NextGEM

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

D5.7: Identification of exposure protocols for a harmonized data collection - Final report

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Contributors and Peer Reviewers

Contributors
Anna Laromaine, Daniel Rodríguez, Núria Garriga, Carlos López (CSIC), Mats-Olof Mattsson, Myrtill Simkó (SPi), Fulvio Schettino (UCAS), Olga Zeni (CNR), Maryse Ledent, Seppe Segers, Birgit Mertens (SC), Francisco Vargas Marcos (MHS), Anna Yulievna Bogdanova (UZH), Mathieu Pruppers, Maarten Velghe (RIVM), Erdal Korkmaz, Sam Aerts, John Bolte (THUAS), Eduardo Soudah (CIMNE), Marco Spirito (TUD), Panos Chatziadam, Nikolaos Petroulakis (FORTH), Gregory Barshtein (HUJI)
Peer Reviewers
Stefanos Fafalios (SANL), Fulvio Schettino (UCAS)

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Glossary of terms and abbreviations used

Abbreviation / Term	Description
5G NR	5G New Radio
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CST	3D EM analysis software package for designing, analysing and optimizing electromagnetic (EM) components and systems
CV	Coefficient of Variation
CW	Continuous Waves
DMP	Data management plan
EMF	ElectroMagnetic Field
ERMES	Electric Regularized Maxwell Equations with Singularities – an open-source software which solves Maxwell's equations in the frequency domain with the Finite Element Method.
FAIR	Findable Accessible Interoperable Reusable
FDTD	Finite-Difference Time-Domain
FEM	Finite Element Method
FIT	Finite Integration Technique
FR1	Frequency Range 1 – 410 MHz to 7.125 GHz
FR2	Frequency Range 2 – 24.25 GHz to 52.6 GHz
GA	Grant Agreement
gNB	Next Generation Node B
GPS	Global Positioning System
GSM	Global System for Mobile communications
GTEM	Gigahertz Transverse Electromagnetic
Hb	Hemoglobin
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IEEE-ICES	Institute of Electrical and Electronics Engineers - International Committee on Electromagnetic Safety

IEI-EMF	Idiopathic Environmental Intolerance attributed to electromagnetic fields (IEI-EMF)
IMU	Inertial Measurement Unit
IUPAC	International Union of Pure and Applied Chemistry
LTE	Long Term Evolution
MD	Menadione
MGS	Madrid Grid Scenario
MoM	Method of Moment
MPE	Multiprotocol Encapsulation
NIKH	NextGEM Innovation & Knowledge Hub
PDE	Personal Distributed Exposimeter
PW	Pulsed Waves
RA	Risk assessment
RCM	Rate of Change Metric
RBCs	Red Blood Cells
RF-EMF	Radiofrequency ElectroMagnetic Field
RLC	Ray Launching Cassino
RMS	Root Mean Square
RTC	Real-time Clock
S3R	Smart Sensor Systems research group
SA	Spectrum Analyzer
SAR	Specific Absorption Rate
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SDR	Software-Defined Radio
SOP	Standard Operating Procedures
TAC	Total Antioxidant Capacity
TP3D	TIMPlan 3D

ULB	Université Libre de Bruxelles
UMTS	Universal Mobile Telecommunications System
UR	Umbrella Review
WAVES	imec-WAVES research group
WP	Work Package

Executive Summary

The deliverable D5.7, "Identification of exposure protocols for a harmonized data collection - Final report", is part of Work Package 5 (WP5) and continues the work done in D5.3 "Identification of exposure protocols for a harmonized data collection – Initial Report".

D5.7 provides an overview of how NextGEM is contributing to the creation of a Risk Assessment (RA) tool, a description of the scope and methodologies used within the project, the objective of each task, the quality criteria, and the results to date of each task, which will facilitate the integration of the RA tool into the NextGEM Innovation & Knowledge Hub (NIKH).

1 Introduction

1.1 Mapping NextGEM Outputs

This section aims 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 5.2- Collection of data for Risk Assessment from Experimental and observational studies	The basic existing assessments of risks associated with EMF exposure need to be improved and this is a capital objective of NextGEM. To this aim, relevant data from exposure assessment, *in vitro* and *in vivo* experiments, the level of evidence resulting from the umbrella reviews (URs) of human observational studies, and the evidence pertaining to experimental studies of carcinogenic effects of EMF in animal and cells models and the results of the human observational studies conducted within NextGEM will be integrated. Common exposure protocols will be defined at early stages of this project, to ensure the harmonized data collection required for a robust risk assessment.
DELIVERABLE	
Deliverable: D5.7: Identification of exposure protocols for a harmonized data collection - Final report (M34) This deliverable will establish the final basis for comparing different bio-experimental studies within the project.	

1.2 Deliverable overview and report structure

Based on the objectives and work carried out in Task 5.2, this document starts with the Executive Summary, followed by the document's introduction in Section 1.

Section 2 titled "Overview of the basic risk assessment associated with EMF", introduces health-related risk assessment (RA) and the previous research within the field of health and EMF.

Section 3 provides relevant data on exposure protocols in NextGEM from two perspectives: the modelling approach and the measurement approach.

Section 4 describes the exposure systems used and the experimental analysis performed in NextGEM, the objectives of each experiment or research approach, their scopes, the measures taken to ensure quality results, expected outcomes, and how this information would fit in the final RA tool.

