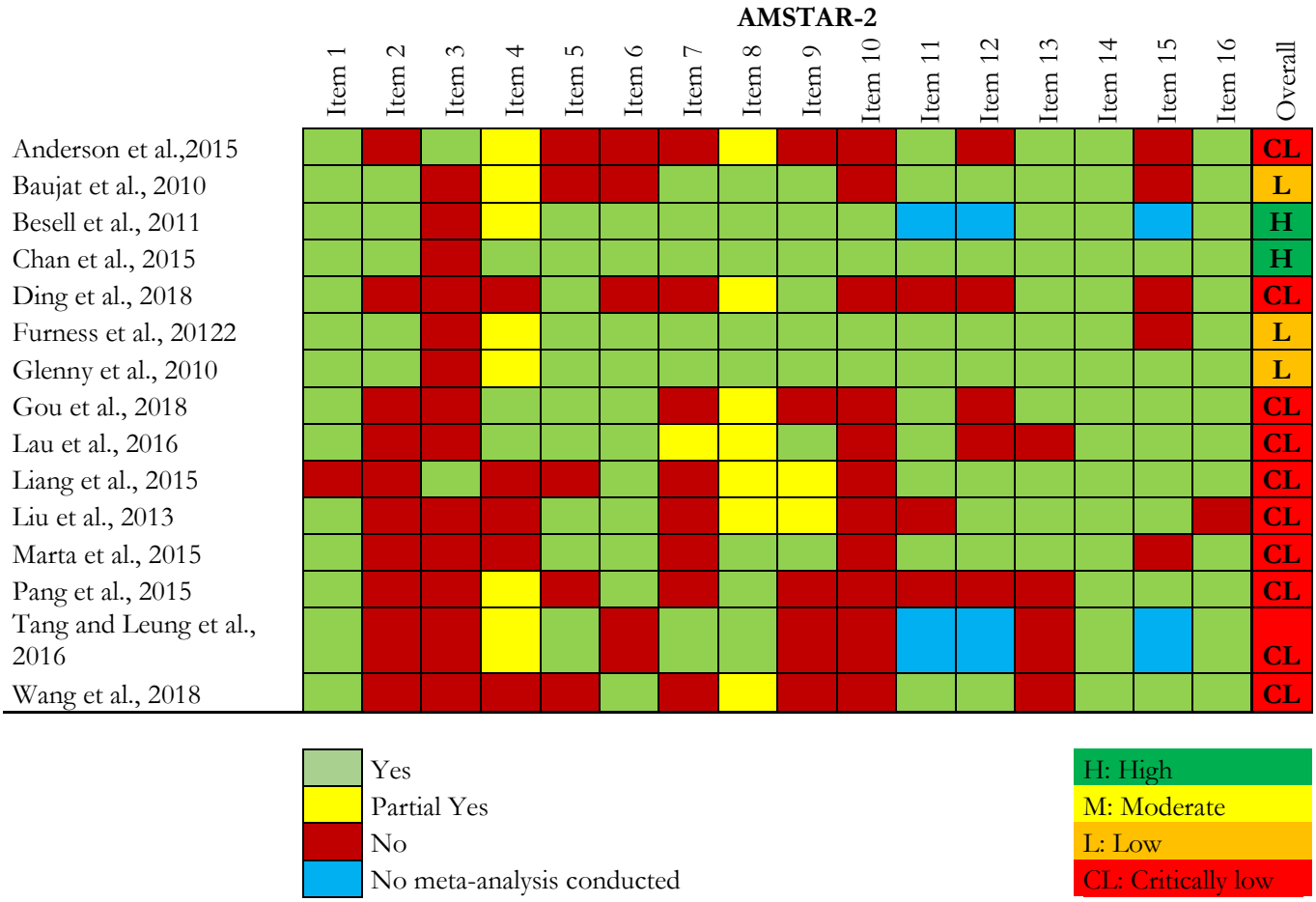

Figure 3: Quality of systematic reviews rated with AMSTAR 2 and displayed as a heat map as an example (modified from [38])

The critical appraisal will be performed independently by two reviewers. Conflicts in the rating of the studies will be resolved by consensus. If no consensus between the two reviewers can be achieved, the conflict will be resolved by arbitration by a third reviewer of the team. The initial individual ratings and the final modified rating after resolving potential conflicts will be recorded. All reviewers involved in the critical appraisal will be trained in a pilot-study. For the pilot-study a sample of 3 relevant studies will be selected from the complete set of relevant studies, after the completion of the study selection stage.

3.8 Advantages and limitations of umbrella reviews

Umbrella reviews are a collection and overview of all relevant systematic reviews and meta-analyses on a specific research topic and follow a strict a-priori defined methodology. They aim to give a complete picture of the field to help e.g., policy makers or health-care professionals to deal with extracting relevant information from an increasing number of systematic reviews and meta-analyses in epidemiology [39].

