NextGEM

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

D5.8: Development of risk assessment models and RA tool – Final version

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Glossary of terms and abbreviations used

Abbreviation / Term	Description
AI	Artificial Intelligence
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
BfS	German Federal Office for Radiation Protection
BMD	Benchmark dose
BMDL	Benchmark dose limit
BMR	Benchmark response
CCARS	Spanish Scientific Advisory Committee on Radio Frequencies and Health
CLUE-H	Cluster EMF and Health
CS	(NextGEM) Case Studies
EBPH	Evidence-Based-Public-Health
EC	European Commission
EMF	Electromagnetic field
EPA	(US) Environmental Protection Agency
GUI	Graphical User Interface
HCN	Health Council of the Netherlands
(H)HRA	(Human) health risk assessment
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IEC	International Electrotechnical Commission
IRGC	International Risk Governance Council
IRGC-RGF	International Risk Governance Council-Risk Governance Framework
ISO	International Organization for Standardization
ISS	Italian National Institute of Health
IUPAC	International Union of Pure and Applied Chemistry
KC	Key Characteristics of carcinogenesis
LOAEL	Lowest-Observed-Adverse-Effect Level

LoE	Lines of evidence
ML	Machine Learning
NGO	Non-governmental organization
NIKH	NextGEM Innovation and Knowledge Hub
NOAEL	No-Observed-Adverse-Effect Level
OECD	Organization for Economic Co-operation and Development
PoD	Point of departure
RA	Risk assessment
RBC	Red Blood Cell
RF	Radiofrequency
RF-EMF	Radiofrequency Electromagnetic field
Rfd	Reference dose
RoB	Risk of bias
RP	Reference point
QC	Quality Criteria
SAR	Specific Absorption Rate
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SRA	Society for Risk Analysis
TK	Toxicokinetics
TD	Toxicodynamics
UN	United Nations
WHO	World Health Organization
WoE	Weight of Evidence

Executive Summary

The Deliverable D5.8 "Development of RA models and RA Tool – Final version" is part of the NextGEM WP5, Risk Assessment, which is one of the main project objectives. The Deliverable gives a background to the processes of risk governance, risk management, and risk assessment. Special emphasis is on the role of risk governance in relation to RF-EMF exposure and possible health effects.

The Deliverable presents the rationale behind health risk assessment and describes in detail the different components of this type of risk assessment. The components are exposure assessment, hazard identification, risk characterisation, and risk assessment. Moreover, uncertainty analysis is considered, which for the stakeholders is necessary to include if the risk assessment would necessitate risk management actions, such as risk mitigation.

The RA process can generate either a qualitative (often based on expert judgement, in a "subjective" fashion) or a quantitative assessment of a potential risk. From the stakeholder's perspective, the latter is often preferable, but that is only possible if enough appropriate data are available, including in-depth studies of dose-response relationships. Regarding RF-EMF and possible health effects in NextGEM, planned studies will focus on field strengths that do not cause tissue heating, suggesting that any possible effects occur at so-called non-thermal levels of exposure. Due to the scarcity of data in this area and the fact that NextGEM likely will not produce dose-response relationships in any considerable amount, the NextGEM RA models that will be used belong to the qualitative form of RA.

The final version of deliverable D5.8 discusses the choice and development of the specific NextGEM RA models. The model will be integrated into an RA Tool, a component of the NextGEM Innovation and Knowledge Hub (NIKH).

As a first step of this development, requirements for an RF-EMF specific RA have been elaborated, focusing on exposure assessment and hazard identification. This has been subjected to a first round of testing, where the overall question has been whether RF-EMF exposures in in vivo and in vitro studies provide evidence that key cellular characteristics of carcinogenesis are affected by RF-EMF. For that purpose, a total of 316 original studies were identified after a literature search and investigated regarding exposure parameters, biological endpoints, and Risk of Bias criteria. The outcome of the analysis is that the present database of in vivo and in vitro studies is so diverse and scattered in its conclusions that no realistic assessment or conclusion could be made. A strong trend was, however, apparent, namely that higher quality studies showed no effect of exposure.

The results of this investigation will be used to validate whether more elaborate RA models that we develop or adapt in NextGEM and integrate into the RA Tool are appropriate. These models will then be used on data from both the projects´ case studies (Work Package 7) and additional experimental data in the project, complemented with data from other studies.

The current version of the NIKH RA Tool already supports several functionalities, namely Hazard Identification, Dose-Response Assessment, Exposure Assessment, Risk Characterization, and Final Assessment. The RA Tool is presently undergoing finalization to integrate the complete set of risk assessment functionalities and will be validated in the case studies in WP7. This process strengthens the significant role of NIKH in advancing EMF and health risk analysis.

1 Introduction

This deliverable (D5.8 Development of risk assessment models and RA tool – Final version) aims to provide the necessary background for human health risk assessment (RA), as a component of the risk governance paradigm. General characteristics of the different stages (modules) of risk assessment are presented, and features of both qualitative and quantitative risk assessment models are presented so that they can be considered for the RA activities that are planned in the NextGEM project.

Considering that experimental studies and overviews of epidemiological findings that take place in NextGEM concern primarily exposure levels that are below exposure guidelines, data regarding evidence of so-called non-thermal effects first needs to be collected so that risk can be assessed. Furthermore, data acquisition from sources outside of the NextGEM project is needed to complement the database for the RA. Such data is collected from scientific publications and databases of competent authorities and evaluated for their appropriateness.

In this Deliverable, the outline and initial results from such data acquisition and analysis are presented. This assessment and its modus operandi are used for the development of the NextGEM RA models. These models will, in turn, be adapted so that the Risk Assessment Tool (RA Tool), which is an integrated part of the NextGEM Information and Knowledge Hub (NIKH), can be developed. The Deliverable includes a preliminary application and validation of a risk assessment model, and the present development status of the RA Tool.

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 5.3 Development and validation of a Risk Assessment model to assist evidence-informed decision making on EMF exposure	Based upon stakeholder (industry, insurers, regulators, and consumers) input, requirements for output information criteria will be identified. Data underpinning the different stages of risk assessment from different lines of evidence will be obtained from activities envisaged by Task 5.1 and 5.2, assessed for their appropriateness for hazard identification and characterization, exposure assessment, risk characterization, and uncertainty analysis. The final product is an evidence-based integrative risk assessment. Any lack or shortcoming of data will feed back to activities in WP3 and 4 for complementation. The models and output parameters identified in this task will be submitted to a dedicated case in WP7 for a first round of sensitivity and performance testing, which, after refinement, will be iterated to involve all case studies.
DELIVERABLE	
Deliverable: D5.8: Development of risk assessment models and RA tool – Final version (M35) This deliverable will identify human exposure, hazard, for risk assessment models and develop the integrated final HRA models.	

1.2 Deliverable overview and report structure

Based on the objectives and work carried out under Task 5.3, the document starts with the Executive Summary followed by the introduction of the document in Section 1.

In Section 2, components and roles of risk governance are outlined.

Section 3 presents an overview of health RA, including stakeholder´s needs and roles.

Section 4 deals with risk assessment models.

In Section 5, health RA in the NextGEM project is presented.

Section 6 introduces the development of risk assessment models, including data acquisition and analysis from a concrete case, in NextGEM and how this contributes to developing the NextGEM RA tool.

Section 7 presents the integration of the risk assessment tool in the NextGEM Innovation and Knowledge Hub.

Finally, Section 8 concludes the Deliverable.

1.3 Updates from previous Deliverable 5.4 "Development of Risk assessment models and RA Tool – Initial Report"

This deliverable is the final, public version of the Development of Risk assessment models and RA. In October 2024, an Initial Report (D5.4) was delivered, but it was not public. This version is an updated and extended version of D5.4, including the following changes:

- All text sections have undergone careful linguistic editing to improve grammar, choice of words, readability, and comprehensibility. Some additional references have been included to better reflect the state-of-the-art .
- Sections 2 and 3 contain the same content and have only been edited for clarity.
- Subsection 4.1 has been partly rewritten to improve clarity. Table 4 in subsection 4.1.3 has been updated.
- Subsection 4.2 has been partly rearranged.
- Subsection 5.1 has been expanded with text that includes the criteria for a Weight of Evidence-based risk assessment.
- Subsection 6.2. has been updated, and the former Figures 10-13 have been replaced with a new Figure and a new Table 7. The text has been updated and revised.
- Section 7 has been revised and expanded, including additions of new Figures.
- Section 8 has been updated to reflect the current status of the work in Task 5.3.

2 Risk governance – its components and roles

Risk governance (RG) refers to the institutions, rules, conventions, processes, and mechanisms by which decisions about risks are taken and implemented. It can be both normative and positive, because it analyses and formulates risk management strategies to avoid and/or reduce the human and economic costs caused by adverse health conditions, natural disasters, economic crises, etc. It is also an umbrella term for other risk-associated activities, notably risk assessment, risk management, and risk communication. The risks in question may include risks to human health, which is the topic of this Deliverable. This section of the document provides definitions of RG and describes its different components of risk governance. It also introduces the principles, roles, and challenges of RG and explains its role in the context of Radiofrequency Electromagnetic Field (RF-EMF) exposure.

2.1 Introduction and definitions

The decisions of public health regulatory authorities on the evaluation of the risks to human health from RF-EMFs must be based on the best scientific evidence (Evidence-Based Public Health - EBPH), which is the application of the best available evidence based on precise, valid and relevant scientific knowledge which is guiding public health policies and practice [1]). However, science has its own limits. To respond to this limitation, the European Commission (EC) has proposed the "Better Regulation Toolbox" [2] that present guidance, tips, and best practice on evidence-informed policymaking, health impact, risk and management assessment, stakeholder participation, and anticipatory governance. The corresponding regulatory instruments should be based on the best available evidence. They should provide a transparent explanation of why some evidence may not be available and why it is appropriate to act in the absence of evidence.

Competent organizations, agencies, scientific societies, academies, universities, and scientific committees use the best evidence to develop recommendations and guidelines for protecting health from exposure to EMF. Fulfilling these principles requires implementing an appropriate RG policy.

What do we mean by risk and risk governance?

Risk has many definitions, but in principle, the risk to human health is considered to be the probability of an adverse effect on human beings or the environment resulting from a given exposure to an agent (chemical, physical, or biological). Risk assessment means different things to different people and is surrounded by misunderstanding and controversy. Some points of controversy involve the interpretation of scientific studies [3].

Risk also refers to uncertainty about, and the severity of the consequences (effects, implications) of an activity or event with respect to something that humans value. The consequences are often seen in relation to some reference values (planned values, objectives, etc.), and the focus is often on negative, undesirable consequences [4].

The International Organization for Standardization (ISO) defines risk as the effect of uncertainty on objectives. This definition can be interpreted in different ways, considering the consequences seen in relation to the objectives. Uncertainty is a key concept in risk conceptualization and risk assessment.

The concept of RG is relatively recent, as it appeared in the European Commission's Science and Society Action Plan (2001)[1]. However, the EC used RG more traditionally and provided a formal notion embracing risk identification, assessment, management, and communication. Thus, RG is a notion introduced to the academic discourse via European networks on risk [5].

Governance refers to the actions, processes, traditions, and institutions by which authority is exercised, and collective decisions are taken and implemented [6].

The scientific foundation for risk assessment and risk management is still somewhat shaky on some issues, in the sense that both theoretical work and practice rely on perspectives and principles that could seriously misguide decision-makers. Examples include the general conception of risk as an expected value or a probability distribution [7].

The Society for Risk Analysis (SRA) defines **risk governance** as "The application of governance principles to the identification, assessment, management and communication of risk. Governance refers to the actions, processes, traditions and institutions by which authority is exercised, and decisions are made and implemented. Risk

[1] Commission of the European Communities Brussels, 04.12.2001 Com(2001) 714 Final Communication From The Commission To The Council, The European Parliament, The Economic And Social Committee And The Committee Of The Regions Science and Society Action plan https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2001:0714:FIN:EN:PDF

governance includes the totality of actors, rules, conventions, processes, and mechanisms concerned with how relevant risk information is collected, analyzed and communicated and management decisions are taken" [8]. Moreover, RG helps to increase the capacity to deal with unexpected consequences of risk, unknown impacts, and social conflicts over trade-offs.

The International Risk Governance Council (IRGC) [6] states that the RG pertains to many actors, individuals, and institutions, both public and private, that deal with risks surrounded by uncertainty, complexity, and/or ambiguity. The Council emphasizes that not all risks are simple; they cannot always be calculated as a function of probability and effect.

The idea is that governance comprises more than government: It includes all the actors and institutions that play a role in assessing, managing, communicating, and regulating risks.

2.2 Risk Governance Components

IRGC is an independent organization that has a proven track record of experience in the concept and practice of risk governance. Since its creation, the IRGC has played an essential role in the development of RG's methodological proposals, aiming to contribute to anticipation and governance. This institution has proposed the **Risk Governance Framework (RGF)** [6].

Figure 1 describes this conceptual Framework and the main components of risk governance, which has been applied to various governance issues in a number of case studies and has established its applicability, efficacy and practicability (e.g., CEN Workshop agreement DIN CWA 16649 on managing emerging technology-related risks, see European Commission/ Institutions of the European Union[2].

The IRGC-RGF is also a source of information for the EC Better regulation, toolkit #12: Risk Assessment & Management[3].

The RGF was developed to provide a structure for combining the conventional practices of RA, management, and communication with the principles of good governance. The RGF provides a good methodological orientation that can be applied to each risk-governing organization. It is a generic resource that can be used in different contexts and for different risks. It offers guidance for the development of comprehensive risk assessment and management.

Identification and handling of risks involve multiple interlinked phases, such as pre-assessment, appraisal, characterization, evaluation, and management. Communication and stakeholders´ involvement, in a way that fully considers the societal context, are crucial cross-cutting aspects for both the risk and the decision about it.

The IRGC-RGF guides coping with risks in situations of high complexity, uncertainty, or ambiguity. The framework also proposes a categorization of risk that is based on the different states of knowledge about each particular risk, distinguishing between *simple*, *complex*, *uncertain*, and *ambiguous* risk problems. It can support the detection of current or potential deficits within the risk governance process and guide their remediation. Its application enables decision-makers to act based on evidence, transparent assumptions, and societal values and interests.

The phases that make up this framework are the following:

The **pre-assessment** process clarifies various perspectives regarding a risk, defines issues, and establishes a baseline for the assessment and management of a risk. This also includes identification and framing, i.e., setting the boundaries of the risk.

Risk appraisal includes assessing the technical and perceived causes and consequences of the risk.

Risk characterization involves the assessment and management of risks based on their dimensions, including complexity, uncertainty, and ambiguity. Simple risks, such as car accidents, may require straightforward regulatory actions, while complex, uncertain, or ambiguous risks may require a different approach to assessment and management due to the involvement of multiple stakeholders and varying perceptions and values. Furthermore, the characteristics of risks may also change over time, affecting longer risk governance processes.

[2] https://www.dinmedia.de/en/technical-rule/din-cwa-16649/192492793.

[3] https://commission.europa.eu/law/law-making-process/planning-and-proposing-law/better-regulation/better-regulation-guidelines-and-toolbox/better-regulation-toolbox_en.

Risk evaluation compares the outcome of risk appraisal to specific criteria in order to determine the significance and acceptability of the risk and prepare decisions. It involves determining the acceptability of a risk and taking into consideration societal values, economic interests, and political considerations. Based on the probability of occurrence and grade of consequences, risks can be categorized as acceptable, tolerable, or intolerable, and ethical, societal, and economic factors must be considered. Potential governance deficits in risk evaluation include overlooking outcomes from risk appraisal, exclusion of stakeholders and their views, lack of transparency, and failure to make robust and relevant decisions for the long term.

Risk management measures include the design and implementation of actions to avoid, reduce, transfer, or retain risks. The systematic decision-making process regarding risk management strategies ought to consider the complexities, uncertainty, and ambiguity of the challenges.

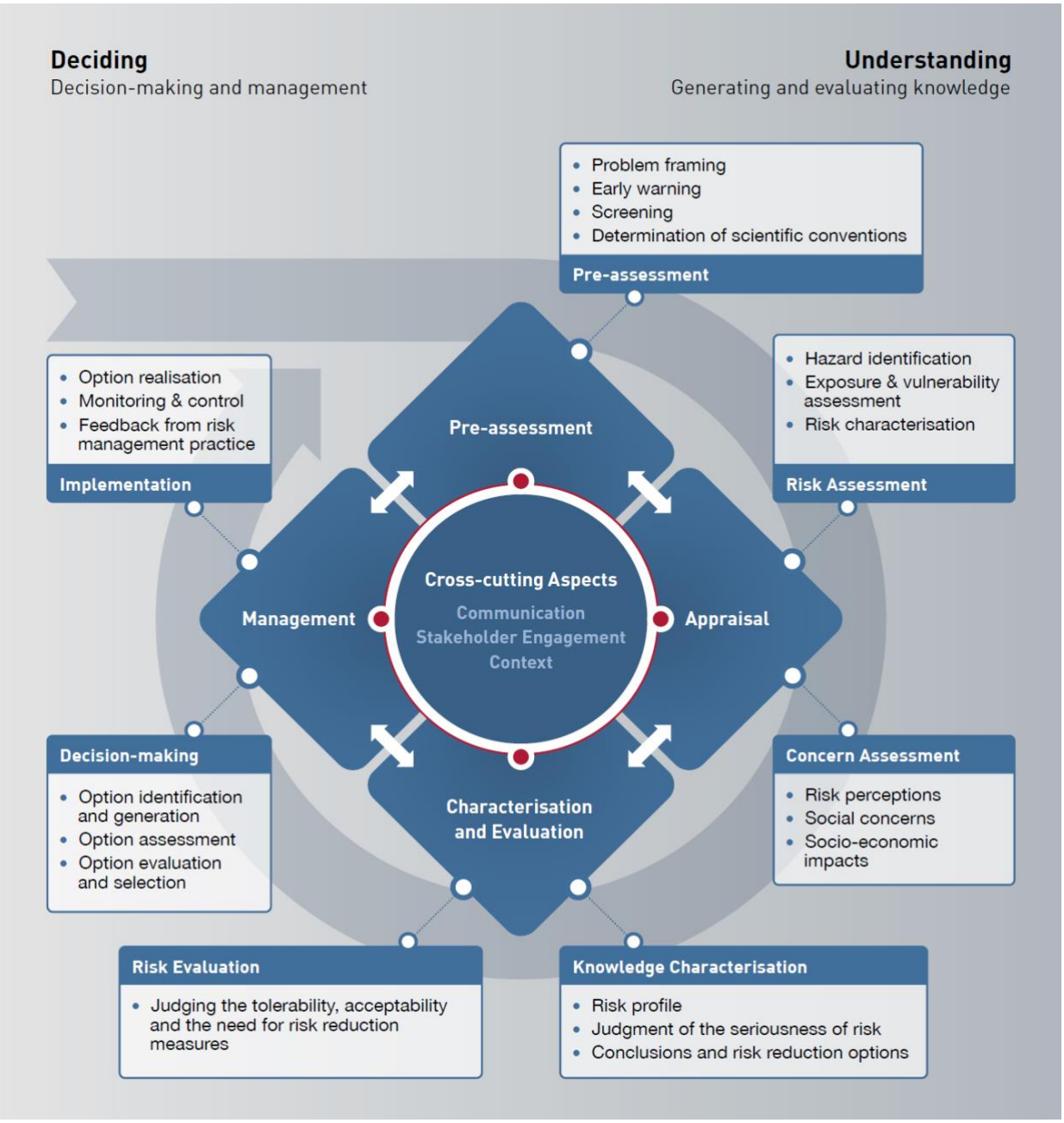


Figure 1: Detailed visual representation of the IRGC Risk Governance Framework. Source: IRGC. (2017). Introduction to the IRGC Risk Governance Framework, revised version. Lausanne: EPFL International Risk Governance Center. [4]

[4] https://irgc.org/wp-content/uploads/2018/09/IRGC.-2017.-An-introduction-to-the-IRGC-Risk-Governance-Framework.-Revised-version..pdf

There are also **Cross-cutting aspects**, which include communication, engaging with stakeholders, and considering context.

After a risk management decision is made, **implementation, monitoring, and review are essential.** This involves incorporating feedback from monitoring and reviewing into possible revisions of assessment and evaluation, establishing a link between risk management outcomes and the need for revisions, and addressing governance deficiencies in implementation.

Effective implementation requires appropriate authority and leadership, effective communication, organizational restructuring, and the allocation of essential resources. For effective risk governance, open, transparent, and inclusive communication is essential, facilitating understanding and trust in risk management. Successful communication involves both internal and external communication, the content of the message, and a two-way information flow.