Section 5 describes the harmonization protocols used for the project's different lines of research.

Finally, Section 6 concludes the deliverable.

1.3 Updates from previous Deliverable 5.3 "Identification of exposure protocols for a harmonized data collection – Initial Report"

This deliverable is the final, public version of the Identification of Exposure Protocols for a Harmonized Data Collection. In August 2024, an Initial Report (D5.3) was delivered, but it was not public. This version is an updated and extended version of D5.3, including the following enhancements:

- The Glossary of Terms has been expanded.
- Section 2 underwent some writing modifications to improve readability and comprehensibility.
- Subsection 2.2 now features Table 2 , which showcases the EMF exposure limits to prevent adverse effects on human health from the 2020 ICNIRP Guidelines [1] Table 3 was also updated.

- Section 3 underwent some writing modifications to improve readability and comprehensibility, and the research described has had its data, objectives, results, and expected results updated to the current state of the project.
- Section 4 underwent some writing modifications to improve readability and comprehensibility, and the research described has had its data, objectives, results, and expected results updated to the current state of the project.
- Subsection 4.4.1 now features Figure 2 and Figure 3.
- Section 5 underwent some writing modifications to improve readability and comprehensibility.

2 Overview of the basic Risk Assessment associated with EMF

This section provides a general overview of Risk Assessment (RA), which lays the foundation for the RA tool and NIKH.

Health RA aims to estimate the risk to a population or an individual from exposure to an agent of concern. The process considers:

- The type, composition or characteristics of the agent
- Its potential to cause harm
- How people may be exposed
- The duration and extent of exposure

The RA is not a stand-alone activity. Instead, it is one of the components of the risk management paradigm, which also includes risk mitigation and risk communication (Figure 1). The outcomes of a health RA are then used for regulatory purposes and risk management activities performed by competent authorities and employers.

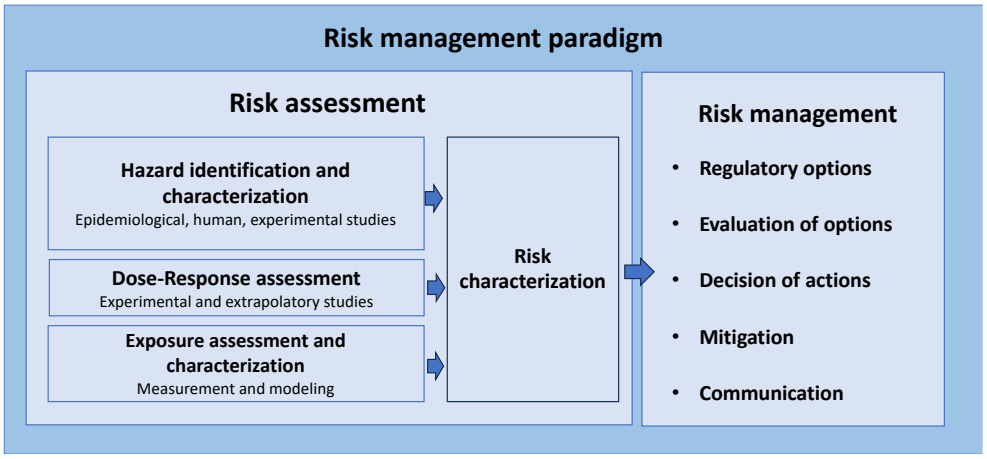

Figure 1: The risk management paradigm.

Risk in the context of human and environmental health is a function of hazard and exposure (from the International Union of Pure and Applied Chemistry (IUPAC), see [2]). Regarding risk assessment, a generally agreed-upon definition is not available. Still, within the community where risk assessment for human health and the environment is performed and observed, it is, for instance, seen by the Society of Toxicology as "a process by which scientists evaluate the potential for adverse health or environmental effects from exposure to naturally occurring or synthetic agents" [3].

The RA of the possible health effects of RF-EMF is similar to a risk assessment for any agent, whether physical, chemical, or biological. However, it is also necessary to consider the feature of dosimetry for *in vivo*, *in vitro*, and *in silico* studies, which makes RF-EMF RA more complicated than RA for other agents. Thus, the main features of RF-EMF RA are (Figure 1):

- Exposure assessment - describes the conditions of exposure. Characterization and determination are made by measuring or estimating exposure (magnitude, frequency/occurrence, and duration).
- Dosimetry - determination of absorbed energy in a biological structure, which is especially relevant for the determination of dose.
- Hazard identification - determines the potential hazard posed by a hazardous agent to human health.
- Hazard characterization - examination of dose-response relationships
- Uncertainty analysis.

A health RA typically evaluates the evidence within several areas of studies ("lines of evidence"), such as epidemiological, human, animal, cellular, modelling, and *in silico* studies. Obtaining data from different types of studies makes it thus possible to integrate the various pieces of data to perform an integrative RA. A more detailed description of the respective stages is available in NextGEM Deliverable D2.1. The conventional approach used for human RA has been hazard-driven, with a firm reliance on the use of laboratory animals as surrogates for humans.

However, the weakest point in many RAs is the proper characterization of exposure (external and internal dose). Consequently, many RAs are qualitative or, at most, semi-quantitative [4], [5], [6] and [7].