Belbasis et al. [39] point out a number of advantages that come with umbrella reviews. First, they offer a "bird eye's view" for a specific research question and therefore can provide an excellent and complete overview. Second, umbrella reviews can save valuable research resources by avoiding to e.g., conducting new epidemiological studies with long follow-up and rather make use of existing and published systematic reviews. Third, umbrella reviews allow to identify potential research gaps in a specific field. Based on the identified areas where evidence is missing, one can formulate recommendations for further research, by e.g., considering common limitations or weaknesses of published studies. Fourth, umbrella reviews can assess the study quality, including effect sizes, uncertainties, heterogeneity, and hints of bias across a research field. This is very valuable for policy makers or decision makers with no advanced training in epidemiology [39].

However, beside the clear advantages umbrella reviews have limitations too. The approach of an umbrella review emerged from systematic reviews. Systematic reviews generally follow well-established guidelines such as the PRISMA statement [29], which give clear guidance on the reporting of systematic reviews and meta-analyses. These guidelines can be used as a solid foundation to conduct of a systematic review to ensure validity, integrity, and reliability of outcomes. Umbrella reviews are still a novel approach and published umbrella reviews show notable variations in the used methodology and reporting [40][41] . However, there are methodologies and methods published that should give guidance on developing an umbrella review including systematic reviews and meta-analyses as the analytical unit of the review [13]. Despite these available standardized and well-described procedures [13], authors do not always adhere to these guidelines, which increases uncertainty around the evidence and interpretability of the results of an umbrella review [42]. This can limit their usefulness for decision and policy making or for health-care professionals.

Most importantly, umbrella reviews can only be informative when multiple systematic reviews and meta-analyses are published with a sufficiently close research question to enable a comparison. One key limitation of umbrella reviews is that the validity of thier findings depends on the quality of both included systematic reviews and meta-analyses, and the primary studies themselves. Umbrella reviews do not generate new evidence. They use and summarize available evidence and therefore can only examine associations that have been examined in available systematic reviews and meta-analyses [43]. In conclusion, if the published systematic reviews and meta-analyses are mainly of low quality and have obvious bias, no meaningful conclusion for policy makers or decision maker can be extracted. However, these findings could still be used to outline the weaknesses and limitations of systematic reviews in that field to improve future reviews [39]. Another issue of umbrella reviews could be an overlap across included studies [45]. Based on the considerations of the JBI methods for umbrella reviews, primary level studies should not be reported in an umbrella review [13] and unlike meta-analysis, umbrella reviews do not use the findings of included meta-analyses to further estimate a combined effect [44]. However, Aromataris et al. [13] point out the need to clearly indicate the overlap of original/primary research in studies in each of the included systematic reviews or meta-analyses.

4 Conclusion

Exposure to RF-EMF has become widespread, encompassing various sectors like telecommunications, medicine, industry, and more. As mobile technology evolved, there is concern regarding potential health effects, especially with the emergence of technologies such as 5G and the IoT. To address these concerns, conducting a health risk assessment for RF-EMF is essential for, supporting decisions by policymakers, and for health-care professionals when informing the public.

The WHO is actively engaged in a project aimed at evaluating the health effects of RF-EMF exposure. In 2018, a global survey involving leading experts in the field helped identify key areas of concern associated with RF-EMF exposure, including cancer, adverse reproductive outcomes, cognitive impairment, human self-reported symptoms, oxidative stress, and heat-related effects, tinnitus, migraine and non-specific symptoms. Cancer emerged as a prominent concern, primarily driven by human studies and public apprehension. To consolidate the available evidence, umbrella reviews are being conducted in NextGEM. The umbrella reviews aim to comprehensively assess available evidence from published systematic reviews and meta-analyses, focusing on human observational studies. This allows us to evaluate a possible causal link between exposure to RF-EMF and the risk of neoplastic diseases. Additional objectives include, identifying relevant systematic reviews and meta-analyses, synthesizing evidence, evaluating heterogeneity among reviews, and critically appraising the quality of identified studies. To account for various exposure conditions (near-field and far-field), two distinct bodies of evidence will be reviewed to assess the neoplasia risk in relation to RF-EMF:

- UR-A for RF-EMF exposure from near-field sources.
- UR-B for RF-EMF exposure from far-field sources.

In conclusion, umbrella reviews offer a comprehensive overview of systematic reviews and meta-analyses on a specific research topic, employing a predefined methodology to provide a holistic perspective for policy makers and health-care professionals facing large and ever-increasing number of epidemiological studies. These reviews bring forth several advantages: a broad perspective on research questions, resource conservation through reliance on existing reviews, identification of research gaps, and assessment of study quality. Contrary to these strengths it is crucial to acknowledge that the validity of umbrella reviews hinges on the quality of the underlying systematic reviews and meta-analyses. They consolidate existing evidence and therefore can only address associations examined in prior systematic reviews and meta-analyses. If these systematic reviews and meta-analyses suffer from bias and low quality, the derived conclusions lack reliability for policy and decision making. Nonetheless, they can spotlight review weaknesses, fostering improvements for future evaluations.

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