In addition to the IRGC-RGF, there are other policies and frameworks promoted by other organizations that have published guidance documents that underline the importance of risk governance and that set principles, establish priorities, recommend processes, or propose other forms of recommendations [8]. Among the most relevant are the following:

- Organizations of the United Nations (UN), such as the UN Office for Disaster Risk Reduction (**UNISDR). Sendai Framework for Disaster Risk Reduction 2015-2030** [9]
- UN Economic Commission for Europe (**UNECE**) published **"Risk Management in Regulatory Framework: Towards a better management of risks."** [10]
- **ISO. Risk Management –Framework and Process - Guidelines"** (ISO/CD 31000, TC 262, dated 2016-04-7)[5].
- Organization for Economic Co-operation and Development (**OECD**) and its Council at Ministerial Level agreed on concrete recommendations to develop effective risk governance in 2014. Its document entitled **"OECD Recommendation on the Governance of Critical Risks"** proposes a fundamental shift in risk governance towards a whole-of-society effort[6].
- National governments are redefining or adapting their strategies, policies, institutions and or mechanisms. Many focus on the need to enhance national security. Prominent examples come from **the Netherlands (NRA/NSP)** and the **United Kingdom (UK NRA)** [11]

2.3 Risk governance principles, roles and challenges

RF-EMF policies are very heterogeneous in Europe, and it is therefore difficult to assess which is or has been the most appropriate one. In this sub-section, we have summarized the most relevant roles and challenges to assist with more effective decision-making. The main principles on which an appropriate RG should be based are:

- Transparency
- Feasibility
- Effectiveness
- Accountability
- Sustainability
- Equity
- Efficacy
- Fairness
- Respect for the law
- Acceptability.

Table 2 shows the main roles and challenges on which good governance should be based according to several authors [[5] [6] [10]].

[5] (https://www.iso.org/iso-31000-risk-management.html)

[6] (https://www.oecd.org/gov/risk/recommendation-on-governance-of-critical-risks.htm)

Table 2: Risk Governance roles and challenges.

Roles	Challenges
1. Better priority setting	• Clear and objective selection of risks. • To incorporate societal values, concerns and risk perception. • To avoid "hyper democracy" and interest groups (mass media pressure, NGOs, infodemics, polarization, fake news, etc.). • To avoid either too little or too much stakeholder involvement in the priority setting.
2. Using standardized methods (protocols) for assessing and managing risks	To use standardized methods and protocols accepted by the scientific community and competent organizations. For example: EU´s Better regulation tool [2].
3. Tackling complexity, uncertainty, and ambiguity	• To promote multi-systemic thinking vs. "silo thinking". Multi-causal approach. • Scenario analysis. • Secondary consequences. • To accept that some uncertainties will not be resolved in a short time. • Acceptability of the risks and different points of views. • To reduce regulatory burden.
4. Risk culture	• Degree of trust in the institutions responsible for risk governance. • Social climate, risk tolerance, civil society involvement, etc.
5. Resolving conflicts	• To manage trade-off (consensus). • To estimate cost-benefits. • To avoid short-term and premature decisions. • To deal with concentrated interest or conflicts of interest. Efforts to avoid a risk may be blocked or weakened. • Inappropriate involvement of stakeholders and lack of consideration for public opinion and values.
6. Governance to change and adapt institutions. Organization and authority to meet anticipated risks.	• To establish early-warning systems. • Human, economic, and technological resources. • Staffing expertise. • Allocation of responsibilities. • Monitoring systems of policies. • Good relationship with science.
7. Communication	• Holistic approach, risk governance as a continuous process (Risk assessment - RA, Risk management - RM, Risk characterization - RCH). • Integration of relevant knowledge, concerns, and perspectives. • Two-way communication. • Understand cognitive or heuristic biases that affect risk perception and concern.

2.4 The role of risk governance in relation to RF-EMF exposure

What is then the best response to an uncertain risk, according to the most recent systematic reviews, which have shown no adverse health risks at exposure levels that are below exposure guidelines?

Communication technologies using RF provide numerous benefits to society, but also raise concerns about adverse hypothetical effects on human health. These concerns are in part based on a few studies of mostly low quality, where effects of "low-level" RF-EMF are found. (See [12] [13] for further discussions about the inverse relation between study quality and findings of RF-EMF effects at low exposure levels). These circumstances point to the need for a robust early warning system, a proactive surveillance system, and a discussion of the need and usefulness of introducing precautionary measures.

The RG of the RF-EMF has certainly not been perfect [11]. With hindsight, it is easier to pinpoint the mistakes and remaining challenges. In most countries, risk management of RF-EMFs has been based on a technical-scientific approach without fully recognizing the many facets of the social dimension to risk management.

Introducing new technologies, such as mobile telephony, always generates an initial rejection in some sectors of society, which is why it is necessary to properly implement an RG that considers the concerns about *inter alia* adverse health effects of all stakeholders in an understandable language. This approach does not diminish or negate the benefits of a new technology such as mobile telephony. However, it must be considered that it is very difficult to establish systems for the rapid detection of unknown effects, and if effects appear after a prolonged period of exposure. Such an example would be the hypothetical appearance of brain tumours, which can take up to 20-30 years to appear.

The adequate involvement of experts, stakeholders, and the public in the risk governance process is a crucial dimension, producing and conveying adaptive and integrative capacity in risk governance institutions. The effectiveness and legitimacy of the risk governance process depend on the management agencies' capacity to resolve complexity, characterize uncertainty, and handle ambiguity by means of communication and deliberation (see Chapter 6 in [14]).

The absence of widely and unequivocally accepted answers (uncertainty) explains the disagreement on the risk of RF-EMF exposure. Good governance should promote the safe and acceptable use of telecommunication technologies by minimizing any potential negative effects of RF-EMF exposure.

The challenge of a good RG is to integrate the different interpretations of scientific evidence that are subject to prior beliefs as to whether RF-EMF could be causing any effects. The good governance principles and roles cited in section 2.3 should promote the welfare associated with new technologies while reducing the negative (social) impacts of RF-EMF exposure.

The RG framework and its challenges can be very effective in appropriately managing these different interpretations of evidence and considering different concerns and perceptions of risk.

3 Health risk assessment – An overview

3.1 Health risk assessment purpose

The concept of "risk" from a physical/chemical/biological agent for human and environmental health has many definitions, although they generally boil down to the fact that it is a function of the agent's hazard potential and that there is an exposure to the agent (from IUPAC, see [15])). The magnitude of this risk is then a concern for different actors, and the process that leads to an estimate of the risk potential is the health RA. Although a single, common definition of the latter is lacking, useful definitions are, e.g., "a process by which scientists evaluate the potential for adverse health or environmental effects from exposure to naturally occurring or synthetic agents" [16]. Another definition of risk, although with a similar outcome, is used by the US Environmental Protection Agency (EPA)[7] who uses the following phrasing:

> "…risk to be the chance of harmful effects to human health or to ecological systems resulting from exposure to an environmental stressor."

A "stressor" is any physical/chemical/biological entity that can induce an adverse effect in humans or ecosystems. EPA uses RA to characterize the nature and magnitude of risks to human health for various populations.

However, the RA of a given agent during specific conditions is not the end of the story. As presented in more detail in Section 2, RA is part of a larger paradigm, risk governance, which includes risk management, as summarized in Figure 2 below. Other important activities associated with risk governance/risk management are furthermore included in Figure 2.

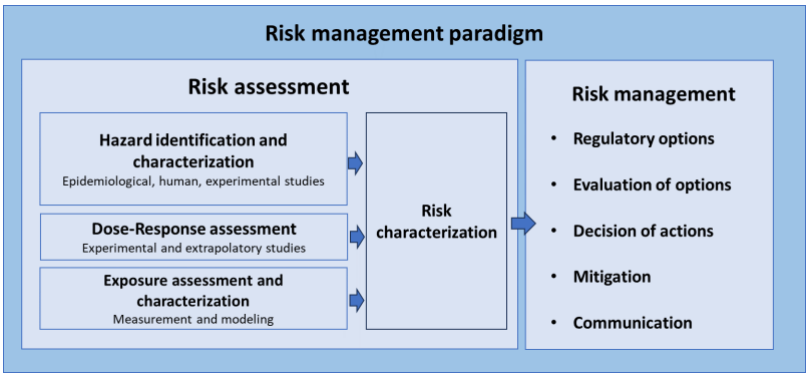


Figure 2: The risk management paradigm

3.2 The different components of an evidence-based health risk assessment

3.2.1 Hazard identification and characterisation

The WHO's Environmental Health Criteria document for exposure to RF-EMF dates to 1993 [17]. To robustly assess the health risks of the exposure, it is important to prioritize the health endpoints that need to be systematically assessed. In particular, the question is whether health effects can also occur with exposure below the ICNIRP limits. These ICNIRP limits aim to protect against the well-understood effects of excessive heating due to exposure to RF-EMF [18].

In the process of developing a new health RA on RF-EMF exposure, the WHO commissioned ten systematic reviews a few years ago. The choice of the relevant health endpoints was made transparently and inclusively [19]. This process involved experts with expertise in systematic review methodology, RF-EMF expertise, and expertise in the relevant health endpoints. The protocols for the different systematic reviews have subsequently been published in the scientific journal Environment International. As of May 2025, most of the systematic reviews for different health endpoints had been published. In addition, in line with the potential relationship between RF-EMF exposure and cancer, two umbrella reviews on epidemiological research are conducted in NextGEM (T5.1).

The result of the hazard identification and characterisation is - in the ideal situation - knowledge of which hazards are possible, and at what doses (some combination of field strength and duration of exposure) or according to which dose-effect relationships the hazards can occur. There may be two possible dose-response relationships,

[7] www.epa.gov/risk

namely threshold exposure level, or a (linear or non-linear) non-threshold dose-response. This last type is used for stochastic effects, like the ones due to ionizing radiation.

3.2.2 Exposure assessment

The next step in the risk assessment process is gathering information on actual exposure levels. In the ideal situation, the exposure is measured in real-time and all types of micro-environments, e.g., home environment (living room, bedroom…), office setting, public spaces, public transport, healthcare facilities, etc. The exposure also depends on the behaviours or activities of the person, for instance, non-user vs. user in 5G settings. In occupational situations, the exposure can be more extreme, for instance, for a worker on a live broadcast antenna mast. In the case results of measurements are scarce or not available at all or in other ways limited, the strength of RF-EMF can be computed or simulated.

3.2.3 Risk characterisation

In the ideal situation, when (1) the full distribution of exposure, or even better, the dose (a combination of field strengths and time spent in that field strength), amongst members of the public and workers is measured or estimated, and (2) all hazards are identified, including their full dose-effect-relationships, the main ingredients are available for calculating the population attributable risks. A conclusion could be: 'when it is assumed that there is a causal relation between the exposure to RF-EMF of frequency X and health endpoint Y, one person out of Z citizens/workers exhibits this health outcome'. So far, no such quantitative characterization regarding RF-EMF risk has been performed. The subject is further discussed in section 4.2, where quantitative RA is presented.

However, in the real world, both the hazard identification and characterization, and the determination of exposure in all its details, are far from complete. Results of epidemiological studies into the health effects of RF-EMF are contradictory, and the quality of studies is often debatable. Exposure assessments must deal with various uncertainties, such as the spatial and temporal variability of the EMFs or the duration of an individual's exposure in a certain scenario. An umbrella review of all the evidence is a possibility to deal with the uncertainties in the hazard identification.

A problem that is increasingly raised by society is that people are exposed to RF-EMF of various frequencies from all sides and by an increasing number of sources. The exposure is cumulative, also over time. ICNIRP has devised a system in their guidelines to add the exposure per frequency, standardized to the limit at that frequency, which protects against thermal effects of exposure. A corresponding system for the case of non-thermal exposure levels does not exist. The mentioned system works for thermal effects, characterized by a threshold, for which frequency-dependent exposure limits have been set, but not for non-thermal effects, for which thresholds have not been identified, exposure limits have not been set, and there is still no mechanistic understanding about any relation between frequency and the health endpoint.

Due to these and other sources of uncertainty, the final RA should consider performing an uncertainty analysis, which will increase transparency and understanding of the assessment, as stressed in section 2.3. Addressing variability and uncertainty can inform decision-makers about the reliability of results and guide the process of refining the exposure assessment. Additional information on uncertainty is available in section 4.3.

3.3 Stakeholders in health risk assessment

Under Article 11 of the Treaty on the European Union (TEU)[8], the EC has to carry out broad consultations with interested parties to ensure that the EU's action is coherent and transparent. Consulting stakeholders is an important means of collecting evidence to support policymaking. Who are the stakeholders? In general terms, the International Risk Governance Center (IRGC) defines stakeholders in the realm of risk governance as "Socially organised groups that are or will be affected by the outcome of the event or the activity from which the risk originates and/or by the risk management options taken to counter the risk." [6] The Society for Risk Assessment defines stakeholder involvement in risk governance as "the process by which organizations or groups of people who may be affected by a risk-related decision can influence the decisions or their implementation". These definitions apply to the stakeholders in health risk assessment.

[8]https://eur-lex.europa.eu/resource.html?uri=cellar:2bf140bf-a3f8-4ab2-b506-fd71826e6da6.0023.02/DOC_1&format=PDF

In the report 'Better regulation' toolbox - July 2023 edition[9] the Commission's consultation system offers stakeholders opportunities to contribute to policymaking, such as on policies, legislation, or evaluations of existing policies through (1) the call for evidence; (2) legislative proposals once they have been agreed on by the Commission; (3) draft acts that add or amend aspects of existing laws (delegated acts); and (4) suggestions to simplify existing EU laws in 'Have Your Say: Simplify!'. 'Better regulation' is governed within the Commission by common principles and follows established processes. The application of these principles and procedures will help to provide a rigorous evidence base to inform decision-making and contribute to making Commission initiatives more effective, coherent, relevant, and efficient. It should also enhance transparency, participation, learning, and accountability. Web-based public consultations, together with targeted consultations, are key elements of a consultation strategy. Stakeholders should be given sufficient time to respond. The stakeholder consultation process has three phases, which are summarised in the scheme below:

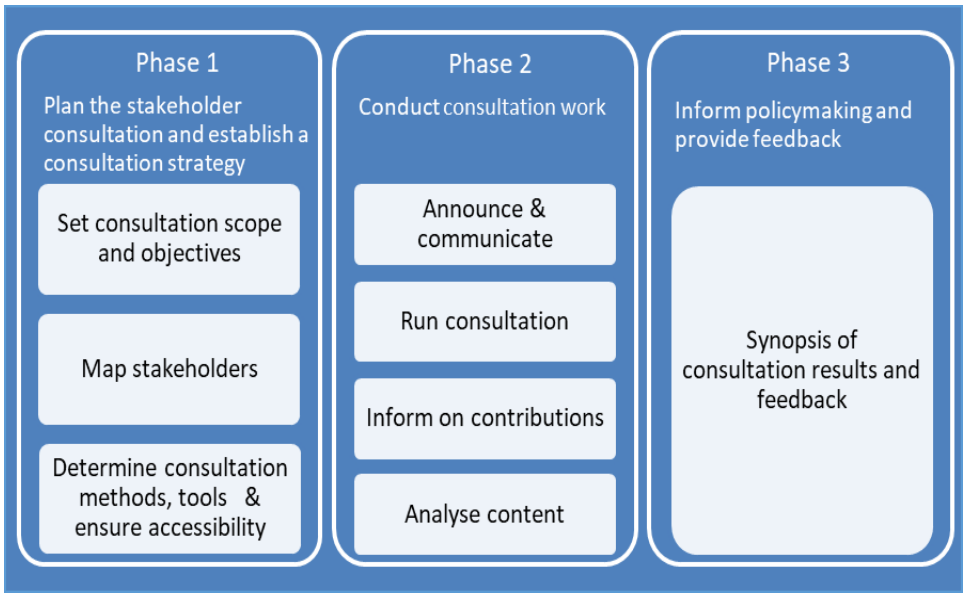


Figure 3: Three phases in the stakeholder consultation process [10]

A recent example of this procedure has been SCHEER's public consultation process on the SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Preliminary Opinion on the need of a revision of the annexes in Council Recommendation 1999/519/EC and Directive 2013/35/EU, in view of the latest scientific evidence available with regard to radiofrequency (100kHz - 300GHz), adopted by written procedure on 16 August 2022[11].

In NextGEM, we consider four types of stakeholders: citizens, governments, academia, and industry. The academic world has methods at its disposal (meta-analyses, pooled analyses, systematic reviews, and umbrella reviews) to draw conclusions from the joint original publications, in which the quality of the original publications and the way in which, for instance, systematic reviews have been conducted play an increasingly significant role. Organisations such as national scientific councils dealing with health (e.g. HCN, BfS, ANSES, CCARS, ISS), as well as international organizations (e.g., ICNIRP, SCHEER, and WHO), make overviews of the scientific findings and draw conclusions from them.

The other stakeholder groups distinguished in NextGEM, namely governments, citizens, and industry, can respond in different ways to the results of scientific research or overarching writings on it. Governments responsible for protecting members of the public and employees at the national or international level usually do not respond to individual original publications. They wait for the science to crystallize more, or for an authoritative organization to issue advice on it. Or governments may ask an authoritative organisation for advice.

Citizens and employees ask questions to governments, industry, and academia, partly based on their perception of health risks. They receive guidelines from governments to reduce any health risk they may be subjected to and

[9] https://commission.europa.eu/law/law-making-process/planning-and-proposing-law/better-regulation/better-regulation-guidelines-and-toolbox_en

[10] https://commission.europa.eu/law/law-making-process/planning-and-proposing-law/better-regulation/better-regulation-guidelines-and-toolbox_en

[11]https://health.ec.europa.eu/system/files/2023-06/scheer_o_044.pdf

have to comply with protective legislation. Governments and industry attach great importance to the fact that this process is based on a thorough assessment of the health risks. In essence, the process consists of a scientific discussion followed by a societal discussion in which different values will play a role for each stakeholder (individual or organization). The scientific and societal discussions are entangled, often unintentionally, but sometimes intentionally, by activist groups. Good science, for example, is bound by agreements about the methods to be used, while in a well-organised democratic society, strict procedures are also followed. The industry needs clarity on the compliance of their products or services in terms of EMF exposure. National and local governments decide through legislation and possibly additional policies how they want to protect citizens and employees from the possible effects of exposure to EMF on their health. Citizens and employees have the right to be protected and to be informed about how the government achieves this. When citizens and workers feel that they are not sufficiently protected, they request information on how to protect themselves by, for example, avoiding or reducing exposure to EMF. Such information is provided in the EU Directive "2013/35/EU DIRECTIVE 2013/35/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 26 June 2013" on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields).[12] The risk analysis at the level of the specific work setting is well defined, for example, for workers with pacemakers. However, evidence-based policy on risks can lead to an over-reliance on data and metrics that are disconnected from the everyday experience of workers and citizens whose needs and interests cannot always be measured or managed [20] [5].

The importance of stakeholder involvement in the risk governance process has been illustrated with reference to the IRGC's risk governance framework cited in Section 2.2 of this deliverable. In another report, the IRGC [8] draws several conclusions about stakeholder involvement in the risk governance process. The main objective of involving stakeholders and members of the general public in the risk governance process is to improve decision-making by risk managers throughout. It is meant to provide a greater understanding of the rationale behind stakeholders' interests, expectations, and motivations that influence their decisions.

Stakeholders can and often should be involved in each stage of the risk governance process, and how they are involved depends on the level of complexity, uncertainty, or ambiguity that characterises the risk knowledge. The most effective stakeholder involvement is done mindfully at each stage of the risk governance process.

However, there are also challenges when involving stakeholders. It is important that risk managers hear from a diverse cross-section of stakeholders and not just from special interests or people or groups with outsize influence on social media. Stakeholder involvement requires commitment, professional structuring, and sufficient resources. It is not a panacea for resolving risk conflicts, but if done well, it has the potential to improve the quality and legitimacy of risk management decisions.

In the context of the risk assessment referred to in this deliverable, there are also other interactions between the distinct stakeholder groups. One example is funding by the government to the academic world for conducting more research or for making overviews of the scientific state of affairs. Another example is the disclosure by the industry of exposure data or data to calculate this exposure.

[12] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:179:0001:0021:en:PDF

4 Risk assessment models

RA is part of the risk management paradigm (outlined in Figure 2). It implies characterizing the risk through hazard identification and characterization, dose-response assessment, and exposure assessment. It aims to identify, quantify, and manage the potential hazards of EMFs. It allows recommendations to be made to protect people and the environment while enabling the continued use of EMF-dependent technologies. RA models are essential tools in this process, providing a scientific basis for risk management. Specifically, for analysing the risks associated with exposure to EMFs, RA models can be used to assess various potential hazards to human health and the environment for different exposure scenarios. The potential hazards include, on the one hand, thermal effects, linked to the rise in tissue temperature due to the absorption of EMFs, and on the other hand, "non-thermal" effects, which include other biological endpoints such as the radical pair mechanism, oxygen and nitrogen radicals, or genotoxicity. Both types of hazards require appropriate RA approaches, as introduced in section 3.2.1.