Several agencies and expert groups (national and transnational) have regularly performed evaluations of the potential for adverse effects of exposure to electromagnetic fields (EMF), including radiofrequency electromagnetic fields (RF-EMF). Several of these evaluations are not RA *per se* but provide possible hazard identifications under the specific conditions considered. A direct coupling between exposure levels, duration, and the magnitude of risk has often not been done. Nevertheless, important and influential documents have been published by WHO in 1993 [8], the European Commission's Scientific Committees SCHEER in 2023 [9], SCENIHR in 2015 [10], the International Commission on Non-Ionizing Radiation Protection (ICNIRP) in 2020 [11], and the Institute of Electrical and Electronics Engineers - International Committee on Electromagnetic Safety (IEEE-ICES) in 2019 [12]; as well as many other nationally assigned expert committees. However, none of these pertains to the newest generation of mobile communication technology, the 5G New Radio (5G NR). Specific criteria for the respective assessments are provided in the documents mentioned above. Furthermore, other publications provide general criteria for EMF health RA, such as Repacholi and Cardis [13] and Mattsson, Simkó et al. [14].

2.1 Exposure assessment of RF-EMF for risk assessment

Exposure assessment is crucial in RA and for the underlying scientific research. This section describes the role of determining exposure within the RA process. Once it has been determined which hazards are possible and above what doses (a combination of field strength and duration of exposure) or according to which dose-effect relationships the hazards display, the next question is what field strengths can occur in the public domain or in an occupational space or how the exposure is distributed over the population.

2.1.1 Exposure assessment in epidemiological studies

Epidemiological studies indicate that there may be a relationship between exposure to RF-EMF and the development or progression of health effects in humans. WHO commissioned ten systematic reviews of the most critical health outcomes, including cancer [15]. The available research on cancer focuses mainly on the development of tumours in the head and neck region as a result of mobile phone use [16], [17] (see also section 2.4).

Epidemiological research concerning RF-EMF is carried out to determine whether there is a possible hazard in relation to exposure. A highly exposed group of people is usually compared with a non- or lowly-exposed group. Especially in the case of health effects with a low incidence in the population, it is usually impossible to distinguish more than two groups of exposed people. To ensure that risk analysis can ultimately be carried out, the measurements of exposure in daily practice must be adapted to the chosen groups of exposed people. There are several reasons why carrying out epidemiological research on EMF and interpreting the findings is a challenge and why it generates uncertainties that vary depending on which effect on health and which source of exposure is under investigation. The key sources of error arise from estimating exposure, controlling for confounders, and the possibility of reverse causality. For example, studies on long-term effects have primarily focused on associations between mobile phone use and head and neck tumours. Such tumours are rare, so the relevant research has mainly involved case-control studies. Participants must retrospectively state how often they have used their mobile phones. This gives rise to considerable uncertainty due to recall bias. Indeed, there are indications that tumour patients give higher estimates of their mobile phone use in retrospect than healthy individuals, which leads to overestimating potential risk factors (false positive finding) [18], [19]. On the other hand, random errors in the exposure estimation can result in significant exposure misclassification, leading to an underestimation of potential risk (false negative finding) [20], [21]. This is particularly true because mobile phones have efficient output power regulation, so the amount of time the mobile phone is used is an imprecise proxy for the radiation dose received by the head.

Due to these limitations, cross-sectional studies provide only limited meaningful information on health effects. As a rule, longitudinal studies are less susceptible to confounding but are very complicated and costly to implement. However, in longitudinal designs, assessing EMF exposure remains a challenge, as it is largely based on self-reporting. Toledano et al. [22] highlight several factors that can affect the validity of mobile phone use reporting.

2.1.2 Exposure assessment in *in vivo* and *in vitro* studies

Additional evidence can be obtained from animal studies about the causality of the correlation found in epidemiological studies. Here, too, the practice is that a limited number of exposure categories are distinguished; however, unlike in epidemiological studies, a comparison with a population of unexposed animals is possible. *In*

vivo studies are quite powerful for health RA. However, the disadvantage of *in vivo* studies lies in the degree to which the results obtained can be extrapolated to humans because of the inter- and intra-species variation.

In vitro assays investigate toxicological, mechanistic, and other relevant effects and provide evidence for a possible understanding of disease development by investigating various biological endpoints. *In vitro* studies have been used mainly for hazard identification. The International Agency for Research on Cancer (IARC) increasingly considers mechanistic (*in vitro*) studies for RA to get information about carcinogenesis, possibly underpinning results from epidemiological studies [23]. Accordingly, *in vitro* studies are increasingly important for RA to understand mechanistic knowledge and perform dose-dependent studies to identify possible threshold(s) for the agent in question.

Many *in vivo* and *in vitro* studies show inconsistent results because of the many biological and physical variables they use (different animal models, cell types, frequencies, SAR values, duration of exposure and observed biological endpoints). The result is a large number of studies that cannot be compared with each other. Consequently, there is no "critical mass" in terms of studies on specific endpoints. Other problems are a lack of reproducibility in the first place and, thus, a lack of replication studies. Other aspects that make evaluating and discussing results difficult are poor quality in describing exposure conditions and a lack of controls (positive, negative, sham) in many studies. Without positive controls, effects cannot be evaluated because it is impossible to compare findings. This means that the results cannot be analysed and understood in the correct context, and data from such publications cannot be included in RA. Experiments must, therefore, always be carried out under strictly controlled exposure conditions using relevant controls (see 2.5).

2.2 Existing exposure risk assessment using modelling approaches

EMF exposure limits establish the maximum allowable radiation levels to prevent adverse effects on human health (see Table 2) [1]. These limits ensure safety in various contexts, including occupational and public environments. During the NextGEM project, computational models (modelling approaches) will be used to evaluate the relevance of the current limits. We will gather data on current exposure conditions, including the intensity, frequency and modulation of the EMF used for the different case studies/experiments carried out during the NextGEM project. These data will be used to create computational models to simulate and analyse how EMFs interact with human bodies, animals and cells, focusing on the effects of mobile phones (local or "near field" exposure) and base stations operating in the 5th generation (5G) communication systems (whole-body or "far field" exposure). The results will allow for prioritizing risks based on their probability and impact and developing appropriate mitigation strategies by re-examining current exposure limits, optimising network deployment, and potentially considering protective shielding.

Table 2: Basic restrictions for electromagnetic field exposure from 100 kHz to 300 GHz, for averaging intervals ≥6 min. From ICNIRP 2020 Guidelines [1]

Exposure scenario	Frequency range	Whole-body average SAR (Wkg^{-1})	Local Head/Torso SAR (Wkg^{-1})	Local Limb SAR (Wkg^{-1})	Local S_{ab} (Wm^{-2})
Occupational	100 kHz to 6 GHz	0.4	10	20	NA
	>6 to 300 GHz	0.4	NA	NA	100
General public	100 kHz to 6 GHz	0.08	2	4	NA
	>6 to 300 GHz	0.08	NA	NA	20

Note:
1. "NA" signifies "not applicable" and does not need to be taken into account when determining compliance.
2. Whole-body average SAR is to be averaged over 30 min.
3. Local SAR and Sab exposures are to be averaged over 6 min.
4. Local SAR is to be averaged over a 10-g cubic mass.
5. Local Sab is to be averaged over a square 4-cm2 surface area of the body. Above 30 GHz, an additional constraint is imposed, such that exposure averaged over a square 1-cm2 surface area of the body is restricted to two times that of the 4-cm2 restriction.

For local exposure, computational models directly solving Maxwell's equations using full-wave techniques such as Finite-Difference Time-Domain (FDTD), Finite Element Method (FEM), Finite Integration Technique (FIT), and Method of Moments (MoM) will be employed. However, these methods are unsuitable for large-area calculations, such as those that are relevant for the whole body, due to high computational memory requirements and costs. An

alternative for assessing exposure for large areas is to use ray tracing and ray casting methods. These methods offer good approximations with lower computational costs. They involve launching rays from an antenna, considering the radiation pattern, and evaluating how they are reflected, transmitted, or diffracted depending on the surrounding materials. The combination of geometric and physical optics allows the characterization of wireless propagation and RF-EMF exposure in complex outdoor/indoor scenarios. Another approach combines heuristic predictions and ray tracing methods to calculate the dominant path between the transmitter and receiver. Deliverable D2.2 describes the statistical, deterministic, and numerical methods for computational electromagnetics.

Assessing exposure in electromagnetism using computational models is essential to guarantee safety in various contexts. However, these methods have disadvantages, such as requiring high computational resources, including large amounts of memory and processing power, making them slow and costly, as mentioned earlier. Complex simulations, especially in three dimensions, can take a long time. Additionally, modelling complex geometries and creating precise meshes are labour-intensive and error-prone processes that can compromise the accuracy and stability of the numerical results. Limitations in modelling materials can be challenging and require sophisticated experiments to determine such electromagnetic exposure. Validation and verification of the results are also crucial but difficult to achieve without precise experimental data. Furthermore, the required specialized software and hardware resources are expensive, and effectively using these tools demands deep knowledge and a considerable learning curve. Therefore, although powerful, these numerical models must be used with caution and an understanding of their limitations.

2.3 Existing sensing technologies to measure EMF exposure

D3.5, as summarised here, presents a detailed analysis of existing sensing technologies. State-of-the-art RF-EMF measurement technologies span high-end commercial instruments and innovative custom-developed sensors, each suited to different applications and measurement requirements. Advances in Software-Defined Radios (SDR) technology and low-cost sensor nodes enhance the feasibility of widespread, continuous RF-EMF monitoring, supporting the development of new sensing solutions for emerging communication technologies.

2.3.1 High-End Commercial Instruments

Frequency Scanning and Selective Instruments: Spectrum Analyzers (SAs) detect, demodulate, and evaluate signals across a wide frequency range. They employ a heterodyne receiver architecture involving RF filtering, down-conversion, and digital signal processing, enabling measurements up to 85 GHz with sensitivity below -160 dBm/Hz and analysis bandwidths over 8 GHz. Network scanners, derived from SAs, are optimized for field campaigns, scanning multiple frequency bands and supporting both passive and active scanning modes.

Two primary methods for assessing RF-EMF exposure include measuring instantaneous electric-field strength ($\mathbf{E}_{\mathbf{avg}}$) and extrapolating maximum exposure ($\mathbf{E}_{\mathbf{max}}$) based on dominant signal beams. Instruments like the N9020A SA and R&S FSV-30, along with tri-axial probes, are frequently used in these assessments.