Indeed, the thermal effects of EMF can be described as deterministic, meaning that there is a threshold beyond which the effects appear inevitably and predictably. In other words, once this dose or intensity threshold is exceeded, the effects will occur with certainty. At high intensities, RF-EMF exposure can cause immediate thermal effects, such as burns or heat stroke. As a result, threshold values can be derived below which the thermal effects will not occur. For example, safety standards for exposure to EMFs, such as those established by ICNIRP [18], are based on defined thresholds to avoid these deterministic thermal effects. The process of establishing ICNIRP's guidelines involves several steps, each taken with a conservative approach to ensure that the exposure limits remain protective, even if a significant margin exceeds them. "For example, the choice of adverse health effects, presumed exposure scenarios, application of reduction factors, and derivation of reference levels are all conducted conservatively. The degree of protection in the exposure levels is thus greater than may be suggested by considering only the reduction factors, which represent only one conservative element of the guidelines." (ICNIRP [18]; p. 3). ICNIRP [18] stressed that there is no evidence suggesting that implementing additional precautionary measures would offer any additional health benefits to the population.

In contrast, the non-thermal effects of EMFs are often described as stochastic because of their probabilistic nature and the lack of an established threshold. However, the question remains as to the actual nature of these non-thermal effects, if any, and/or their biological and health significance. Unlike deterministic thermal effects, non-thermal effects are not well understood, and their mechanisms of action are poorly investigated. It implies that no clear threshold has yet been established. Some studies have suggested associations between long-term exposure to low-intensity RF-EMF and health problems, such as an increased risk of certain types of cancer. These associations are often weak and controversial; they illustrate an increase in risk rather than a certainty of effect, typical of stochastic effects. As described in Section 3.2.1, the aim of the systematic reviews commissioned by the World Health Organization (WHO) is to contribute to the process of developing a new health RA on the non-thermal effects of RF-EMF exposure. This approach ensures that the assessment is based on the most relevant and comprehensive evidence available.

Within the framework of NextGEM, it is these non-thermal effects that are being studied, and it is therefore on these that we will focus in the NextGEM risk analysis.

Overall, there are two main types of RA models: qualitative and quantitative. Qualitative models are pragmatic but subjective, whereas quantitative models are objective and data-driven but also resource and time-consuming. If data and resources are sufficient, preference is given to quantitative RAs, unless the risk management decision can be adequately taken in a narrative or categorical fashion. Overall, the choice for the type of RA will be driven by the risk manager's questions, available data, the nature of the uncertainties, the skills of the assessors, the effectiveness of outputs in informing and supporting decision-makers, and the number and robustness of the assumptions made in the assessment [21]. Both types of models are described in more detail in this section.

4.1 Qualitative risk assessment

4.1.1 Overview

Qualitative RA has been defined as "an assessment based on inadequate data for numerical risk expressions but that allows risk ranking or risk discrimination into classes when previous expert knowledge and recognition of uncertainties exist" [22]. There is no internationally agreed-upon approach on how to perform a qualitative RA, but these assessments generally rely primarily on ratings, rankings, and narrative descriptions [23].

Its simplicity and flexibility make it a widely used method in risk management, despite its limitations in precision and subjectivity.

4.1.2 Methods of qualitative analysis

Below are examples of commonly used qualitative methods for assessing the risks associated with EMFs.

4.1.2.1 Weight of evidence

As defined by WHO (2009)[13], Weight of evidence (WoE) is "A process in which all of the evidence considered relevant for a risk assessment is evaluated and weighted" (WHO, 2009; p.A-41). This process is useful for organising evidence into groups or categories, referred to as lines of evidence, "a set of relevant information of similar type grouped to assess a hypothesis" [24]

Key considerations for weighing evidence include:

(1) Quality: Information should be evaluated for its completeness and quality. Evidence can be gathered from animal studies, human epidemiological studies, *in vitro* experiments, and mechanistic studies.
(2) Relevance: the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation. The quality of each study needs to be assessed, considering factors like study design (based on defined quality criteria), sample size, and consistency of results.
(3) Reliability: the inherent quality of a test report or a publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings (see Klimisch scoring system: 1. Reliable without restrictions, 2. Reliable with restrictions, 3. Not reliable, 4. Not assignable [25] .
(4) Adequacy: the usefulness of the data for hazard and risk assessment.

The integration of evidence and the formulation of conclusions is generally done by panels of experts who consider factors such as the strength of the association, any dose-response relationship, and biological plausibility.

Examples of RA based on WoE

International Agency for Research on Cancer (IARC) Monographs Programme classification of agents with respect to their carcinogenicity

A review of the evidence is based on epidemiological and animal studies, as well as mechanistic studies: (1) a Working Group of international experts assembles and critically reviews the evidence from studies of human populations that assess the links between exposure to an agent and the development of cancer. These studies include cohort, case-control, and ecological studies; (2) Animal research is evaluated to determine whether exposure to an agent causes cancer under controlled conditions; (3) The biological mechanisms by which an agent can induce cancer are also considered. This includes data on genotoxicity, effects on cell proliferation, and other biological endpoints.

Classification is based on the following scale of strength of evidence:

(1) Sufficient evidence of carcinogenicity in humans, where the evidence shows convincingly that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing the development of cancer in exposed humans.
(2) Limited evidence, where the evidence is less convincing, often because of the quality of the studies or uncertainties about other factors.
(3) Inadequate evidence, when the evidence is insufficient to classify the agent as carcinogenic or non-carcinogenic.

The agents are classified into these groups depending on their carcinogenicity to humans:

- *Group 1*: Carcinogenic to humans (sufficient evidence for cancer in humans).
- *Group 2A*: Probably carcinogenic to humans (limited evidence for cancer in humans and sufficient evidence in experimental animals).
- *Group 2B*: Possibly carcinogenic to humans (limited evidence in humans and less than sufficient evidence in experimental animals).
- *Group 3*: Not classifiable as to its carcinogenicity to humans (inadequate evidence in humans and inadequate evidence in experimental animals).

[13]https://iris.who.int/bitstream/handle/10665/44065/WHO_EHC_240_eng.pdf

Further information on the process is illustrated here[14]. Importantly, IARC[15] stresses that "The classification does not indicate the level of risk associated with exposure (risk assessment)".

IARC [26], placed RF-EMF in category 2B ('possibly carcinogenic to humans'); the placement was based on a rigorous assessment of the data available at the time (2011). This category is assigned when there is limited evidence of carcinogenicity in humans and insufficient or limited evidence in animals. Moreover, evidence on the potential biological mechanisms of RF-EMF carcinogenicity was also limited. Unlike ionising radiation, which is well known to cause direct damage to DNA, no clear mechanism has been established to explain how non-ionising RF-EMFs might cause cancer. The 2B classification reflects a cautious approach, recognising that the available evidence was limited and inconclusive. and that further monitoring was required. The classification has been based on studies that have shown a possible association between intensive mobile phone use and an increased risk of glioma and acoustic neuroma [26].

Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

In its methods for RA in its Final *Opinion on the need of a revision of the annexes in Council Recommendation 1999/519/EC and Directive 2013/35/EU, in view of the latest scientific evidence available regarding RF (100kHz - 300GHz)* [27], the SCHEER states: "The SCHEER has considered meta-analyses, systematic reviews, and, when necessary, narrative or scope reviews and single research papers published since 2015 on radiofrequency electromagnetic fields (100 kHz to 300 GHz). The SCHEER could not identify the moderate or strong levels of evidence for adverse health effects resulting from chronic or acute RF-EMF exposure from existing technology at levels below the limits set in the annexes of Council Recommendation 1999/519/EC and Directive 2013/35/EU. The SCHEER advises positively on the need of a technical revision of the annexes in Council Recommendation 1999/519/EC and Directive 2013/35/EU concerning radiofrequency electromagnetic fields (100 kHz to 300 GHz), because there is a need to recognize the recently introduced dosimetry quantities and establish limits for them." ([27]; p.2).

In its scientific work, the SCHEER relies on the Memorandum on Weight of Evidence (WoE) and uncertainties [28], i.e., the search for relevant information and data for the SCHEER comprises identifying, collecting, and selecting possible sources of evidence in order to perform a risk assessment and/or to answer the specific questions being asked. For each line of evidence, the criteria of validity, reliability, and relevance need to be applied, and the overall quality must be assessed. In the integration of the different lines of evidence, the strength of the overall evidence depends on the consistency and the quality of the results. The weighing of the total evidence is then presented in a standardized format that classifies results of analysis for human and environmental risks in terms of: (1) Strong weight of evidence: Coherent evidence from a primary line of evidence (human, animal, environment) and one or more other lines of evidence (LoE) (in particular mode/mechanistic studies) in the absence of conflicting evidence from one of the other LoE (no important data gaps); (2) Moderate weight of evidence: good evidence from a primary line of evidence but evidence from several other lines is missing (important data gaps); (3) Weak weight of evidence: weak evidence from the primary LoE (severe data gaps); (4) Uncertain weight of evidence: due to conflicting information from different LoE that cannot be explained in scientific terms; (5) Weighing of evidence not possible: No suitable evidence available. ([27] ; p. 6-7)

4.1.2.2 Risk matrix

This RA model aims to assess risks according to (i) the probability (or likelihood) of occurrence ("exposure") and (ii) the severity of the effects ("hazard"). Each of the two parameters is typically characterized into three or more bands using descriptor terms such as low, moderate, or high. For each combination of the likelihood of exposure and the hazard band, the resultant risk is described, resulting in a risk matrix (Table 3). Overall, there are 4 main steps when performing a qualitative risk assessment based on the risk matrix [29]:

(i) Selection or design of the appropriate risk matrix: There is no standardized risk matrix, and consequently, the risk matrix that is most suitable for the risk assessment should be either selected or constructed.
(ii) Assignment of agent of interest to hazard band: For chemicals, the assignment to the hazard band is based on the chemical classification and hazard statements.
(iii) Evaluation of the likelihood of exposure: This parameter is established by estimating the exposure, and if possible and available, by comparing with benchmark values. The assessment and information available will drive the selection of the type of method.

[14] https://monographs.iarc.who.int/wp-content/uploads/2019/07/2019-SR-001-Revised_Preamble.pdf.

[15] https://www.iarc.who.int/infographics/iarc-monographs-classification/

(iv) Establishment of the risk: By combining the hazard band and the likelihood of exposure, the resultant risk can be derived from the risk matrix.

Table 3: Example of a simple risk matrix. A high potential risk is marked in red, moderate risk in orange, and low risk in green. (Modified from [29])

Likelihood of exposure	Hazard band		
	Low	***Moderate***	***High***
High	Moderate risk	High risk	High risk
Moderate	Low risk	Moderate risk	High risk
Low	Low risk	Low risk	Moderate risk

4.1.2.3 Scenario Analysis

This method implies creating scenarios based on possible exposure conditions and assessing the potential impacts on human health. A scenario for smartphone users might consider variables such as the duration of daily use and the distance between the phone and the head.

Different exposure scenarios are used by ICNIRP [18]) in the description of their guidelines. For example:

- Occupational exposure versus exposure of the general public: Workers are exposed to EMF in controlled environments. They are trained to understand the risks and apply protective measures. The result is that less stringent restrictions are applied than for the general public.
    - An exception is applied to the exposure of pregnant women: Regardless of the exposure scenario, the foetus is treated as a member of the general public, and the exposure limits applied are therefore those applicable to the general public.
- Localized exposure and whole-body exposure: Exposure can involve either specific parts of the body (localized) or the whole body. Limits are defined separately for these two types of exposure according to thermal effects, with specific thresholds for type 1 (all tissues in the upper arm, forearm, hand, thigh, leg, foot, pinna and the cornea, anterior chamber and iris of the eye, epidermal, dermal, fat, muscle, and bone tissue) and type 2 (all tissues in the head, eye, abdomen, back, thorax, and pelvis) tissues.
- Frequency range: The guidelines cover exposure to RF-EMF in the frequency range from 100 kHz to 300 GHz, and different considerations are applied depending on the frequency band:
    - Below 6 GHz: The guidelines define limits based on the specific absorption rate (SAR), which measures the energy absorbed per unit mass of tissue (W/kg).
    - Above 6 GHz: The metric used to define exposure limits is the power density (W/m^2), due to that the absorption of the energy occurs only within the surface tissues. Local exposure is averaged over a surface of 4 cm^2.
    - Above 30 GHz: The guidelines consider the possibility of exposure to focal beams, which can cause localized heating in small areas of the body. Therefore, a spatial average of 1 cm^2 is considered "to ensure that the operational adverse health effect thresholds are not exceeded over smaller regions" ([18]; p. 8).

ICNIRP basic restrictions and reference levels are based on these different scenarios.

In contrast, several exposure scenarios fall outside the scope of the ICNIRP guidelines. These include:

1) Medical procedures, e.g., radiofrequency ablation and hyperthermia, that require medical expertise to balance potential harm against therapeutic benefits.
2) Volunteers in research, but study protocols need to be approved by an ethics committee, including an evaluation of potential risks and benefits.
3) Cosmetic procedures: Exposure to EMFs from cosmetic treatments performed without oversight from qualified medical practitioners is subject to the guidelines, but any exemptions would be managed by national regulatory bodies.

4) Electromagnetic compatibility, which is the potential for EMF to interfere with electrical equipment, is out of the scope of the ICNIRP guidelines [18]), but managed by the International Electrotechnical Commission (IEC) 2014[16]

4.1.3 Current status within NextGEM

To evaluate the risk that non-thermal effects of RF-EMF occur, the evidence on the existence of such effects first needs to be collected so it can be assessed in a WoE approach. In NextGEM, two umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on EMF exposure are being conducted (T5.1). RA will also benefit from the collaborative work performed in the framework of the Horizon Europe Cluster CLUE-H (Cluster on EMF and Health).

Moreover, we are conducting triennial literature reviews on non-thermal effects of RF-EMFs, including 5G. From the beginning of NextGEM, 189 studies have been retrieved and critically analysed regarding their quality and the appropriateness of their results (Table 4).

The current outcome of this literature review highlights the recurring methodological problems (based on predefined quality criteria) and calls for greater rigour in the conduct of experiments. As a result, no clear evidence of non-thermal effects has been found so far.

Table 4: Follow-up of the literature published since the beginning of the NextGEM project in July 2022.

	Categories	Number of studies on RF (5G)	FR1 <6GHz	FR2 >6GHz	100kHz-300GHz
Experimental studies	Reviews	18 (2)	8		10
	Neoplastic diseases	18	18		
	Nervous system effects and neuro-behavioural disorders	27(5)	27		
	Reproductive and developmental effects	24 (5)	23	1	
	Other effects	32 (5)	31	1	
	Total	**119 (17)**	**107**	**2**	**10**
Epidemiological studies	Reviews and meta-analyses	15	5		10
	Mobile phone use	39 (4)	39		
	Residential exposure	8 (2)	7		1
	Human experimental research	8 (1)	8		
	Total	**70 (7)**	**59**	**.**	**20**
Total		**189 (24)**	**166**	**2**	**30**

Within NextGEM, scenarios are being explored as part of WP7, where three case studies (CS) are carried out, investigating potential effects of indoor levels of RF radiation on reproduction and development of vulnerable people (CS1), defining optimized outdoor urban planning and 5G design architecture and investigations for public awareness of cancer-related hazards in the 5G FR1 band (CS2), and investigating biophysical mechanisms in red blood cells (RBCs) of exposure to the 5G FR2 band in indoor and outdoor environment (CS3).

4.2 Quantitative risk assessment

4.2.1 Overview

Unlike qualitative risk analysis, which focuses on descriptive and subjective RA, quantitative analysis uses numerical data, probabilistic calculations, and statistical models to estimate the probabilities and impacts of risks. These models make it possible to identify and quantify the risks associated with specific exposures, providing a basis for drawing up guidelines and policies to protect public health.

The first important step is the dose-response evaluation, which aims to characterize the relationship between the dose of an agent administered or received and the incidence of an adverse health effect in the exposed population. There may be different dose-response/effect relationships, either linear or non-linear, with or without thresholds.

[16] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014L0030

Various factors such as the mode of exposure, its duration, the frequency (in the case of EMFs) and susceptibility can influence the form of the relationship (Figure 4).

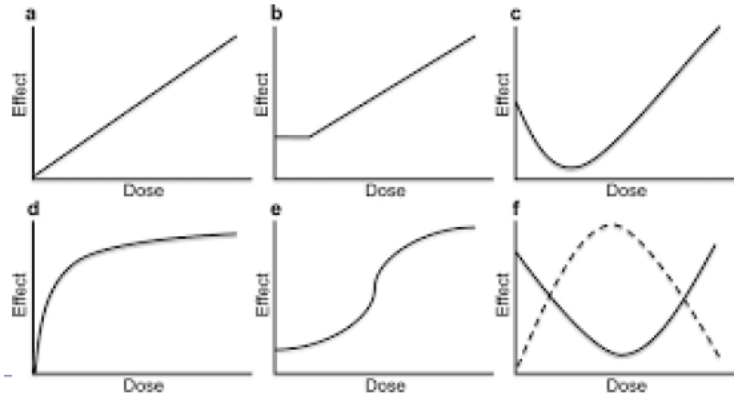


Figure 4: Examples of dose-response relationships (from [30])

In the absence of any identified non-thermal effects in the domain of RF-EMF, we describe here some models used in the risk analysis of chemical substances.

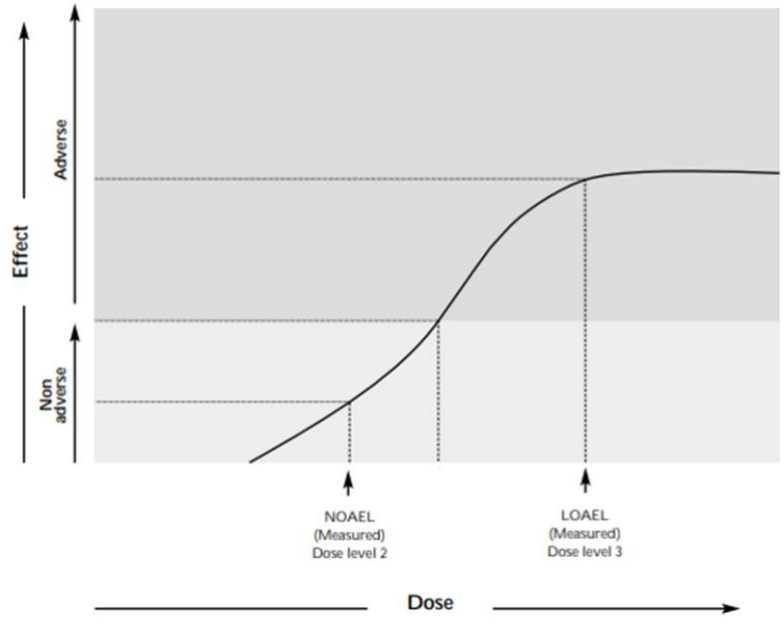
4.2.2 Methods of quantitative risk assessment

A quantitative risk assessment approach starts with the selection of an adequate reference point. For chemicals, the two most commonly used types of reference points are NO(A)EL values and BMD values.

4.2.2.1 No-Observed-Adverse-Effect Level (NOAEL)

NOAEL refers to the highest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure. The NOAEL approach applies to all toxicological effects considered to have a threshold (Fig. 5). This is derived as follows:

(1) For each adverse effect/endpoint, identify the highest experimental dose level where effects were not detected, using expert opinion and statistical tests to compare each dose group with the control group.
(2) The study NOAEL is the lowest relevant NOAEL obtained for any of the adverse effects detected in the study (i.e., for the critical effect of the study).



(3)

Figure 5: Illustration of the NOAEL and LOAEL [31]

In the interpretation of the NOAEL, it is important to note that the NOAEL may correspond to a dose level where (adverse) effects are either absent or too small to have been detected across the studies considered. Moreover, the magnitude of any possible effect at the NOAEL remains unknown. Therefore, the NOAEL does

not necessarily correspond to a "no effect" dose, but it indicates that no statistically or biologically significant adverse effects were observed at that level. Indeed, "the size of the estimated effect at the NOAEL is, on average over several studies, close to 10% (quantal responses) or 5% (continuous responses)" ([32], p. 9).

In contrast, the Lowest-Observed-Adverse-Effect Level (LOAEL) represents the lowest exposure level at which statistically or biologically significant increases in the frequency or severity of adverse effects are observed, comparing the exposed population with an appropriate control group. In other words, while the NOAEL represents the highest level of exposure without any observed negative effects, the LOAEL is the lowest level at which effects have been detected. When a NOAEL is not available, the LOAEL can be used to derive it, applying an uncertainty factor (UF): NOAEL = LOAEL/UF [32].

4.2.2.2 Benchmark dose (BMD)

In contrast to the NOAEL approach, the BMD approach applies to all toxicological effects, both those considered to be with and without a threshold. It makes use of all the dose–response data to estimate the shape of the overall dose–response relationship for a particular endpoint. The BMD approach is based on mathematical models being fitted to the experimental data within the observable range and estimates the dose that causes a low but measurable response (the Benchmark response BMR), typically chosen at a 5 or 10% incidence above the control. The BMD lower limit (BMDL) refers to the corresponding lower limits of a one-sided 95% confidence interval on the BMD. This value is normally used as the Reference Point (RP) [32].

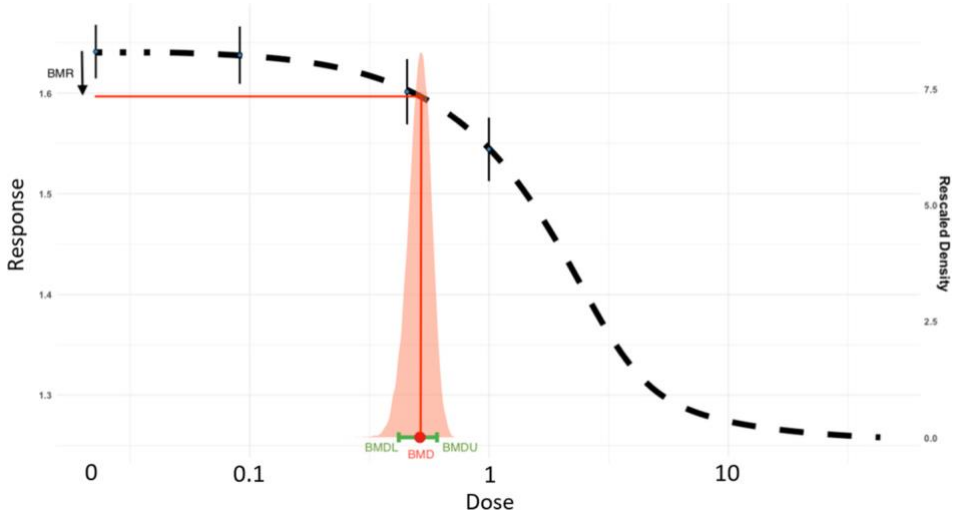


Figure 6: Key concepts for the Benchmark Dose (BMD) [33].

Figure 6 presents the key concepts for the BMD approach, where the plotted vertical lines represent the mean responses along with their standard deviations [32] A dashed curve shows the fitted dose-response model, which may be one of several individual models or an averaged model. This curve is used to estimate the BMD, defined as the dose associated with a small, biologically meaningful change in response, known as the Benchmark Response (BMR). The density plot displays the posterior distribution of the BMD, with a green line at its base indicating the limits of the two-sided 90% credible interval for the BMD, determined by the 5% tail probabilities on either side. The BMDL represents the 95% one-sided lower bound, and the BMDU the 95% one-sided upper bound, both within this 90% credible interval. Note that the estimated background response (median response of the control group) may differ from the observed background response. Finally, the BMR is defined as a change relative to the background response predicted by the fitted model.

The observed mean responses plus or minus the observed standard deviation are plotted as vertical lines. The dashed curve is a fitted dose–response model, either one of the different individual dose–response models or the averaged model. This curve determines the point estimate of the BMD, which is generally defined as a dose that corresponds to a low but biologically relevant change in response, denoted the BMR. The density shows the posterior distribution of the BMD, and the green line at the bottom of the density indicates the boundaries of the two-sided 90% credible interval of the BMD (defined by the 5% left and right tail probabilities of that posterior distribution). The BMDL is the 95% one-sided lower bound of the 90% credible interval for the BMD. Likewise, the BMDU is the 95% one-sided upper bound of the 90% credible interval for the BMD. It should be noted that the estimated background response (the median response of the control group) does not necessarily coincide with

the observed background response. The BMR is defined as a change with regard to the background response predicted by the fitted model [32]

The essential steps of the BMD approach are (see [32] for further details):

(1) Selection of potential critical endpoints.
(2) Specification of BMR: a percentage increase or decrease in response compared with the background response. Ideally, the increase/decrease in BMR should be within the range of experimental response to avoid extrapolation. For quantal data, a 10% extra risk is generally taken as BMR, whereas for continuous data, the BMR depends on the nature of the selected endpoint. Selection of the BMR for continuous data should be based on Expert knowledge elicitation (EKE), which could be informed by, e.g. the effect size theory, which is based on the % change compared to the background (generally 5%; higher percentages possible for endpoints with large variation in data within a group and/or relatively high maximum response).
(3) Performing Bayesian model averaging using a set of predefined dose-response models and calculation of the BMD credible interval for the averaged model for each of the critical endpoints.
(4) Selection of an overall study BMDL, i.e., the critical BMDL of the study, from the obtained set of BMD credible intervals for the different potentially critical endpoints.

When selecting an adequate RP for the RA, it is important to consider concepts such as ***biological relevance*** and ***statistical significance.***

The concept of **biological relevance** implies a biological effect of interest that is considered important based on expert judgment. Its use refers to an effect of interest or to the size of an effect that is considered important and biologically meaningful and which, in risk assessment, may have consequences for human health. A definition was provided by [33]:

"an effect considered by expert judgement as important and meaningful for human, animal, plant or environmental health" (p. 5).

In this context, it is assumed that a "normal" biological state can be defined, and the definition of normality is closely linked to the adversity of an effect observed during toxicity testing or in epidemiological studies.

Distinguishing adverse effects from physiological adaptive effects is crucial in identifying a NOAEL from experimental toxicity studies, but also when using the BMD approach.

Consideration should be given as to whether the effect is causally related to exposure to the agent, and the nature of the effect should also be considered**,** *inter alia***,** if it is a homeostatic, adaptive, directly or indirectly adverse, or beneficial effect. For effects where the size of the effect is critical, it should be assessed whether the magnitude of the effect is sufficient to be of biological relevance and, thereby, of importance for the assessment outcome.

Statistical significance relates to where, for instance, a difference in concentrations (e.g., of a hazardous substance in two exposed populations) or a difference in proportions (e.g., of tumour-bearing individuals), the difference is unlikely to have occurred **by chance** alone. "**Significant"** does not necessarily mean "important" or "meaningful" but is a statistical statement on the property and information content of the observed data.

4.3 Uncertainty and risk of bias

4.3.1 Uncertainties in human health risk assessment

Human response to any kind of exposure depends on the toxicity of an agent and the extent of exposure. Uncertainties in human health risk assessment (HHRA) can usually be divided into four modules/components (exposure assessment, hazard identification, dose-response assessment, and risk characterization). Typical uncertainties regarding each module are presented in Table 4 below.

4.3.1.1 Uncertainties in exposure assessment

Exposure assessment traces events from source to final monitoring, which attempts to estimate the duration, frequency, and magnitude of the exposure to a designated target group or in specific micro-environments. It is anticipated that such an assessment will determine the source of toxicants, their transportation through environmental media, and their external exposure and monitoring under various exposure scenarios. Exposure assessment techniques are usually based on an estimation of total pollutant exposure and availability, both of which involve uncertainties associated with methods, models, and parameters. Model uncertainties stem from model structure, detail, validation, extrapolation, resolution, boundary, scenario reasonableness, etc.

4.3.1.2 Uncertainties in hazard identification

Hazard identification attempts to determine whether the agent can cause adverse health outcomes based on various types of evidence for toxicity. The International Agency for Research on Cancer (IARC) is the World Health Organisation's (WHO) specialized cancer agency, and part of its remit is to classify agents based on the strength of scientific evidence of their carcinogenicity, as described in Section 4.1.2.1. Recently, the title of the IARC Monographs series was changed to the IARC Monographs on the Identification of Carcinogenic Hazards to Humans. This change is an important clarification because hazard identification is conducted within the Monographs, as distinct from risk assessment, where exposure response characterization is used to estimate cancer risk for a given scenario and level of exposure. The IARC classifications of carcinogenicity for humans of an agent were also changed to Group 1: is carcinogenic, 2A: is probably carcinogenic, 2B: is possibly carcinogenic, and 3: not classifiable [34]. Key issues involved in the procedure include how to weigh positive and negative results, crucial research, and sensitivity endpoints for final judgments.

Except for uncertainties when identifying hazards from human and animal studies, uncertainties exist when using the ancillary information from in vitro assays or quantitative structure–activity relationships (QSAR) to help with identification. Previously, it was a common assumption that *in vitro* investigations are not reliable for a complete biological system, and more importantly, a finding from an *in vitro* test is not predictive of *in vivo* results. The procedures IARC uses to determine hazard classifications were amended to give greater WoE on mechanisms from *in vitro* studies that may help predict carcinogenicity in humans [34]. This change in classifying agents could be important for assessing carcinogenicity of RF-EMF exposure, particularly as it was classified as "2B – Possibly Carcinogenic" by IARC using their methodology that was heavily weighted to epidemiological and *in vivo* studies. Further, there is a possibility that IARC will review this classification for RF-EMF, using this revised methodology in the near future [35]. The uncertainty regarding *in vitro* studies has limited the prediction and application of the *in vitro* model when support from mechanistically relevant biological data is lacking [36].

4.3.1.3 Uncertainties in dose–response assessment

The aim of dose–response assessment is to establish the dose–response curve or extrapolate the reference dose (Rfd; which produces a non-cancer effect if ionizing radiation or chemicals are the agents).

During the extrapolation from the point of departure (PoD; the PoD aims to define the point where the dose-response curve moves away from background and can be used as a basis for the setting of health-based exposure limits) to the equipotent human dose, interspecies and intraspecies uncertainties are probably the most important factors. Species differences stem from metabolic, functional, and structural variations. Specifically, the interspecies uncertainty can be divided into two aspects: toxicokinetic (TK) and toxicodynamic (TD) differences. While interspecies uncertainty describes the differences in dose–response between animals and humans, the intraspecies uncertainties account for variations in sensitivity within the human population (International Programme on Chemical Safety, 2014)[17]. The interspecies and intraspecies differences can be divided into TK and TD, which allow each component to be determined by relevant, available agent-specific data.

Table 5: Overview of typical sources of uncertainty for the different stages of risk assessment.

RA module	Goal	Source of uncertainty
Exposure assessment	To estimate the duration, frequency, and magnitude of the exposure to a target group	**Scenario**: descriptive errors, aggregation errors, judgment errors, and incomplete analysis **Model**: assumptions for the correlation among exposure events, including model structure, detail, validation, extrapolation, resolution, boundary **Parameter**: in specifying the point or distribution estimate, including measurement errors, sample uncertainty, data type, extrapolation uncertainty, and statistical distribution selection
Hazard identification	To determine whether the agent can cause health	Weight of the multiple LoE Risk of Bias

[17]https://osha.europa.eu/en/themes/dangerous-substances/practical-tools-dangerous-substances/health-and-safety-guides-international-programme-chemical-safety

	outcomes based on various lines of evidence	
Dose–response assessment	To establish the dose–response curve or set the reference dose (or 'virtually safe dose')	Database-related: data quality; heterogeneity among studies Extrapolation: extrapolating reference dose from the PoD, including interspecies and intraspecies variations, exposure duration, and model selection Risk of Bias
Risk characterization	To describe the nature, likelihood, and magnitude of a health-related effect from exposure to an agent	The summary of all the above-mentioned uncertainties Decision rule: due to toxicity criteria, site-specific scenario, and parameter selection in the assessment process The quantitative and qualitative uncertainty characterization as primary consideration informs the risk manager about confidence in the data; and secondly, describes benefits to the greatest extent possible.

4.3.1.4 Uncertainties in risk characterization

Risk characterization is a process that describes the nature, likelihood, and magnitude of adverse effects by integrating toxicological and exposure information. Selections of data and models result in multiple options regarding the estimated risk, and a sophisticated HHRA should retain all materials employed in the entire process for further editing [37]). Uncertainties here, defined as decision-rule uncertainties, would be propagated due to the exposure scenario and toxicity selection. A case is the World Health Organization (WHO) utilizing the disability-adjusted life-year since the 1990s to consistently assess the burden of disease across diseases, risk factors, and regions. During this process, the choices of disability weights, discounting, and age weighting affected the reliability of the outcomes, as demonstrated by a several-fold division of the risk that was observed when the discounting was assumed to be 3% and zero for lifetime exposure. The quantitative and qualitative uncertainty characterization in risk characterization would firstly inform the risk manager about confidence in the data and, secondly, describe benefits to the greatest extent possible.

4.3.2 RF-EMF related uncertainties and Risk of Bias

One longstanding characteristic of the RF-EMF bioeffects literature is that many studies report "statistically significant" effects ($p<0.05$) of exposure, regardless of the exposure conditions (frequency, SAR, exposure duration) and the biological endpoints. Many, if not most, of these effects are close to the level of noise or random variability in the data, and many of the studies are small and preliminary in design. The question arises which of the reported biological effects are real and have biological significance.

Gelman (blog, 3/10/2024)[18] as well as many other authors (e.g., [38] have noted the importance of rigor and reliability of studies. These concepts differ from "quality", which may refer to innovative experimental approaches or theories. Several agencies (in the US, e.g., the National Toxicology Program, and OECD in the international arena) provide standard protocols for risk studies to be used in regulatory submissions.

Since few EMF bioeffect studies are performed compliant with OECD or NTP specifications, some way is needed to assess the rigor and reliability of studies as minimal requirements for inclusion in systematic reviews or other evidence synthesis. One approach that has been used in evaluating the EMF bioeffects literature is to assess "risk of bias" (RoB), which, if excessive, will exempt them from being considered in systematic reviews and for risk assessment by competent authorities. Widely used sets of criteria for assessing RoB, in general, include the Cochrane Collaborative RoB tool for randomized clinical trials [39] and a set of nine criteria in the OHAT RoB tool for human and animal studies [40]. Specifically for research into the health effects of RF-EMF, several groups have listed criteria that are highly relevant when evaluating the quality of studies in this area (see e.g., [41] [42] [12] [43]). These criteria include and are, to a large extent, similar to many of the criteria listed in the OHAT paper:

Exposure conditions: Clearly described exposure conditions are the first and foremost criterion to determine if a study suffers from RoB. These conditions include information regarding frequency, signal modulation, exposure

[18]https://errorstatistics.com/2024/09/11/an-exchange-between-a-gelman-and-d-mayo-on-abandoning-statistical-significance-5-years-ago/

duration, as well as a clearly described dosimetry. A more detailed description should include the following parameters:

- **Exposure conditions**: Clearly described exposure conditions are the first and foremost criterion to determine if a study suffers from RoB. These conditions include information regarding frequency, signal modulation, and exposure duration, as well as a clearly described dosimetry. A more detailed description should include the following parameters:
    - Exposure setup is not always correctly/completely described (besides the use of mobile phone, base station, laptop, etc.).
    - Dosimetry (the calculation and assessment of the energy absorbed in the biological material (e.g., in the form of SAR)) is often calculated, for example by modelling, but not validated by measurements.
    - The use of the term "sham" is correctly used if it indicates that a similar exposure condition, including a similar exposure setup in an inactivated state, is used. However, the term may also incorrectly indicate the absence of RF-EMF exposure in another setting, which does not provide an otherwise identical environment.
- **Study design**: Clear description of the used biological material and assay(s), including positive and negative controls, to detect whether a) the used assay works and b) possible effect sizes can be better understood/ interpreted. Also, sham exposure, temperature control, and blinding are necessary.
- **Statistics**: It is important to know whether the sample size can show a possible effect or not, or whether it is more of a random result (both in the direction of "effect" and "no effect"), and if bias can be excluded. Clear descriptions of the number of technical repetitions (samples) and independent experiments, as well as the statistical analysis used, are necessary.

Few papers fulfil all these criteria, which makes evidence-based risk assessment difficult and not satisfactory for the use of regulatory bodies. To complicate matters even more, experiments may or may not have been conducted. In some cases, similar or even identical data and figures are presented in different publications and different contexts, for example, with different exposure settings. The work of some research groups is simply not trustworthy, because no matter what the study is about, very strong effects were found and presented in all publications.

5 Human health risk assessment in NextGEM

5.1 The overall approach in NextGEM to health risk assessment

As described previously in this Deliverable (Section 3.1 and subsequent sections), a health risk assessment consists of several components, including hazard identification, exposure assessment, risk characterization, including elucidating potential dose-responses, and a risk assessment that also considers uncertainties in the different components.

Risk assessments of environmental agents' effects on human health are either qualitative or quantitative (e.g. [44], described in detail in sections 4.1 and 4.2). The former is more easily performed and quicker, using knowledge and experience of the assessor(s) and typically ranks possible risks. A quantitative risk assessment, on the other hand, relies on objective, measurable data. These data can differ significantly between what kind of agent is assessed regarding its potential risk for human health (see [45] for further discussion). For quantitative risk assessment, it will also be necessary not only to detect whether an agent is hazardous, but also the mechanism of interaction of the agent with the components in the target cells needs to be taken into account [46].

The assessments performed in NextGEM will be evidence-based, using data from already available sources (such as published scientific articles, assessments made by competent authorities, and other competent stakeholders) and data from research activities performed within the NextGEM project and in CLUE-H. A WoE approach will be used for the RA, based on the criteria described in detail in [47]. The different stages of the WoE approach are described in [48]. In short, the assessment aims to include data from all available LoE (i.e. exposure assessments and dosimetry; *in vitro* and *in vivo* experimental studies; studies on human subjects (both experimental studies and epidemiology); modelling and simulation), reflecting mechanisms of action as far as they are known and available. The LoE should be integrated and expressed as WoE conclusions. A suitable model has been presented in a document from the EC Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [47], which will also be implemented in the RA performed by NextGEM and included in the NextGEM RA Tool. That model uses the following criteria to weigh the evidence:

- Weighing not possible
- Uncertain weight of evidence
- Weak weight of evidence
- Moderate weight of evidence
- Strong weight of evidence

5.2 Epidemiological considerations

In general, several types of epidemiological studies contribute to assessing carcinogenicity in humans, including cohort, case-control, ecological, and intervention studies, mainly, and occasionally randomized trials and case reports, and series. Cohort and case-control studies are the most informative, relating individual exposures to cancer occurrence and providing estimates of relative risk. Intervention studies offer strong causal evidence, while ecological studies, using population-level data, can be informative despite being prone to confounding. Case reports and series can provide compelling evidence in unique circumstances or as a starting point for further investigation. Studies of benign neoplasms, pre-neoplastic lesions, and malignant precursors can also be relevant, as they can strengthen inferences from cancer studies. These studies may share risk factors with malignant tumours or be part of the causal path to malignancies, providing additional insights into carcinogenic processes [49].

Epidemiological studies, however, are susceptible to various sources of error, including chance, bias, and confounding. Chance, or random variation, can produce misleading results, especially in smaller studies, and is indicated by confidence intervals around effect estimates. Bias, stemming from factors in study design or conduct, can distort the true association between an agent and disease. Types of bias include selection bias, information bias, and confounding. Selection bias occurs when study participation is influenced by exposure or outcome, while information bias results from inaccuracies in exposure or outcome measurement. The latter often encompasses recall bias. Confounding involves mixing extraneous effects with those of interest, potentially leading to spurious associations. These sources of error require expert judgment to integrate and rate their potential impact on the study's results. The study's ability to demonstrate a true association, or lack thereof, between the agent and cancer is crucial. Key determinants of informativeness include having a large enough study population for precise estimates, sufficient time from exposure to outcome, adequate exposure contrast, and well-defined exposure and outcome windows. The assessment of study quality, both explicitly by the authors and critically by experts, is therefore important for appropriately weighting the evidence brought by any given epidemiological study.

Independent epidemiological studies of the same agent can yield inconsistent results, making interpretation challenging. The ability of epidemiological evidence to inform about an agent's carcinogenicity depends on both the quantity and the quality of the evidence. A single study is usually insufficient; multiple studies are often required. Consistent results across different studies and methods support a causal relationship, while inconsistencies require further investigation. High-quality studies showing no positive association or an inverse relationship can suggest a lack of carcinogenicity, provided they rule out bias, confounding, and misclassification. These studies should be consistent, with combined estimates of relative risk at or below unity and narrow confidence intervals. Evidence of non-carcinogenicity applies only to specific cancer types, exposure levels, and populations studied. Long latency periods and critical exposure windows, such as with diethylstilboestrol and certain cancers, must also be considered [50]. Evidence is strengthened when it aligns with physiological and biological knowledge, including target organ exposure, latency, and tumour characteristics.