Broadband Field Meters and Area Monitors: Broadband field meters with tri-axial probes, such as the Narda FieldMan, measure total electric field strength across wide frequency ranges. These devices often feature diode-based or true Root Mean Square (RMS) sensors, with sensitivities as low as 0.2 V/m for FR1 and 0.7 V/m for FR2 bands. Area monitors, such as the Narda AMB series and WaveControl MonitEM, offer autonomous operation with enhanced sensitivity (0.01-0.05 V/m) and broadband and selective monitoring capabilities.

2.3.2 Custom-Developed Instruments and Sensors

SDR-Based Sensor Nodes: SDRs provide a cost-effective, compact solution for RF-EMF exposure measurements. SDRs, such as the Adalm-Pluto, can be reprogrammed to operate across broad frequency ranges (up to 6 GHz), enabling detailed time-domain and frequency-domain analysis. Due to their programmability and adaptability, these nodes are essential for large-scale deployments.

Hardware-Based Compact Measurement Nodes: With the rise of the Internet of Things, low-cost, compact sensor nodes are being developed for continuous RF-EMF monitoring. These nodes, such as the S3R and WAVES, use specific frequency bands and incorporate bandpass filters, low-noise amplifiers, and power detectors to convert RF signals to measurable data. They are designed for ease of deployment and can measure multiple bands relevant to Global System for Mobile Communications (GSM), Universal Mobile Telecommunications System (UMTS), Long Term Evolution (LTE), Wi-Fi, and 5G NR.

2.3.3 Exposimeters

Commercial Exposimeters: Devices like the ExpoM-RF 4 and EME Spy Evolution are widely used for personal exposure measurements. These exposimeters cover frequencies up to 6 GHz, offering customizable frequency bands, high sensitivity (0.005 to 0.05 V/m), and dynamic ranges of 56 to 60 dB. They also feature GPS logging and user-defined sampling intervals for detailed exposure tracking.

Lab-Built Exposimeters: Innovative designs like the Personal Distributed Exposimeter[1] (PDE) and the PDE helmet aim to reduce measurement uncertainties caused by body shadowing. These devices use multiple nodes or antennas distributed on the body or head to capture comprehensive exposure data. Other lab-built systems mimic spectrum analyzers, offering high-resolution measurements across a broad frequency range with significant dynamic power measurement capabilities.

2.3.4 Software application

An application like xMobiSense(Plus) [24], [25] is able to capture a large amount of data on the phone's telecom traffic, making it useful in certain epidemiological settings.

The XMobiSense(Plus) app, as used in the COSMOS project[2], is an Android application developed to collect detailed data on mobile phone usage in order to assess potential health effects related to exposure to RF-EMF. By tracking how frequently users make calls, use data, or hold their phone during calls, the app provides researchers with more accurate insights than traditional self-administered questionnaires. It aims to support studies on the impact of phone usage on health while ensuring privacy by not recording personal information such as call numbers or message content.

2.3.5 Data management

Activities such as measurements, calibration, numerical simulations, and biological studies produce data. Data management in EMF sensing involves collecting, securing, and analyzing data from various activities. Field surveys detect daily, and occupational exposures linked to absorbed fields in the body through simulations and related to biological effects via *in vitro* and *in vivo* studies.

Data collection involves specific challenges due to the stochastic nature of 5G NR networks, which necessitate high external sampling rates. This results in large volumes of data and increased power consumption. While lab environments can effectively manage these high data rates, autonomous field devices require trade-offs, such as high-density sampling over shorter periods, to optimize performance and power efficiency.

2.4 Evidence from Umbrella Reviews of Human Observational Studies on EMF Health Risks

2.4.1 Objective

We understand scientific evidence as the body of knowledge relevant to a given topic and informative regarding specific public health questions. Scientific evidence is verifiable and should be reproducible by qualified researchers. The quality of the evidence indicates the extent to which we can be confident that the effect estimator is correct, and the strength of a recommendation shows the extent to which we can be confident that implementing the recommendation carries more benefit than risk.

Within NextGEM, the objective of this analysis is to provide a systematic review of the main factors and value drivers that influence the population's confidence and risk perception (D2.3, Task 5.1) to provide the systematic literature reviews, umbrella reviews of systematic reviews, and meta-analyses of epidemiological studies on EMF exposure and cancer in the general and working population provided by human observational studies.

2.4.2 Quality criteria

Systematic literature reviews effectively answer a research question in a protocolized, reproducible, and explicit manner. Given their strict protocol, in particular, for those registered in PROSPERO [26], they minimize the risk of bias, thus allowing informed decisions based on the best evidence.

Analysing the quality of studies allows one to rank the weight of evidence and the strength of their recommendations. However, the exponential growth of scientific information makes it very difficult to select,

[1] https://www.waves.intec.ugent.be/research/wireless/wbans/PDE

[2] https://thecosmosproject.org/xmobisense-app/

summarize, and assess the evidence capable of informing effective public health decision-making. Not all studies that are labelled or disseminated as scientific are equally valid. For example, well-designed human studies (randomized and blinded), systematic reviews, and meta-analyses have more scientific rigour and, therefore, more value than single case studies.

Most of the studies in this section are systematic reviews that meet standardized quality and validity criteria accepted by the scientific community (e.g., PRISMA [27], Grade of Evidence-SCHEER [28], etc.)

2.4.3 Scope and Expected Results

In Table 3, we summarize the revised epidemiological studies and systematic reviews on health effects and RA of RF-EMF (100 kHz-300 GHz) and 5G and some of the conclusions of these agencies and committees that support the decisions of public health authorities. These publications set the framework and study for further developments within NextGEM.

To improve the quality, relevance, and reliability of observational epidemiological studies, the World Health Organization (WHO) has promoted a project to assess the potential health effects of RF-EMF exposure in the general and working population. A protocol for a systematic review of human observational studies on the risk of neoplastic diseases has been published [29]. Applying this protocol to conduct these studies should help improve the quality of such studies and reduce subjective and biased interpretations of study results.

Agencies and committees have conducted RA and systematic reviews of all health effects (fertility and reproduction, symptoms affecting health, electromagnetic hypersensitivity, neurological, immunological and neuroendocrine, haematological effects, etc.) associated with RF-EMFs. The most studied adverse effects are related to mobile phone use and its association with brain malignant (glioma) tumours or benign (meningioma, acoustic neuroma, salivary gland) tumours.

These agencies' conclusions state that there is no scientific evidence that exposure to emission levels below those set out in the Recommendation of the Council of Health Ministers of the European Union on Public Exposure to Electromagnetic Fields and by ICNIRP guidelines produces health effects in the population.

Analysis of trends in the incidence rates of tumours of the central nervous system (CNS) over long periods can help identify risk factors related to the aetiology (causes) and prevention of the disease. According to data published by REDECAN (Spanish Network of Cancer Registries) [30] and ISCIII [31], no relationship is observed in Spain between the number of mobile phone users and the incidence of brain tumours and leukaemias. Similar conclusions are found for the Nordic countries [32].

Meta-analyses of epidemiological studies examining the risk of cancer in the following tumour locations and types: head, malignant brain cancer (gliomas), benign brain tumour (meningiomas), acoustic neuromas, pituitary gland tumours, and salivary gland tumours, do not show an increased risk associated with prolonged use (at least 10 years) of mobile phones. Although some case-control studies have reported significant increases in risk in people with moderate mobile phone use, these observations are inconsistent with results from cohort studies, and with brain tumour incidence rates over time, despite increased exposure.

Experimental provocation studies with volunteers who claim to have an Idiopathic Environmental Intolerance attributed to electromagnetic fields (IEI-EMF) fail to demonstrate they are capable of detecting EMF when exposed to them.

All agencies, institutions, and authorities involved with assessing the health risks of people exposed to RF-EMF agree that no evidence of health risks derived from exposure to RF-EMF emitted by radio stations at levels below limit guidelines has been observed.

The update and summary of the best scientific evidence obtained from the most recently published systematic reviews on health effects, cancer and RA of RF-EMF conducted by national and international agencies, organisations, and committees with proven expertise and professional competence, will allow us within NextGEM, to identify whether these reviews have observed any association or causal relationship between RF exposure and cancer, especially CNS tumours.

Table 3: Systematic reviews on health effects and risk assessment of RF-EMF (100 kHz-300 GHz) and 5G

Organisation	Methodology / Type of Study	Conclusions
ISS Italy 2019 [33]	Systematic review and meta-analysis of studies published between 1999-2017	There is no scientific evidence that exposure to radio frequencies "can cause cancer in humans or animals. According to current epidemiological evidence, the use of mobile phones is not associated with the incidence of neoplasms in the areas most exposed to radiofrequency during voice calls." The possible association between exposure and cancer risk has been weakened and does not require "changes in the configuration of current protection standards." No increased risks of malignant (glioma) or benign (meningioma, acoustic neuroma, salivary gland tumours) are detected in relation to long-term use (10 years) of mobile phones.
WHO 2020 [34]	Evidence revision. Statements on 5G	No adverse health effects related to exposure to wireless technologies have been observed on health effects from studies of the entire RF spectrum. So far, very few studies have been conducted on 5G as its deployment is in its infancy. The WHO is conducting an EMF RA, which will be published when it is finalized.
HCN The Netherlands 2020 [17]	Narrative review[3] on 5G. Recommendations.	There is no reason to stop or restrict the use of these frequencies. Monitoring exposure levels during and after the deployment of the 5G network in order to estimate its long-term effects. Conduct further epidemiological research on the relationship of 5G to tumour incidence and other health effects, Experimental studies in the 26 GHz bands and studies on human exposure to 3G, 4G and 5G networks. - Do not use 26 GHz frequencies until potential health effects are investigated. - Apply ICNIRP guidelines in the Netherlands with a precautionary approach and keep exposure as low as possible.
ANSES France 2018 [35] **and 2022** [36]	Systematic review on electromagnetic hypersensitivity (2018) Narrative review on 5G (2022)	Published studies do not provide convincing evidence of a causal relationship between exposure to radiofrequency fields and symptoms reported by people claiming to be electromagnetic hypersensitive to them. There is currently no scientific basis for linking exposure to electromagnetic fields and such symptoms. In relation to 5G, it has been estimated that its deployment in the 3.5 GHz frequency is "unlikely" to present new health risks, although for the 26 GHz frequency band - which is planned to be launched later - the data are not yet "sufficient" to draw conclusions. Exposure induced by 5G deployment in the 3.5 GHz frequency band does not constitute a new health risk.
ICNIRP 2020 [1]	Narrative systematic revision of scientific evidence. Risk assessment Guidelines.	No adverse health effects from electromagnetic emissions from mobile phone networks at reference levels established by ICNIRP. ICNIRP 2020 guidelines establish no more restrictive exposure levels than the 1998 ones. Additional restrictions have been introduced to consider situations in which the ICNIRP (1998) restrictions did not adequately account for, due to the appearance of new technological developments since then, such as aspects related to 5G technologies.
SSK Germany 2021 [37]	Narrative and scoping review. FR1 frequencies (2G, 3G, 4G and 5G).	There are no health risks for exposed persons (within the framework of the maximum values set for base stations and receiving apparatus). The greatest risk comes from receiving devices ("near-body") and not from base stations. They indicate that 88% of the exposure of the human brain comes from the mobile phone (smartphone).
JRC EU 2021 [38]	Systematic narrative review (last 5 years).	No adverse health effects from electromagnetic emissions from mobile phone networks were observed in this study. No correlation detected between mobile phone use and the incidence of brain and central nervous system tumours.
SCHEER EU 2022 [9]	Systematic review.	A revision of the annexes in the Council Recommendation 1999/519/EC and Directive 2013/35/EU. Meta-analyses, systematic reviews, and, when necessary, narrative or scope reviews and single