For health risk assessment, all relevant and available scientific evidence should be used. However, current evidence can consist of dozens or even hundreds of primary studies presenting complex, multifaceted, and even conflicting evidence, posing challenges to deriving accurate conclusions. Systematic reviews and meta-analyses 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 and meta-analyses are a good evidence synthesis tool and crucial for evidence-based decision-making [51]. A surge of systematic reviews and meta-analyses published over the past two decades bears testament to the strong demand for this form of evidence synthesis [52].

However, concerns have been raised regarding the rapidly increasing number of systematic reviews and meta-analyses. These concerns include the potential susceptibility to bias in these studies, and the massive production of conflicted, redundant, low-quality, and potentially misleading evidence synthesis articles [53]. These concerns also apply to the RF-EMF and cancer topic. Ioannidis [53] 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.

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 for risk assessment [54]. 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 [51] [55]. 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 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, which is based on a scoring system that assesses the methodological quality of systematic reviews, can be used in umbrella reviews to grade the reliability of evidence on a certain topic [56]. The total score reflects the quality of the systematic review.

Belbasis et al. [57] point out a number of advantages that come with umbrella reviews. First, they offer a "bird´s eye 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 instead making use of existing and published systematic reviews. Third, umbrella reviews allow the identification of potential research gaps in a specific field. Based on the identified areas where evidence is missing, one can formulate recommendations for further research, 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 [57].

To explore the potential risks of RF-EMF exposure and cancer, NextGEM conducts two umbrella reviews: one focusing on far-field exposure to RF-EMF and the other on near-field exposure.

5.3 Experimental considerations

To elucidate the potential risk of RF-EMF exposure, NextGEM performs experimental studies by focusing on carcinogenicity, reproductive, and developmental effects. These studies, using *in vitro*, *in vivo*, *ex vivo* and human models, aim to explore the potential effects and attempt to elucidate the non-thermal biological mechanisms underlying these effects. Biochemical and biophysical mechanisms of EMF responses are explored at the level of proteins and cells. Moreover, experiments on humans at exposure levels that reflect actual human exposure as

closely as possible will also be carried out. As part of the studies of biophysical mechanisms, thermal effects on blood components are also evaluated, which aims to specify the role of the possible thermal component on the observed effects. The studies are carried out on different biological models and consider different outcomes, as summarized in Figure 7.

Human neuroblastoma cells (SH-SY5Y) and human keratinocytes (HaCaT), cultured *in vitro*, are used to examine the effects of exposure to RF-EMF on cancer-related endpoints by applying several assays from cytotoxicity to cytogenetics, gene expression, and epigenetics. These assays allow the exploration of different possible actions of EMF, through processes such as oxidative stress, cell death and proliferation, DNA or chromosomal damages, changing levels in gene expression, and mechanisms regulating gene expression without altering the DNA sequence.

A selection of genes of interest (up- or down-regulated and linked to cancer-related outcomes) will be done and their expression will be investigated on human lymphocytes from healthy donors exposed *ex vivo*, and in buccal cells of heavy and light mobile phone users (oral communication, with the mobile phone antenna closed to the cheek).

Reproductive and development-related outcomes will be investigated in the model organism *C. elegans*. The use of this model organism allows for the simultaneous study of molecular endpoints (similar to those studied in *in vitro* experiments) and relevant physiological traits. Biochemical and biophysical mechanisms of EMF response will include the use of aqueous solutions of ions and biomolecules, and the effects of temperature increases will be compared with exposure to RF-EMF at non-thermal levels. After this first step at the molecular level, similar experiments will be carried out on proteins and whole blood. Human experiments are performed in WP4 (Task 4.4) and in the WP7 case study 3 to validate whether the results observed in less complex systems are also applicable to a higher level of biological organisation. This latter human pilot study will make it possible to explore the effects of RF-EMF under real exposure conditions.

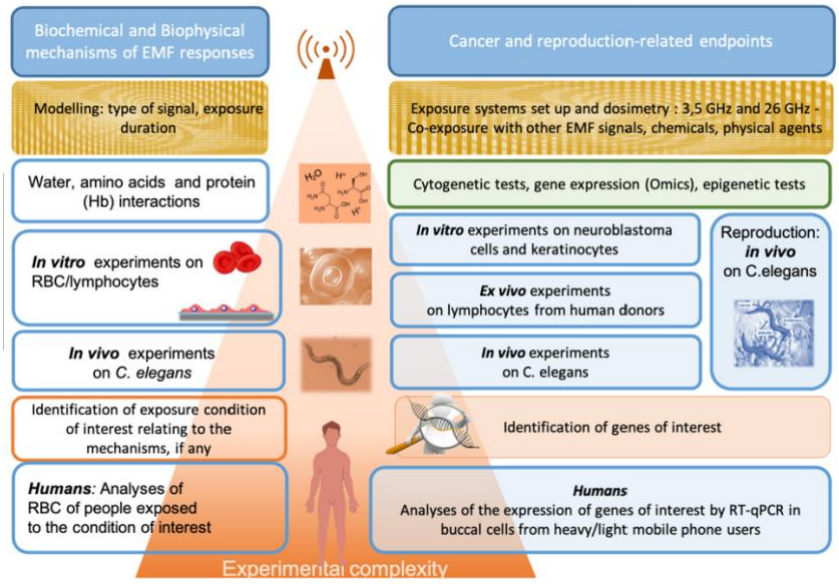


Figure 7: Overall strategy for experimental studies in NextGEM

The overall approach of the experimental studies in NextGEM, involves the use of increasingly complex systems that are closer and closer to the actual exposure situation, enabling more accurate conclusions to be drawn about the biological mechanisms likely to be involved. This is an appropriate process for risk assessment.

Like epidemiological studies, experimental studies are subject to several potential sources of error that can influence the results and interpretation of the data. Experimental studies can be subject to random error, particularly concerning biological variability between samples (cells or organisms). To limit this error, the control of the biological material, precise measurements of the effects, and replicates are essential to validate the results. Furthermore, given past incongruency in the literature when it comes to results, the effects, if any, will likely be very small. Hence, it's important to ensure the errors in our measurements are minimized.

Bias linked to the experimental set-ups can occur through e.g. poorly controlled experimental conditions. To minimise these biases, negative and positive controls need to be incorporated, as well as blind approaches in in vitro and in vivo experiments, and double-blind approaches in human studies. Furthermore, substantial effort has been devoted to developing and implementing state-of-the-art dosimetry for the different exposure scenarios that

are used within the project. Accordingly, standardized operating protocols (SOPs) have been developed and validated prior to the execution of the experiments to ensure standardized, high-quality, and reproducible experimental procedures within each partner's site and between partner sites. For experiments involving humans, either controlled exposure or real-life exposure (mobile phone users), appropriate ethical considerations are strictly considered.

5.4 Case studies´ considerations

Three case studies (CS) are performed in NextGEM where the project´s results from WP3-5 will be applied and validated. The CS are chosen so that they cover different groups of geographical and socio-economic conditions and include vulnerable population groups that are exposed to different signals (multiple EMF exposure, including 4G, and 5G signals, including FR1 or FR2). The three CS are:

- CS1. Potential effects of indoor levels of RF exposure on vulnerable people on reproduction and development.
- CS2. Optimized outdoor urban planning and 5G design architecture and investigations for public awareness of cancer-related health hazards.
- CS3. Health effects of exposure to mmWave EMF in indoor and outdoor environments.

All CS are in environments that reflect exposure conditions as realistically as possible. All CS are thus suitable for validating the chosen RA models and for validating the RA Tool that is a component of the NextGEM Information and Knowledge Hub (NIKH). The rationale for CS1 is that the COVID-19 pandemic situation has increased the indoor exposure of the general public to the EMF emitted by multiple sources, such as wireless personal communication devices (Wi-Fi, Bluetooth) or other applications (security scanners, smart meters, and medical equipment) in conjunction with the ambient environmental exposure. The effect that such EMF exposure can have on the health of vulnerable people, such as pregnant women or children, has not been studied. In addition, the potential exposure to EMF and other physical or chemical agents has increased concerns regarding fertility and children´s development. Therefore, the scope is to investigate potential EMF effects on vulnerable people by analysing the existing literature and by using *C. elegans* and exposure modelling approaches, to establish possible thresholds for safe/unsafe situations of single and multiple exposures and the potential risk to fertility and children's development. The outcome of the research will generate the basis for practical guidelines.

The rationale for CS2 is that 5G systems are considered the key technology to enable not only a wide range of application scenarios, but also the effective spreading of the smart city concept. Devices are foreseen for different locations, both outdoors and indoors, from underground to sky coverage for unmanned aerial vehicle (UAV) applications. Moreover, the use of MaMIMO antennas (and the higher frequency bands used in FR2) has completely changed the requirements for coverage and management of the network. RF-EMF will only be present when and where it is needed. In parallel to measurements, computations will be performed on simulated and real scenarios to analyse the effect of MaMIMO antennas and transmitter positions on field distribution. However, there are concerns that this technology increases the risks of carcinogenesis (the focus of this CS) and other adverse health outcomes. The scope of this CS is to assess the urban planning and exposure management for 5G NR location design architecture to examine the possibility of cell site distribution in the urban environment to minimize the exposure and to analyse the field distribution over the territory due to MaMIMO antennas. Selected realistic conditions will be tested to investigate biological responses in the presence and absence of other agents (combined exposures).

Finally, the motivation for CS3 is that the 5G system is expected to enable smart industries by providing massive and reliable high-bandwidth communication links and create high-bandwidth campus environments supporting high data rate connectivity. To support such connectivity demands, 5G wireless networks will employ mmWave frequency bands (FR2, above 24.25 GHz). In such scenarios, the EMF exposure in specific locations will be highly dynamic in time and space, based on the user's data request and spatial movement in each area. The passive EMF exposure of individuals will then vary considerably compared to 4G/LTE cases. Users with different demands in the same workplace are exposed to various sources of EMF. However, the adoption of mmWaves, and the usage of beam steering devices in both indoor and outdoor environments (e.g., campus, industrial) require the development of novel measurement devices and deeper analysis to evaluate the potential health risks or symptoms due to the directional EMF exposure at high frequencies. Exposure assessment of 5G signals in the FR2 band according to personalized demands in indoor and outdoor environments and the investigation of biophysical mechanisms in RBCs of exposure to these signals are the principal scopes of CS3.

6 Development of NextGEM risk assessment models and their integration into the NextGEM RA Tool

A primary objective of the NextGEM project is to identify appropriate risk assessment models for the health effects of RF-EMF exposure and further develop one or more models that can be used within the project. These models will ultimately be integrated into the NextGEM RA Tool, which is intended to be a component in the NextGEM Knowledge and Innovation Hub (NIKH). The finally developed risk assessment model(s) will be validated in the NextGEM Case Studies, together with a validation of the developed RA Tool.

The different stages (modules) of RA are presented in detail in section 4 of this Deliverable. The outcome of the process is a qualitative or a quantitative RA (as described in sections 4.1 and 4.2). As mentioned there, the most likely approach in NextGEM will be a qualitative RA, of which there are several models. The one(s) that will be employed will be decided at a later stage, when specific and relevant data are available. The present section aims to present in more detail the chosen approach for the two initial RA modules, viz., the hazard identification and the exposure assessment. This approach also provides the components and procedures that are necessary for the development of the RA Tool.

This section also presents an example of an RA intended to assess the effects of RF-EMF in vivo and in vitro on Key Characteristics (KC) of carcinogenesis. This work has used traditional (non-artificial intelligence (AI) or machine learning (ML) supported) approaches and will serve as validation of outcomes of the RA Tool.

6.1 Stages in NextGEM RA model and RA Tool development

The NextGEM RA model(s) will be carefully adapted to EMF research results on health-related topics. Based on the two initial modules of RA, exposure assessment and hazard identification, all available information from the literature and ongoing studies will be made usable and accessible. All data can then be transparently assessed and evaluated. As illustrated in Figure 8, both modules are included in the risk assessment analysis, whereby specific scenarios can be selected.

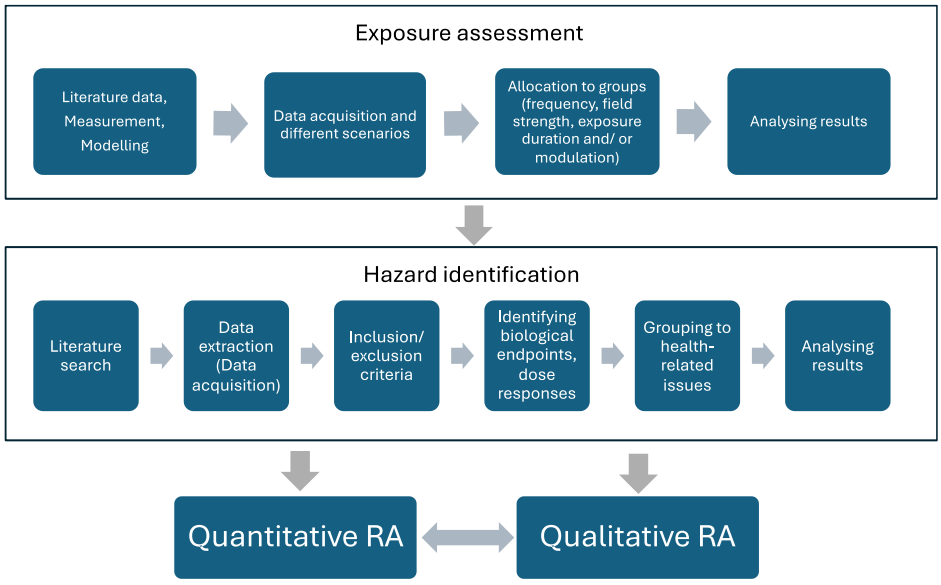


Figure 8: Structure of the general NextGEM RA-model.

For the RA Tool, different search or filter criteria for each of the fields (boxes) within Figure 8 are developed. Each of the search functions is accessible via radio buttons and drop-down menus.

Exposure assessment

Detailed descriptions of the exposure protocols used in NextGEM are provided in Deliverable D5.7. Furthermore, detailed descriptions of EMF sensing technologies and measuring equipment, as well as modelling approaches to assess internal and external exposure, are provided in Deliverables D3.5 and D3.6, respectively. For the necessary RA information, the RA models need to address the following procedures:

- Search literature data
- Measurement

- Modelling
- Data acquisition and different scenarios
- Allocation to groups (frequency, field strength, exposure duration, and/ or modulation)

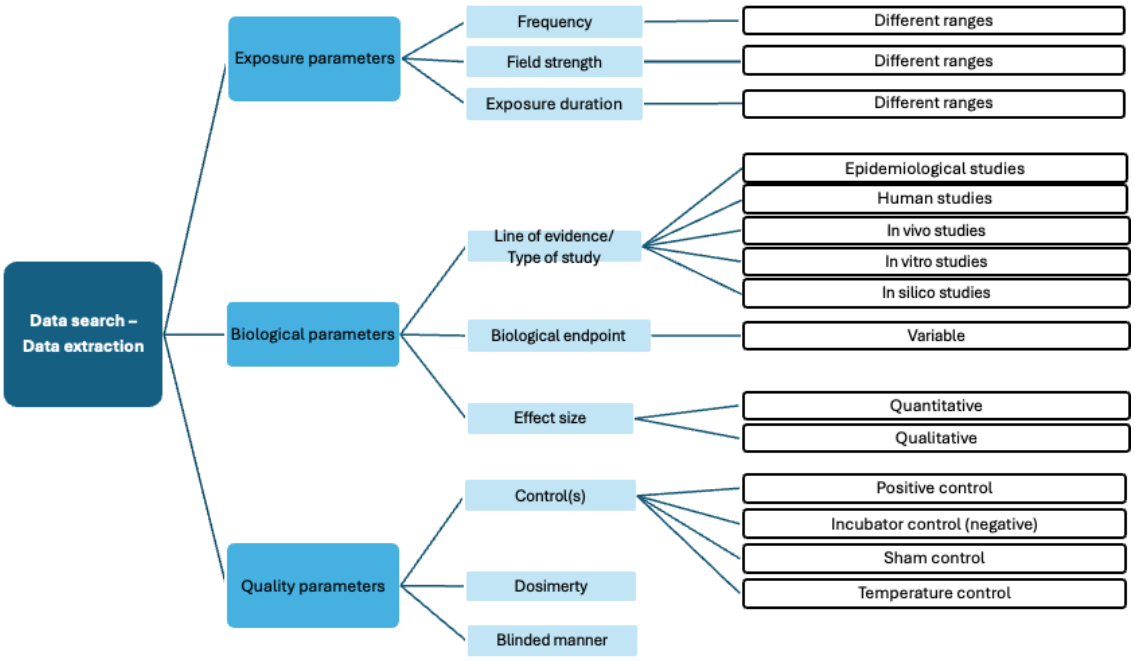


Figure 9: Scheme of the workflow of data extraction for NextGEM RA model and RA Tool

Hazard identification

Regarding this stage of RA, the necessary procedures are:

- **Literature search**: To generate a complete literature database of EMF-related literature, different search engines (PubMed, EMF-Portal, etc.) are connected to the NextGEM NIKH. Consequently, links to the publications will be available. Furthermore, newly generated information, such as from NextGEM case studies and other experimental studies, as well as from CLUE-H activities, will be available.
- **Data extraction (Data acquisition):** The goal is to extract all relevant data from the publications to create a complete database regarding exposure parameters, biological parameters, and quality parameters (see Figure 9). It will include all parameters regarding **1)** exposure condition (frequency, modulation, field strength, and exposure duration), **2)** biological parameters (line of evidence, biological endpoints, and effect size). Further, **3**) the quality parameters will give information about the RoB assessment, including the assessment of the application of the relevant control conditions (see also table 6), dosimetry, and if the study was performed in a blinded manner.
- **Inclusion/ exclusion criteria:** Under this field, it will be possible to select parameters regarding defined criteria for study quality (Risk of Bias criteria), both from a biomedical and physical point of view (see [58], Table 6 below). Accordingly, high-quality studies can be selected for RA, studies with inadequate experimental conditions can be excluded, and/or separately analysed.
- **Identifying biological endpoints, dose-responses:** Under this field, the available and relevant biological endpoints will be selected for the analysis with special emphasis on the possibility and appropriateness for dose-response investigations.
- **Grouping to health-related issues:** Various health-related topics, such as cancer development, involve multiple biological endpoints, hence, multiple endpoints can be grouped here. For example, the endpoints cell proliferation and cell death (apoptosis or necrosis) are part of cancer development, so these and other endpoints can be clustered for further analysis of cancer development.

Table 6: Simplified risk of bias (RoB) criteria for *in vitro* and *in vivo* studies. (Adapted from [58] [59] [60])

Quality parameters	Description
Positive controls	Positive controls (controls treated with a well-known agent that induces the effect under investigation) are needed to confirm the sensitivity of the experimental methods to assess the endpoint. For in vivo studies there are historical outcomes that can be used as positive controls.
Negative controls	Negative controls (generally controls with samples placed in incubators with no other intervention) to provide information on the background level of the endpoint under examination. For in vivo studies there are historical controls that can be used for negative controls.
Sham controls	Sham-exposed controls (control groups in exactly the same equipment and environmental conditions without exposure to RF-EMF) are needed to simulate identical exposure conditions. Without sham controls it is not possible to attribute effects to the exposure.
Temperature control	Adequate temperature control within the sample that is recorded during exposure to RF-EMF can allow the identification of non-thermal effects from those due to heating.
Appropriate dosimetry	A detailed or adequate description of dosimetry sufficient to allow replication/confirmation studies by independent laboratories. Studies using mobile phones or similar devices are deemed inappropriate as sources of exposure (because of the lack of proper dosimetry).
Blinding	Blinding scientists to which groups are exposed/non-exposed, as well as to the final analyses, are needed to avoid individual/observer bias.

6.2 Data analysis – An example

This is an assessment of evidence needed to determine whether exposure to RF-EMF exposures, below the levels recommended in the ICNIRP ([18]) guidelines can influence any of the ten key characteristics (KCs) of human carcinogens developed by the IARC. We define the 10 KCs and their relevance to carcinogenesis; review in vivo and in vitro studies relevant to the KCs; and conduct a risk of bias (RoB) analysis using 6 criteria.