[3] "Narrative review is an umbrella term for a collection of review types in which the review process goes beyond an opinion or commentary. In a narrative review, researchers can pursue an extensive description and interpretation of previously published writing on a chosen topic." [105]

		research papers published after and including 2015 on RF-EMF (100 kHz to 300 GHz). Not identify moderate or strong level of evidence for adverse health effects resulting from chronic or acute RF-EMF exposure at levels below the limits set in the annexes of Council Recommendation 1999/519/EC and Directive 2013/35/EU. Advises positively on the need of a technical revision of the annexes in Council Recommendation 1999/519/EC and Directive 2013/35/EU about radiofrequency electromagnetic fields (100 kHz to 300 GHz).
SSM Sweden 2022 [39]	Systematic review.	No new established causal relationships between EMF exposure and health risk have been identified. The new evidence indicates that there is no risk to the health of the population exposed to RF from Base Stations, wireless networks, radio and TV transmitters, or wireless data networks used in schools or homes. Regarding electromagnetic hypersensitivity, the SSM has already established (2016) in previous reports that the studies analysed do not provide evidence that exposure to EMF is a causal factor.
CCARS Spain 2024 [40]	Systematic review (2020-2022)	The report provides a comprehensive and updated overview of RF-EMF studies and their potential effects on human health, highlighting the importance of ongoing and rigorous research. From evaluating the state of science and considering all the studies analysed, it can be deduced that no significant adverse effects on human health are identified, and the need to maintain constant monitoring and evaluation of all mobile telecommunications technologies, including 5G, is emphasized. International collaboration and scientific consensus will be essential to inform future public health policies and safety recommendations.
SSM Sweden 2024 [41]	Systematic review Reviews studies on electromagnetic fields (EMF) and health risks, published from January 2021 up to and including December 2021	The report gives the authority an overview and provides an important basis for RA. No new established causal relationships between EMF exposure and health risk have been identified. New research on brain tumours and mobile phone use aligns with previous research suggesting mostly an absence of risk. The thyroid gland is potentially highly exposed during mobile phone calls, but little research on thyroid cancer has been conducted so far. The results of the research review give no reason to change any reference levels or recommendations in the field. However, the observations of biological effects in animals due to weak radio wave exposure clearly show the importance of maintaining the Swedish Environmental Code precautionary thinking.
Karipidis et al. 2024 [42]	Systematic review. Reliance on evidence based on GRADE. PROSPERO Risk of Bias Assessment (OHAT Office of Health Assessment and Translation) 1994-2022.	The objective of this review was to assess the quality and strength of the evidence provided by human observational studies for a causal association between exposure to RF-EMF and risk of the most investigated neoplastic diseases Exposure to RF-EMF from mobile phones is not associated with an increase in glioma, meningioma, acoustic neurinoma, pituitary tumours, salivary gland tumours and paediatric tumours (children, adolescents and young adults).
Karipidis et al. 2025 [43]	Systematic review. Reliance on evidence based on GRADE. PROSPERO Risk of Bias Assessment (OHAT Office of Health Assessment and Translation) 1994-2022. 26 articles, which were published between 1988 and 2019.	It is the second part of the previous study which is published in two articles. This part is based on the study of less researched neoplasms, which include lymphohematopoietic system tumours, thyroid cancer and oral cavity/pharynx cancer, in relation to wireless phone use, or occupational RF exposure. For near field RF-EMF exposure to the head from mobile phones does not increase the risk of leukaemia, non-Hodgkin's lymphoma or thyroid cancer. For occupational RF-EMF exposure does not increase the risk of lymphohematopoietic system tumours or oral cavity/pharynx cancer. There was not sufficient evidence to assess the effect of whole-body far-field RF-EMF exposure from fixed-site transmitters (broadcasting antennas or base stations), or the effect of RF-EMF from any source on any other important neoplasms.