The 10 KCs are according to [61]:

KC1. Is electrophilic or can be metabolically activated to an electrophile

KC2. Is genotoxic

KC3. Alters DNA repair or causes genomic instability

KC4. Induces epigenetic alterations

KC5. Induces oxidative stress

KC6. Induces chronic inflammation

KC7. Is immunosuppressive

KC8. Modulates receptor-mediated effects

KC9. Causes immortalization

KC10. Alters cell proliferation, cell death or nutrient supply

The RoB criteria in Table 6 address the internal validity of studies, i.e., whether the reported changes associated with exposure were causally related to the exposure. Studies can (and should) be evaluated in a different framework as well, which broadly considers whether the study management was sufficient to produce reliable and reproducible results. Toxicology studies for submission to regulatory agencies are typically required to follow Good Laboratory Practices (GLP), a burdensome set of procedures involving detailed standard operating procedures, prespecified protocols for acquiring and evaluating data, policies for dealing with outlying data points, etc. [62].

Furthermore, we did not include KC studies on genotoxicity or oxidative stress since Romeo et al [63] and Meyer et al [64] recently published relevant systematic reviews, but note their respective conclusions. From the other 8

KCs, we identified 119 in vitro and 40 in vitro measurements of in vivo studies through 30 June 2023, with 38% reporting statistically significant effects of exposure. We identified a strong association between the quality of the study and outcome, with those meeting more RoB criteria less likely to report statistically significant effects. Effects were reported over the entire frequency range, exposure levels, and biological endpoints, with no apparent pattern of exposure parameters resulting in effects. Only KC10 (alters cell proliferation, cell death or nutrient supply) has sufficient studies to analyse, but the other KCs had few studies and diverse endpoints. A few relatively high-quality positive studies require follow-up through additional targeted studies. The heterogeneity and overall poor study quality suggest the need for high-quality studies on these endpoints, preferably adhering to standards such as the Organization for Economic Co-operation and Development [62].

6.2.1 Results and Discussion

The analysis of the data has recently been published [65]. A synopsis of the paper is presented in this subsection. Results show the distribution of studies by KC and study quality. Table 7 summarizes the number of in vivo and in vitro studies and the number of "positive" studies (i.e., studies that show an effect) for each of the 8 KCs we reviewed. Only one of the 8 KCs, KC10 (Alters cell proliferation, cell death, or nutrient supply), had a comparable number of studies to those examined in the [63], [64] reviews. Furthermore, Table 7 shows that, overall, the vast majority of higher-quality studies (meeting the 5/6 RoBs) were negative. Sixty-eight of the 179 studies (38%) reported statistically significant effects, and of the 29 studies meeting the 5/6 RoBs, only 3 (10%) were positive. Similarly, for the 129 studies on KC10: "alters cell proliferation, cell death or nutrient supply", 30 studies (23%) reported a statistically significant effect, but none of these met the 5/6 RoBs.

Table 7: Number of in vitro and in vivo studies assessed for each of the 8 analyzed IARC KCs, and whether they reported a statistically significant effect of exposure. Empty cells ("0") indicate that no studies were identified in the review or that no studies met the 5/6 RoB criteria (RoB C).

Key characteristics	Total in vivo studies	Studies reporting statistically significant effects	Studies meeting 5 or 6 RoB C	Positive studies meeting 5 or 6 RoB C	Total in vitro studies	Studies reporting statistically significant effects	Studies meeting 5 or 6 RoB C	Positive studies meeting 5 or 6 RoB C
	In vivo				In vitro			
Electrophilic or metabolic	1	1	0	0	0	0	0	0
Genotoxicity	Covered in Romeo et al. (2024)							
DNA repair or causes genomic instability	4	4	0	0	5	5	0	0
Epigenetic alterations	1	1	0	0	1	1	00	
Oxidative stress	Covered in Myer et al. (2024)							
Chronic inflammation	0	0	0	0	10	8	0	0
Immuno-suppressive-Immune response	17	12	1	0	0	0	0	0
Receptor-mediated effects	1	1	0	0	2	2	1	1
Immortal-ization	0	0	0	0	8	3	2	2
Alters cell proliferation, cell death or nutrient supply	19	9	2	0	110	21	23	0
Total	**43**	**28**	**3**	**0**	**136**	**42**	**26**	**3**

The overall failure to meet what would be considered good experimental design is striking. Figure 10 shows the fraction of studies meeting each of the RoB criteria. A majority of studies failed to meet (or at least failed to describe meeting) three RoB criteria (C2, C3, C5). In part, this may reflect limitations in the documentation of studies, which were often reported in brief papers, or (as we believe) simple poor practice.
We have made a robust argument against the use of the 'vote counting' approach to evidence synthesis. The majority of studies on oxidative stress reported statistically significant effects of exposure; however, the proportion of positive studies decreased in more rigorous studies (i.e., those that met a greater number of RoB criteria). This result represents a central conclusion of our review. This result is also confirmed by the conclusions of [63], [64], who also observed a decrease in the proportion of positive studies in studies with higher RoB values.

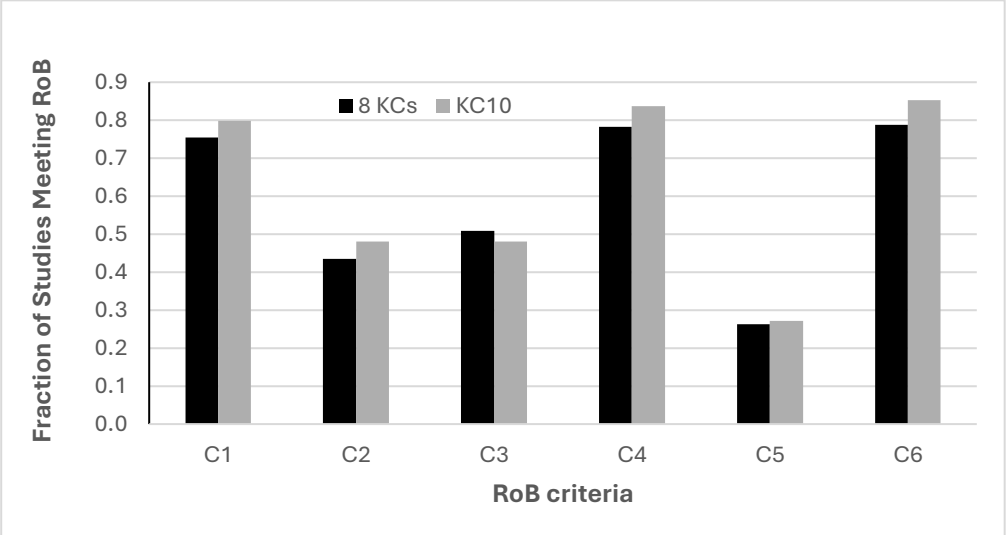


Figure 10: Fraction of studies meeting different RoB criteria (C). Data are shown separately for KC10 and the KCs combined in the included study.

We examined whether an obvious pattern existed with reported effects vs. exposure level and detected, that most studies used frequencies employed by cellular telephone systems (variously near 900, 950, 1800, 1900 MHz), a few used 2450 MHz (the industrial scientific medical band used by Wi-Fi and other technologies) and a limited number used other frequencies.

Studies reported multiple exposures (varying frequency and exposure level, given as specific absorption rate (SAR)). A few studies also reported exposure in terms of incident power density, which were chiefly at the higher frequencies, typically > 5 GHz. Strikingly, effects were reported over the entire range of frequencies and exposure levels employed, with no apparent demarcation separating positive from negative studies. This suggests the absence of a relationship between KCs and exposure. The simplest explanation is that some or most of the "positive" findings were affected by bias, particularly the lower-quality studies. Other explanations may be possible: the studies using the lowest exposure levels (SARs) typically used longer-term exposures. For the largest group of studies, further evaluation, including consideration of effect size, might yield SAR/exposure duration relationships that are not apparent.

In conclusion, it became apparent that the present database of in vitro and in vivo studies was so diverse and scattered in their quality that helpful outcomes of SRs on most of the KCs would be unfeasible, and any conclusions from such reviews would have very low confidence. The two PRISMA-compliant SRs ([63], [64] as well as previous comprehensive reviews on in vitro and in vivo genotoxicity studies (e.g. [66]), and our review of studies on the 8 KCs has all reached the same conclusion: there is clearly a need for much higher quality RF-EMF bioeffects studies on these KCs.

7 Integration of Risk Assessment Tool in the NextGEM Innovation and Knowledge Hub

To achieve the overall scope of risk governance, including risk identification, assessment, management, and communication, the RA Tool provides comprehensive analysis capabilities, offering guidance on risk mitigation and communication as needed. The NextGEM Innovation and Knowledge Hub (NIKH) plays a vital role in effectively integrating the defined risk assessment models to conduct human health risk assessments for mobile communication technologies within the RA Tool. The RA Tool is designed to meet stakeholders' needs across various risk management activities, including assessment, mitigation, and communication, and can be utilized by different competent stakeholders through its integration with NIKH.

The RA Tool is embedded within NIKH by extending and reusing the platform's existing functionalities. It is seamlessly integrated with the Graphical User Interface (GUI), designed to offer users a centralized and intuitive platform for evaluating and managing RF-EMF exposure risks. The GUI provides a user-friendly experience tailored to risk assessors, including scientists and professionals from competent authorities, as they carry out risk assessment activities.

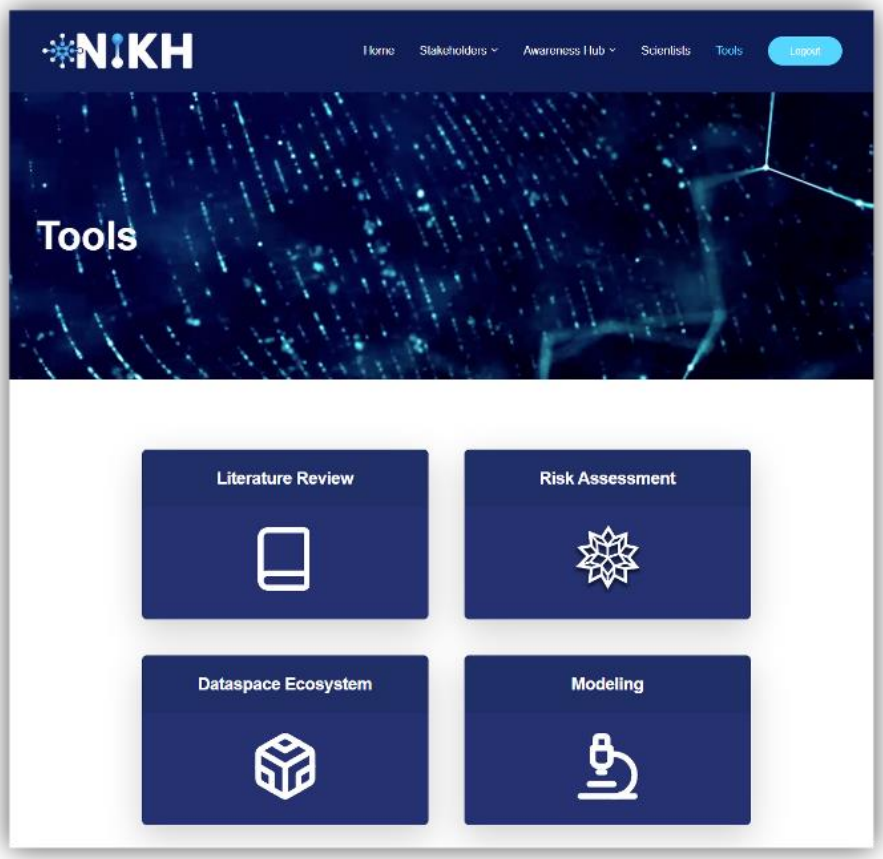


Figure 11: NIKH Tools and RA tool

The NIKH platform encompasses various capabilities essential for effective RA, including tools for literature insertion and data management. Specifically, as shown in Figure 11, the NIKH platform offers four distinct tools: Literature Review, Risk Assessment, Data Management, and Modelling.

7.1 Creating a Risk Assessment in NIKH

As a first step within the "Risk Assessment" tool, NIKH offers the choice to either create a new Risk Assessment or work on an already existing Risk Assessment (Figure 12 (a)). Upon entering basic identification information such as Name, Institution, Description, Keywords, Assessors, and Type of assessment (quantitative or qualitative) in the "New Risk Assessment" form, as presented in Figure 12 (b), a new Risk Assessment is initiated.

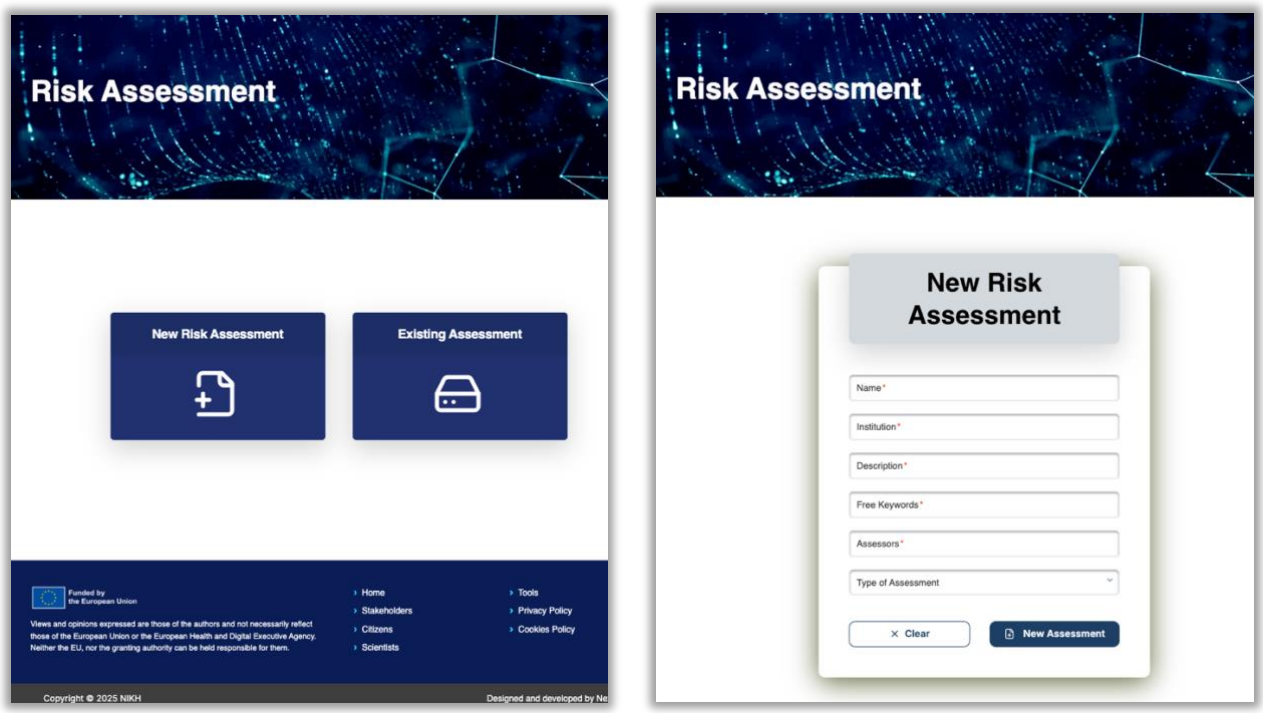


Figure 12: (a) Creation of a new Risk Assessment or editing an existing one (b) New risk assessment form

Choosing "Existing Assessment," the user is presented with a list of all the assessments that have been entered into NIKH, with a choice to either modify them, as we will describe further down, or to delete them from NIKH's database (Figure 13).

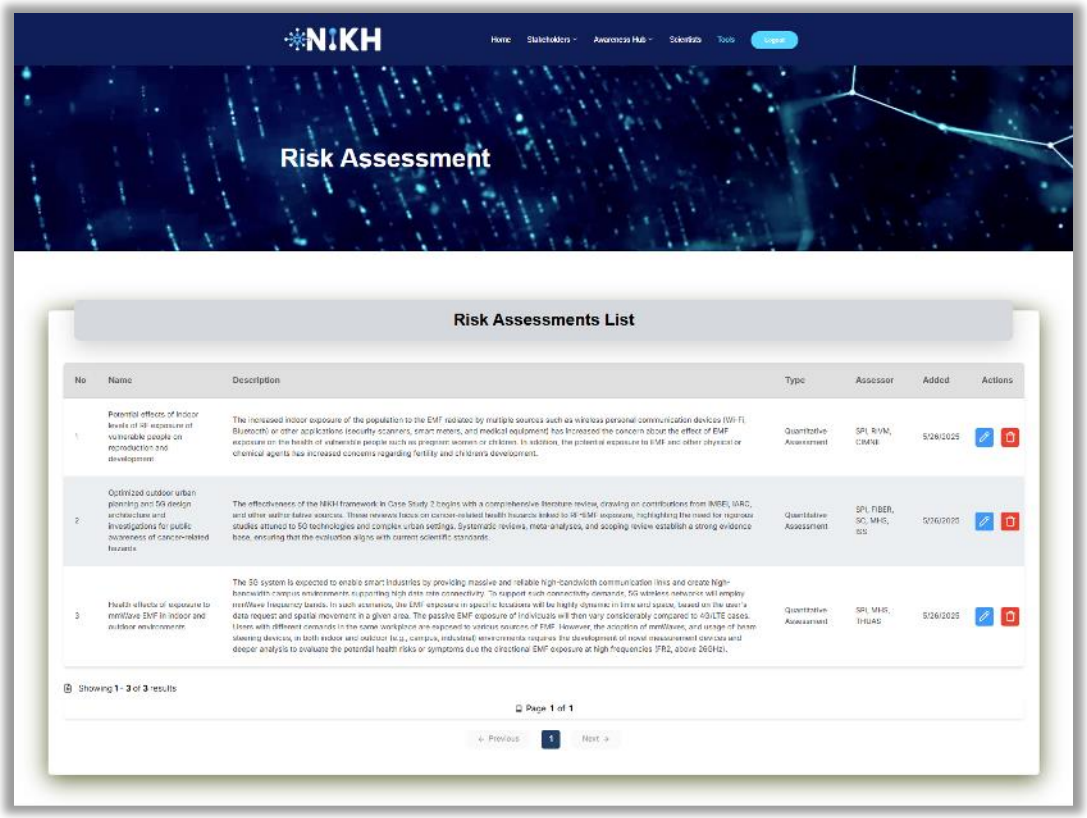


Figure 13: List of existing assessments in NIKH.

After the creation or editing of an existing risk assessment, the assessor is forwarded to another page (Figure 14) containing the four crucial steps of the standard RA methodology: Hazard Identification, Dose-Response Assessment, Exposure Assessment, and Risk Characterization.

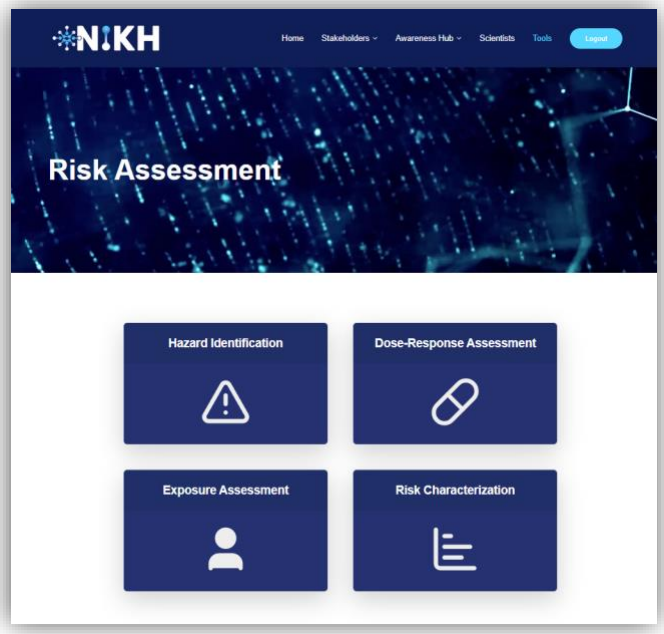


Figure 14: Risk Assessment methodology steps.

7.2 Hazard identification

The Hazard Identification step involves determining whether an environmental agent, such as RF-EMF, has the potential to cause adverse effects based on different lines of evidence coming from human studies, in vivo, in vitro, in silico, and epidemiological studies. The Hazard Identification page in the NIKH, as presented in Figure 15, leverages risk assessors to examine available literature to identify potential health effects based on relevant studies. Accordingly, the RA tool provides an interface with literature databases as it is crucial to perform an investigation of the literature along all lines of evidence, as to be able to identify if the stressor causes harm.

Figure 15: NIKH's Hazard Identification page.

7.2.1 Lines of evidence

The lines of evidence which are included within the "Hazard Identification" page in NIKH (Figure 15) to identify whether the stressor causes adverse health effects under specific conditions by examining biological, mechanistic, computational, and population-level data, are the following:

- **Human Studies**: Investigate controlled exposures and clinical outcomes directly in humans to assess potential health effects.
- **In Vivo Studies:** Assess biological and physiological effects of the stressor in whole-animal models.
- **In Vitro Studies:** Examine cellular or molecular responses to the stressor under controlled lab conditions.
- **In Silico Studies**: Use computational models and simulations to predict biological interactions or outcomes
- **Epidemiological Studies**: Analyse population-level data to identify statistical associations between exposure and health outcomes.

7.2.2 Literature review

Based on the procedure outlined in the previous section, conducting a health risk assessment begins with a literature search for the different lines of evidence. Literature search in the NIKH enables assessors to customize selection criteria, streamline their research process, and efficiently access extensive datasets in a single step. The RA tool supports the extraction of various data types from multiple sources. These include results from NextGEM's experimental activities as well as similar datasets from other projects in the CLUE-H cluster. Each literature search is automatically saved, allowing users to revisit and manage their search history through a dedicated Literature Review History page (Figure 15). This feature enhances traceability and ease of access to previous searches. Apart from that, the tool gives assessors the capability to assessors to add literature from online repositories or by DOI. It can also import and export literature as .xls files.

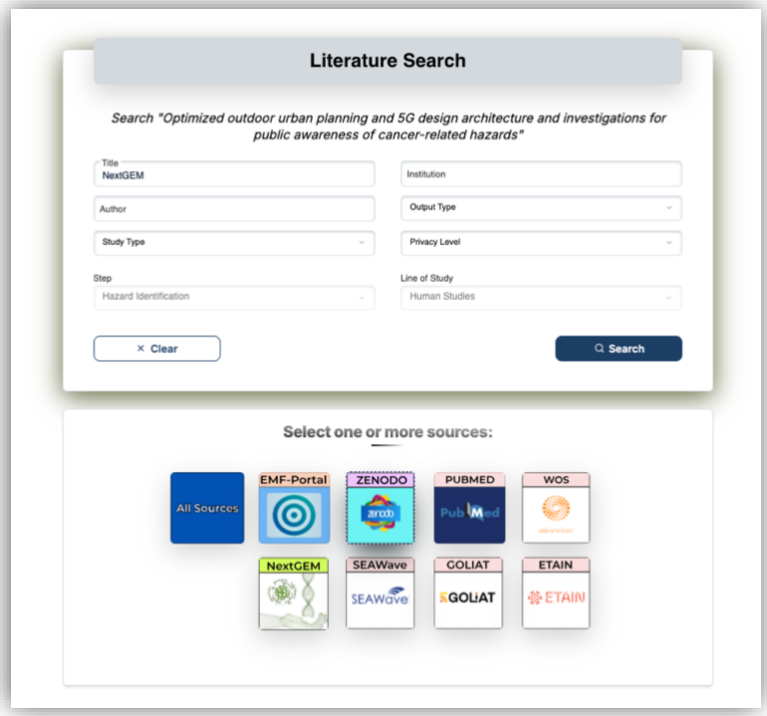


Figure 16: NIKH's Literature search

The RA tool facilitates this step by allowing users to search literature from various sources integrated within the tool. Specifically, it can extract data from external repositories such as Zenodo, EMF-Portal, PubMed, and Web of Science. To support its assessment tasks and data management needs, NIKH has incorporated results from the NextGEM project as well as from other projects within the European Cluster of EMF and Health (CLUE-H). For instance, the NextGEM and SEAWave projects have established a dedicated community on Zenodo to store all related publications. The GOLIAT project uses Dataverse, while the ETAIN project shares its results via Yoda.

These platforms provide users with consolidated access to information from a range of EMF-related initiatives and repositories. When users select third-party services, they can retrieve a unified set of materials collected from all selected sources at once. As illustrated in Figure 16, users can filter their search by specifying fields such as Title, Institution, Author, Output Type, Study Type, and Privacy Level. Additionally, users can broaden their search by applying different criteria to retrieve more results from the same or other sources.

7.2.3 Inclusion/ exclusion criteria

Following the literature search, the NIKH platform applies a structured three-step approach for the inclusion and exclusion of relevant sources. Building on the initial search and selection process, registered users can initiate a new literature search, identify and eliminate duplicate entries across multiple sources, and combine different queries to perform a comprehensive analysis.

- **Deduplication:** In the first step, the tool can proceed to a deduplication of papers based on selected parameters such as Title and DOI. This allows users to merge duplicates retrieved from different sources efficiently
- **Title and Abstract**: In the second step, each paper is screened based on its Title and Abstract, and classified as irrelevant, relevant, or unclear. To support this screening process, users can view individual paper metadata through the "more" button or opt to download all metadata in Excel format for offline review (Figure 17).
- **Full paper Screening**: In the third step, all papers marked as relevant or unclear undergo a full paper screening. After this detailed examination, papers are categorized as irrelevant, relevant but ineligible, or relevant and eligible for inclusion in the risk assessment. Once the final review is completed, the RA tool stores the list of relevant and eligible literature (Figure 18). This finalized dataset can then be saved and downloaded, providing the foundation for the subsequent steps in the health risk assessment process.

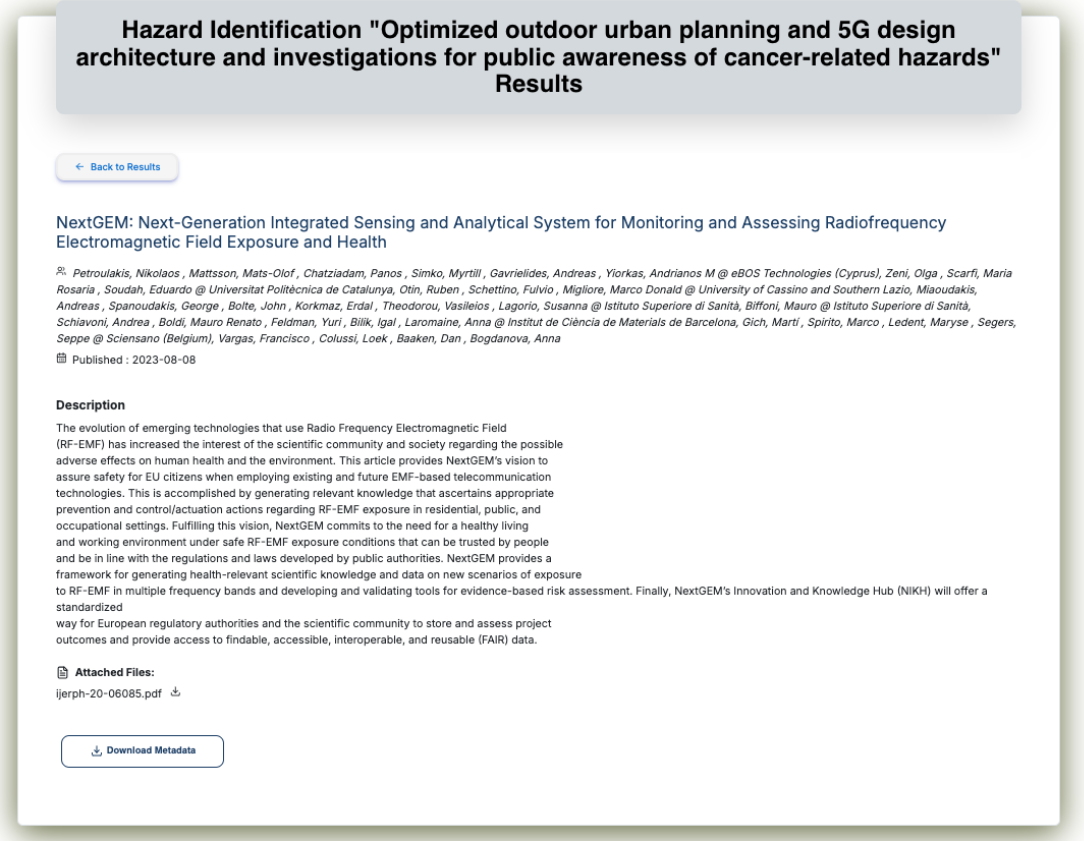


Figure 17: RA tool - More details for the Title/Abstract screening

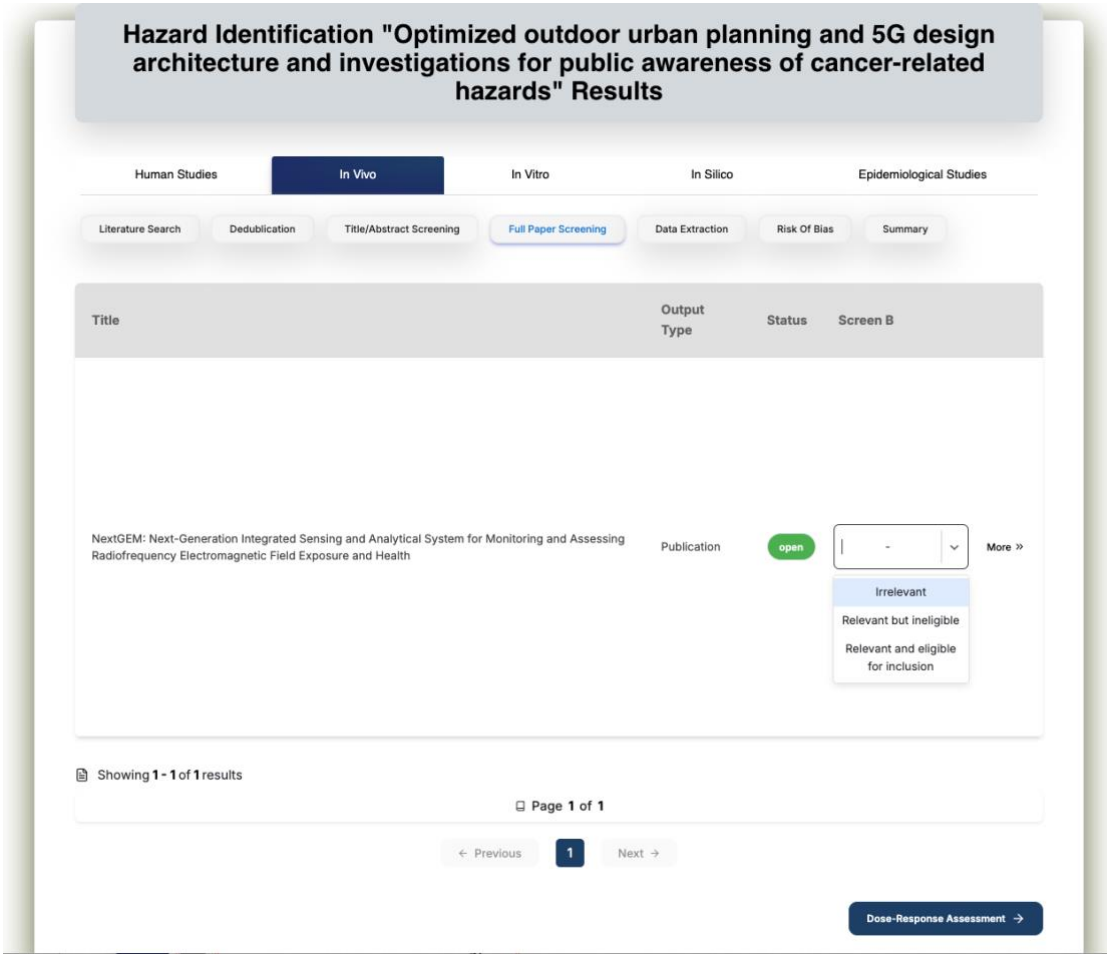


Figure 18: RA tool full paper screening

7.2.4 Data Extraction

Once papers are classified as "Relevant and Eligible for Inclusion", the tool provides a form/questionnaire for each paper (Figure 19), allowing users to extract and record the necessary data for the paper review process. The Data Extraction questionnaire includes the following questions:

- Exposure Parameters related questions
  - **Frequency (Different ranges)**: Frequency of EMF exposure.
  - **Field Strength (Different ranges)**: Electromagnetic field strengh.
  - **Exposure Duration (Different ranges)**: Total time or duration of exposure.
- Biological Parameters related questions
  - **Lines of Evidence**: Study type from predefined biological evidence categories (drop-down selector from Epidemiological, Human, In Vivo, In Vitro, or In Silico).
  - **Biological Endpoint (Variable)**: Observed biological effect or health outcome.
  - **Effect Size (Quantitative or Qualitative)**: Quantitative or Qualitative description of the observed effect.
- Quality Parameters related questions
  - **Control Type**: Type of experimental control used in the study (drop-down selector from Positive Control, Incubator Control, Sham Control, or Temperature Control).
  - **Dosimetry**: Information on how exposure levels were measured or calculated.
  - **Blinded Manner**: Whether the study was conducted with blinding and how.

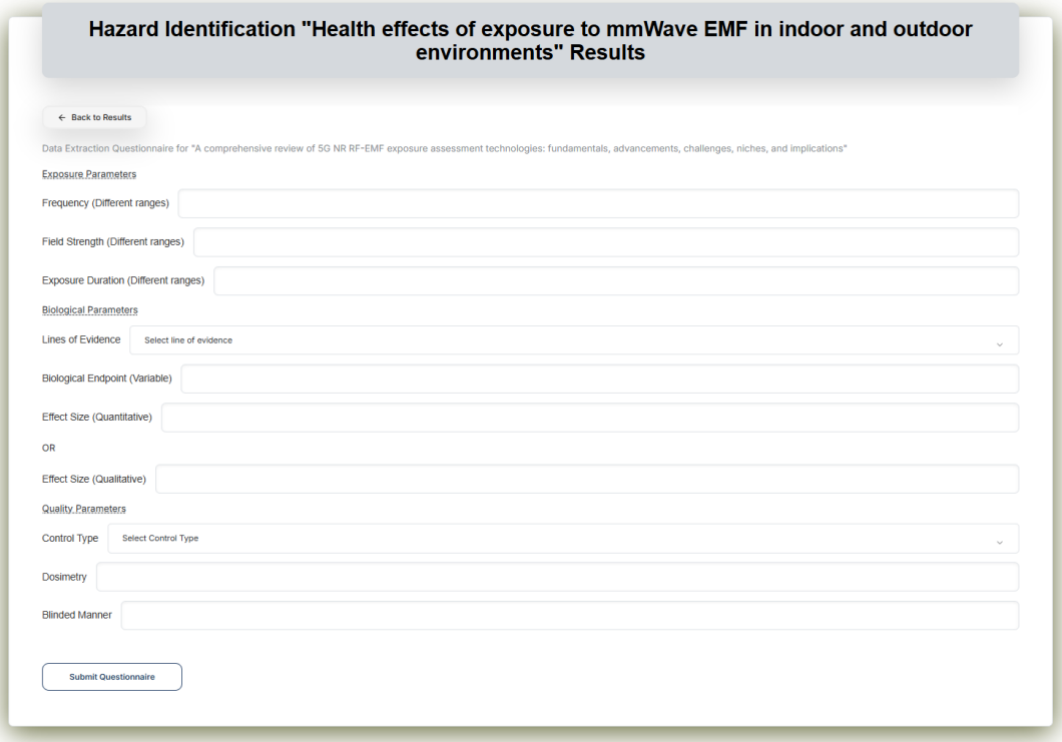


Figure 19: The Data Extraction questionnaire.

7.2.5 Risk of Bias

The tool also includes a dedicated form for evaluating the risk of bias for each paper. Assessors can answer predefined questions specific to the selected line of evidence, based on the selected risk of bias assessment method. More specifically, the RA tool is based on the OHAT RoB for Human and Epidemiological studies, and an adapted custom RoB specifically for in vitro, in vivo studies and in silico studies as described in Table 6.

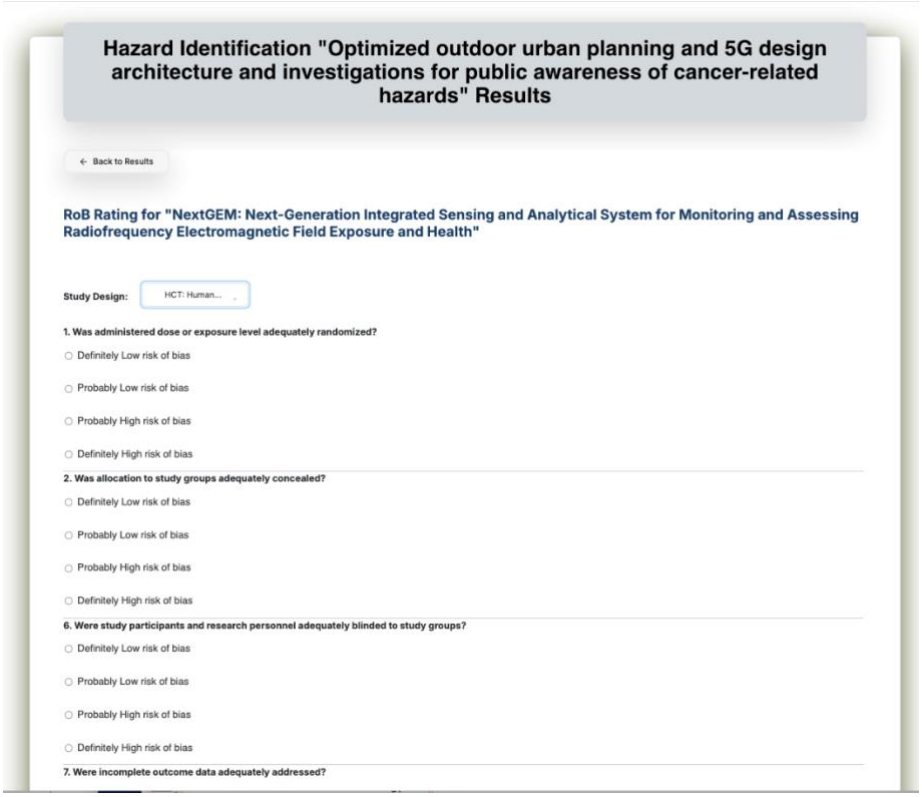


Figure 20: OHAT Risk of Bias for human and epidemiological studies

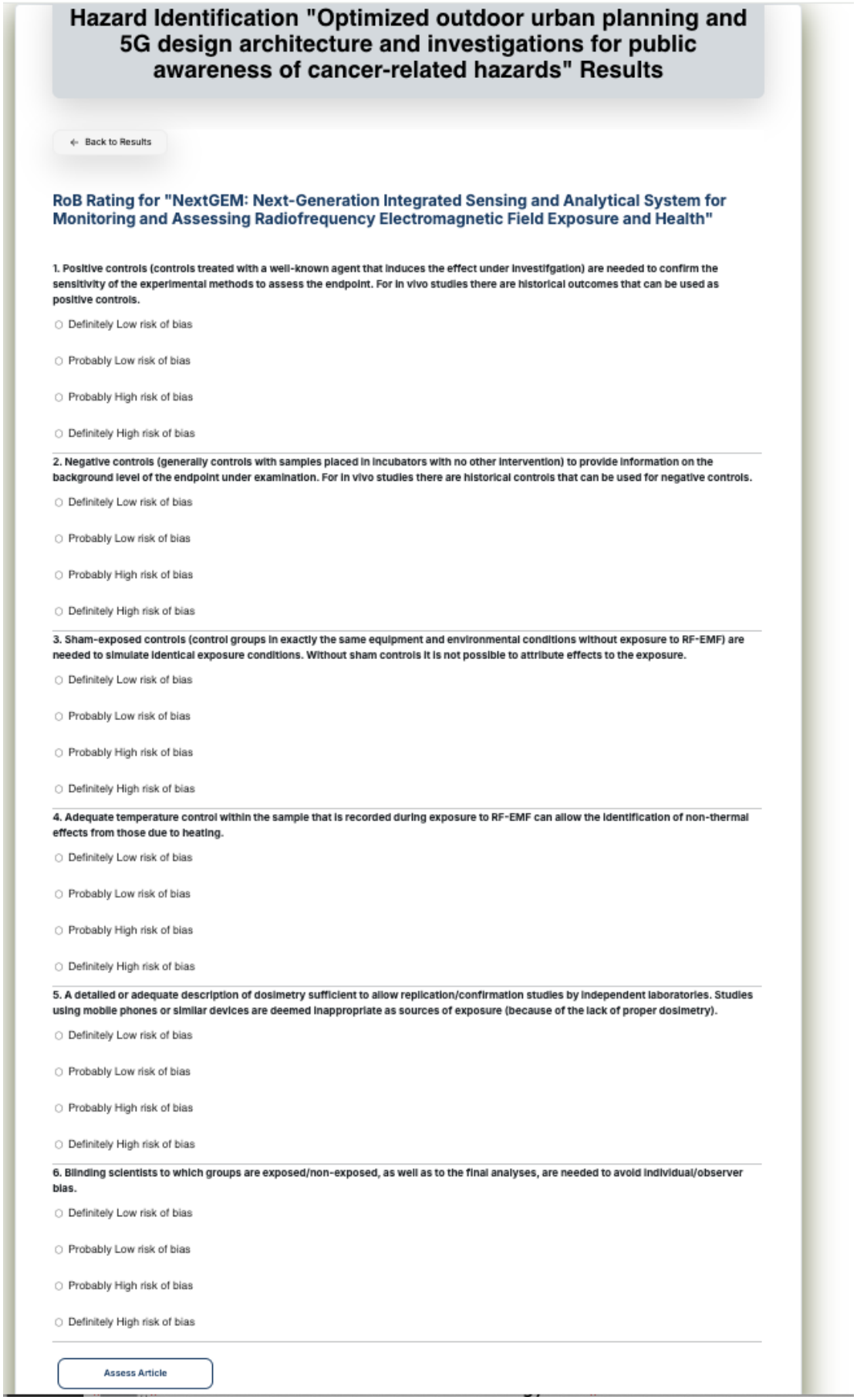


Figure 21: Adapted RoB for in vitro, in vivo and in silico studies

7.2.6 Summary

The final step in the protocol involves synthesizing the results and incorporating insights gained through the risk of bias evaluation process for all the different investigated references for the different lines of evidence, as presented in Figure 22.

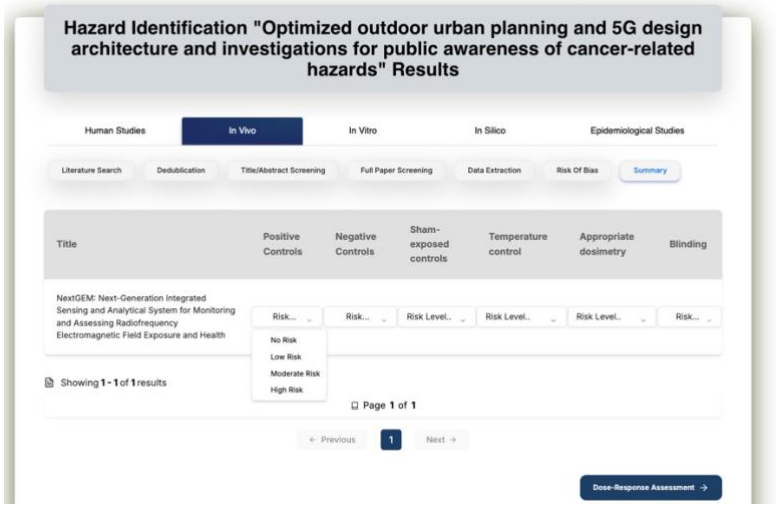


Figure 22: Summary of Adapted RoB for in vitro, in vivo, and in silico studies

Based on the summary for the different lines of evidence, the assessor can identify hazards on different health and effects and biological endpoints. Finally, the Hazard Identification page as well as the rest of the steps within NIKH's Risk Assessment methodologies (dose responses and exposure assessment) follow a similar approach the literature search but the main differences are the lines of evidence, data extraction and risk of bias.

7.3 Dose-Response Assessment

In the Dose-Response Assessment step (Figure 23), the risk assessor(s) aim to define the quantitative relationship between the level of exposure to an agent (e.g., RF-EMF) and the likelihood or severity of observed health outcomes. This step relies on data derived from experimental studies, controlled human studies, or computational modeling outputs. Epidemiological studies are not included in this step due to insufficient exposure precision and a lack of controlled conditions needed for quantifying dose-effect relationships.

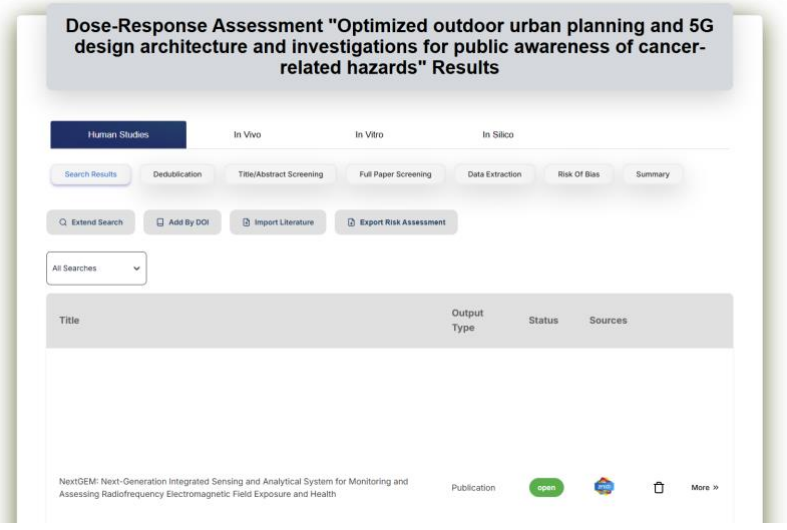


Figure 23: NIKH's Dose-Response Assessment form.

An approach similar to the one used in the Hazard Identification step is followed here. It begins with a literature search and continues through a structured assessment of each line of evidence: Human Studies, In Vivo, In Vitro, and In Silico. For each line of evidence, and each of the selected literature items, the same choices are available to the assessor as those described in the "Lines of evidence" sub-section in Section 7.2.

In the context of EMF research, dose-response data are notably scarce, with often only one or two applicable studies available. As a result, this step cannot be fully operationalized in most EMF-related assessments, and risk assessors are frequently limited to qualitative estimation. Nevertheless, the structured approach of the RA tool ensures consistency in how available data are processed and interpreted. The structured inputs collected during Dose-Response Assessment are carried forward to the Risk Characterization phase, where they contribute to estimating overall risk levels and establishing the weight of evidence for decision-making.

7.4 Exposure Assessment

Once Hazard Identification and Dose-Response Assessment have been completed, the risk assessor proceeds to the Exposure Assessment step (Figure 24), where the frequency, duration, and adequacy of exposure to the identified stressor are evaluated. In the context of EMF assessments within NextGEM, this refers to RF-EMF exposures resulting from various sources and technologies.

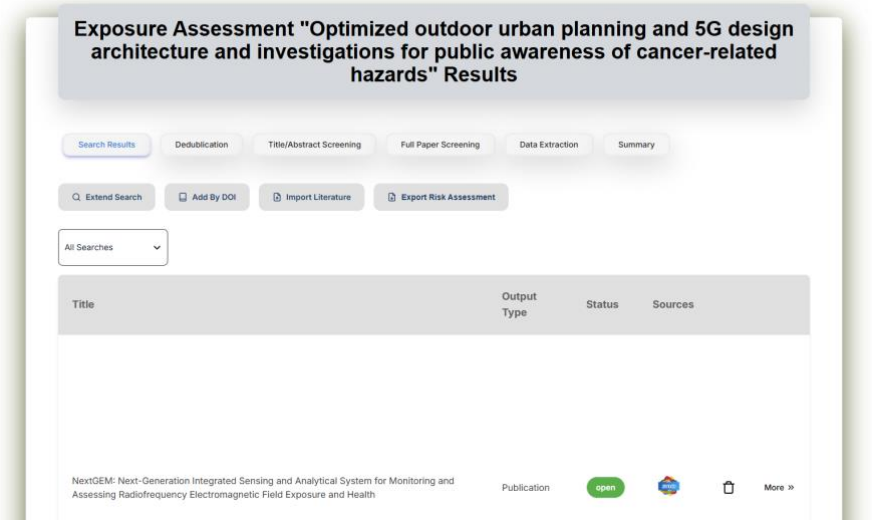


Figure 24: NIKH's Exposure Assessment form.

The NIKH platform allows users to input or retrieve exposure data from both modeling and measurement-based studies. Each reference is listed individually, with the following fields completed per study:

- Frequency, reported in hertz (Hz)
- Exposure duration, recorded in minutes, hours, or days
- Type of assessment, specified as either modeling or measurement
- Adequacy (yes or no), depending on whether the exposure assessment includes adequate dosimetry

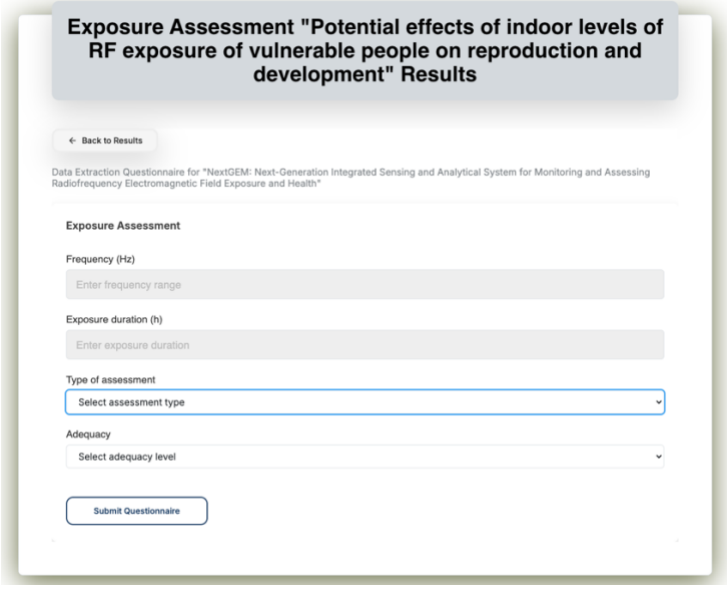


Figure 25: Exposure Assessment Data Extraction form.

References that include multiple frequencies or durations must be reported separately. This ensures that all exposure scenarios are distinctly recorded and appropriately evaluated. This structured format enables assessors to characterize the exposure context for each included study, document the methodological approach, and determine the relevance and quality of the exposure assessment in support of the overall risk evaluation.

7.5 Risk Characterization

Risk Characterization is the third step in the risk assessment process. It includes and evaluates the suitability of collected information at all stages of risk analysis, including hazard identification, dose responses, and exposure assessment. A key function of the risk characterization is to correlate biological endpoints and dose-response from relevant studies of different lines of evidence (i.e., in vitro, in vivo, human studies) and exposure assessment in relationships with health outcomes, aligning with the overall goals of EMF risk assessment.

In this step, the Risk Characterization is used to structure input from the previous steps by assessing each line of evidence (human studies, in vivo, in vitro, in silico and epidemiological studies) across multiple dimensions, as depicted in Figure 26.

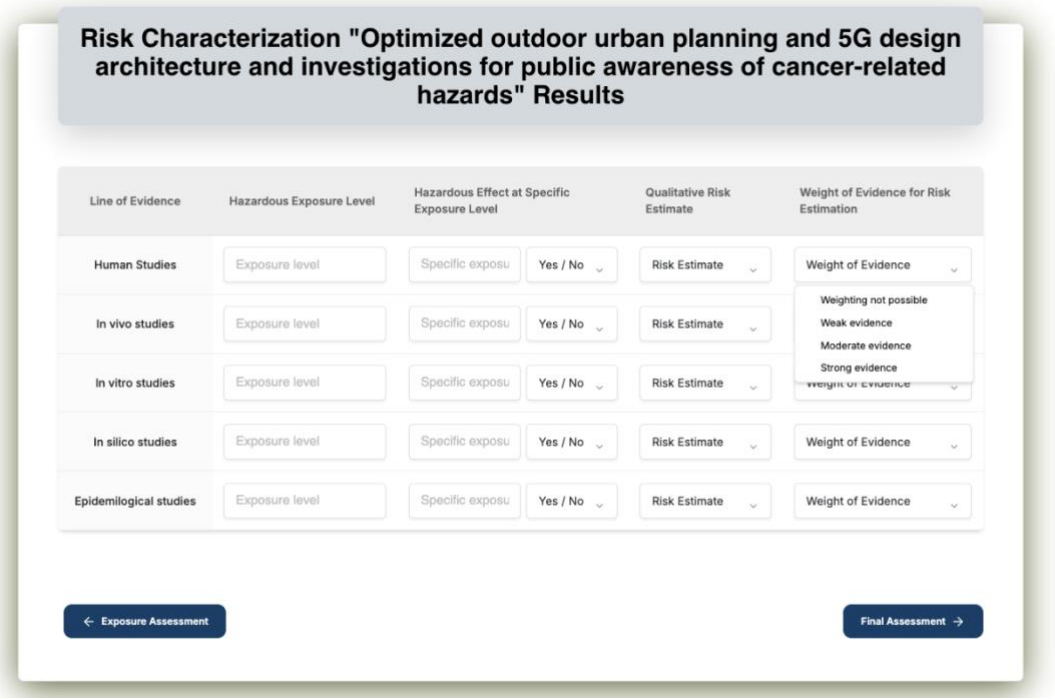


Figure 26: NIKH's Risk Characterization form.

The form includes four different fields for risk estimation corresponding to the investigated lines of evidence and different types of scientific data source assessments (human studies, in vivo studies, in vitro studies, in silico studies, and epidemiological studies). More specifically, to characterize a risk, the form collects the following:

- **Hazardous exposure Level**: Textual or numeric input describing the exposure level that is considered hazardous within that evidence line.
- **Hazardous Effect at a Specific Exposure Level**: Specific exposure level and Choice of Yes/No indicating whether a hazardous effect was observed at that specific exposure level.
- **Qualitative Risk Estimate**: Qualitative risk estimation by the assessor for low risk, moderate risk, or high risk
- **Weight of Evidence for Risk Estimation** - Weight of evidence of the assessor: Strong Evidence, Moderate Evidence, Weak/Uncertain Evidence, and Weighting Not Possible

7.6 Final assessment

After completing the four main steps of the risk assessment workflow, Hazard Identification, Dose-Response Assessment, Exposure Assessment, and Risk Characterization, the NIKH platform presents a Final Assessment page that consolidates all collected information and analytical judgments into a structured summary.

The final assessment will include the human health risk assessment as a process to estimate the probability of adverse health effects in humans who may be exposed to a physical or chemical agent in the environment, at present or in the future.

This page includes three main key components: the risk description, the health risk governance, and the risk estimation matrix, as can be seen in the Figure 27.

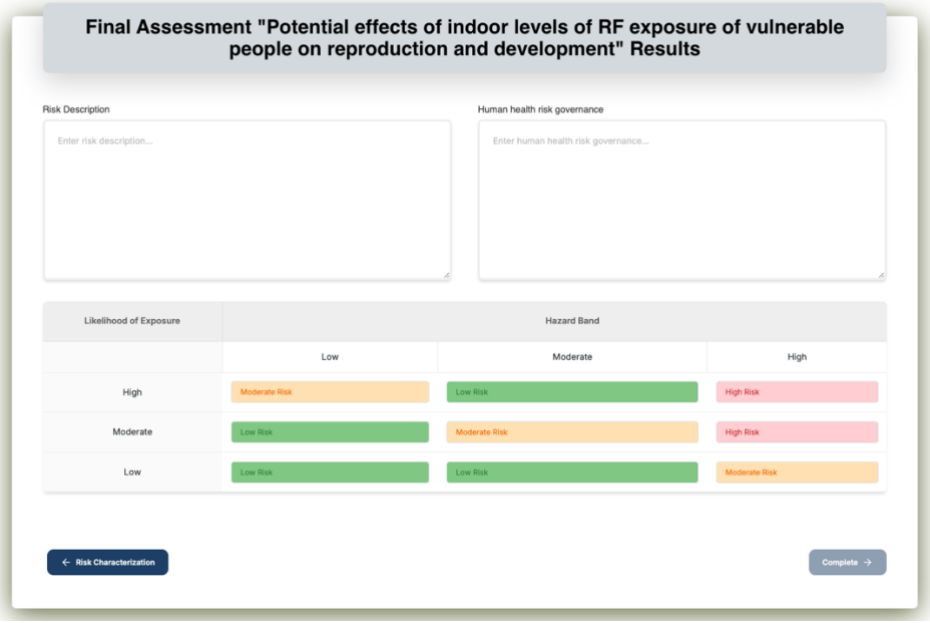


Figure 27: Final assessment form

More specifically, in the risk description form, the assessor can interpret the risk results, whether harmful effects are expected based on the available data by incorporating insights from each line of evidence (human studies, in vivo, in vitro, in silico, and epidemiological studies) as follows:

- **Risk description**: The risk description provides contextual interpretation of the risk characterization and estimation and clarifies whether harmful effects are expected based on the available data, taking into account RoB assessments. This structured format allows the weight of evidence for risk estimation to be clearly reported and traced back to specific types of data and assumptions.
- **Human health risk governance:** The health risk governance includes the analysis with regard to the human health risk governance needs, including risk communication, risk management, and regulation. Once the analysis is complete, the tool provides assessors with appropriate risk management strategies, supporting effective risk communication and mitigation efforts. The outputs are designed to meet the needs of relevant stakeholders, including scientists, regulators, and the general public, enhancing informed decisions.
- **Risk matrix**: Finally, the last part of this form includes the weight of evidence analysis, supported by a visual representation of overall risk levels. Risk estimation is calculated by combining the likelihood of exposure with the hazard band identified in earlier steps. The matrix displayed on the final report summarizes these intersections, assigning final qualitative risk levels (low, moderate, high) accordingly. For example, a scenario with a high likelihood of exposure and moderate hazard results in a high-risk rating, while a low exposure likelihood with low hazard results in a low risk.

Finally, when all the above steps are completed, the RA tool aims to generate a complete report that documents the entire risk assessment process, including all steps taken and results obtained. Since dedicated models and functionalities are still under development, efforts are underway to incorporate additional metadata from a variety of sources. Depending on the quality and quantity of available data, covering exposure assessment, hazard identification, and hazard characterization, the tool can perform risk assessment within the GUI of the RA Tool in the NIKH. This functionality allows users to conduct comprehensive risk evaluations efficiently, positioning the platform as a valuable resource for evidence-based decision-making and targeted risk management in RF-EMF exposure scenarios. Although the current version of the NIKH RA tool already supports several functionalities, the RA assessment tool is undergoing finalization to integrate the full set of risk assessment functionalities and will be validated in the case studies in WP7. This strengthens the significant role of NIKH in advancing EMF and health risk analysis.

8 Conclusions

This Deliverable has presented the major features of risk management, including the various components of risk assessment and the roles and expectations of stakeholders in these processes. Special emphasis is placed on human health risk assessment of RF-EMF exposures. For that purpose, more in-depth discussions of different risk assessment models (both qualitative and quantitative) and the specific considerations that are needed for the risk assessments in NextGEM are presented in the Deliverable. These considerations include the different LoE (epidemiology, human studies, in vivo studies, in vitro studies, in silico studies) that are included in the risk assessments, with a focus on exposures that do not give rise to tissue heating. The experimental work within the project is also performed at these exposure levels.

The Deliverable suggests that it is most realistic to adopt a qualitative risk assessment model for the continuing work. Such a model needs to be developed, adapted for the specific requirements of the projects, and tested and validated with data generated within the project (from ongoing experimental work and the coming case studies) and with additional data from the scientific literature. At present, the most appropriate model is a Weight of Evidence (WoE) model, considering all lines of evidence. This approach is also adopted for the development of the RA Tool, which is integrated into the NextGEM NIKH. A first step in developing and testing a WoE assessment model has been taken and is presented in the Deliverable, where published data from in vivo and in vitro studies have been collected and assessed regarding RF-EMF effects on key characteristics of carcinogenesis. We identified a strong association between the quality of the study and outcome, with those meeting more RoB criteria less likely to report statistically significant effects. Effects were reported over the entire frequency range, exposure levels, and biological endpoints, with no apparent pattern of exposure parameters resulting in effects. A few relatively high-quality positive studies require follow-up through additional targeted studies. The heterogeneity and overall poor study quality suggest the need for high-quality studies on these endpoints, preferably adhering to standards such as the Organization for Economic Co-operation and Development (OECD, 2018).

The current version of the NIKH RA Tool presented here already supports several functionalities, namely Hazard Identification, Dose-Response Assessment, Exposure Assessment, Risk Characterization, and Final Assessment. The RA Tool is presently undergoing finalization to integrate the complete set of risk assessment functionalities and will be validated in the case studies in WP7, where a further adaptation of the WoE assessment model will also take place. This process strengthens the significant role of NIKH in advancing EMF and health risk analysis.

Important lessons learned from the work are that the choice of useful risk assessment models is limited, and that the specific considerations regarding NextGEM activities necessitate customizing existing models for qualitative risk assessment. Furthermore, the model development, testing, and validation must go in step with the development of the RA Tool. Finally, the amount of useful data for risk assessment is limited due to disparity in experimental design and RoB issues.

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