2.5 Determination of parameters and experiments to be improved to obtain robust assessment

Experimental (*in vivo*, *in vitro*) studies investigate causal relationships between dependent or independent variables and measure their effect on one or more variables to detect/test cause-and-effect relationships. In research on RF-EMF, it is necessary to obtain a detailed assessment of the RF-EMF dose and detailed information on the source-specific exposure duration and output power (exposure conditions, duration, field strength, SAR). This information is required to carry out dose-dependent experiments and ensure a study's reproducibility.

It is well known that many results reported in the research literature (in biomedicine and psychology, but also in various other disciplines) cannot be independently reproduced, which undermines the foundations of science. The irreproducibility is due to various factors that decidedly influence experimental outcomes. Planning the design and execution of the experiment enables high-quality results and reproducibility. In contrast, a lack of planning may result in a study being statistically underpowered, having no or inadequate controls, having selective data analysis, inappropriate statistical analysis and/or investigator bias or fraud. Moreover, the lack of validation/authentication of the reagents used in the experiments can also lead to irreproducibility. This includes, besides the reagents, the used cell lines, the animal models and antibodies, etc., in a study [44]. A further irreproducibility problem, particularly in RF-EMF research, is an unsuitable exposure setup and the lack of proper dosimetry. In many studies, mobile phones or WLAN routers, etc., are used as exposure sources to investigate the effects of RF-EMF. Since the exposure conditions cannot be described correctly by applying such exposure sources, the experiments are neither useful for RA nor reproducible and difficult or impossible to analyse.

In a detailed review by IARC [45], it was concluded that many laboratory studies had methodological flaws and weaknesses in reporting, such as the absence of sham-exposed or cage-control groups, the use of mobile phones as the exposure source, and failure to measure exposure to RF, the use of small numbers of cells (samples for evaluating, e.g. genetic damage), and lack of dosimetry. It was also pointed out that many studies were affected by significant temperature increases in cell cultures, resulting in thermal effects that could not be distinguished from non-thermal RF-induced changes. Proper temperature control during the exposure could give answers in such a condition. However, many studies do not use correct temperature controls. As a result, RF-EMF studies, particularly *in vitro* studies, have produced rather contradictory results. In many cases, determining whether certain effects occur has not been possible.

Details of what constitutes a high-quality *in vitro* study have been described before [46], [47] and [48]. In summary, high-quality studies must include an accurately and reliably described exposure system, adequate description of the dosimetry, data analyses using standard methods, the use of positive, sham exposure and temperature controls as appropriate for the study, blinded data collection and analysis to avoid individual bias, and at least three independent experiments for each outcome to allow good statistical analyses.

Here, we focus on the importance of clearly describing the exposure conditions since that is the number one tenet for the investigations. Guidelines for systematic reviews in public health exist and have been widely used for a long time [49]. However, no published guidelines exist for systematic reviews of mechanistic (*in vitro*) studies with an *in vitro* exposure setting [50].

Thus, what exposure metrics are needed for good quality, well-controlled *in vitro* exposure to RF-EMF? According to Romeo et al. 2021 [51] the following criteria are crucial:

- **Frequency bands:** 100 kHz to < 10 MHz; 10 MHz to ≤ 6 GHz; > 6 GHz to ≤ 300 GHz
- **Metrics:**
    - Induced electric field (E_{ind}, V/m) in the 100 kHz-10 MHz range
    - Specific Absorption Rate (SAR, W/kg) in the 10 MHz – 6 GHz range
    - Power density (PD) of the incident field (W/m^2) in the 6 GHz – 300 GHz range
- **Signal characteristics:** continuous waves (CW); pulsed waves (PW)
- **Exposure duration** (min, hours, days)

Furthermore, a very clearly described dosimetry for the biological system used (cell monolayer, tissue, organ, etc.) is essential. This and the above-mentioned conditions are prerequisites for a proper exposure assessment for *in vitro* experiments. High-quality studies must meet the proper controls against which the data can be compared. Thus, to control the environmental conditions without RF-EMF exposure, either incubator (negative) or sham-exposed (sham) control samples are needed. As a further criterion to exclude experimentation bias, it is important to perform the experiments in a blinded manner.

3 Relevant data of exposure protocols in NextGEM

As discussed in Section 2.5, it is paramount to properly embed the relevant dataset in the exposure protocols to obtain good qualitative results and enable their reproducibility.

When dealing with non-constant envelope-modulated signals as those employed in the various telecommunication standards (i.e., 3G, 4G, and 5G), this poses the challenge of how to create a strong stimulus correlation between the *in vitro*, *in vivo*, and personal exposure of humans in emulative and realistic scenarios. To tackle this challenging task, the NextGEM consortium has defined a 5G-compliant signal frame record, which will be employed by the partners in the *in vitro*, *in vivo*, and emulative scenarios. These signal frames provide full consistency with the stimulus used in a real 5G communication link over a signal duration of 20 milliseconds.

The signals are then generated in a continuous loop during the experiment's duration. Given the continuous variability of a real communication signal (i.e., its non-periodicity), the defined frame only represents one possible occurrence, providing frequency and time variation of the signal respecting the 5G protocols.

The exposure protocols defined in the NextGEM project are set to provide trustworthy results and enable reproducibility by using consistent stimuli among the various exposure experiments and providing an accurate assessment of the various parameters influencing the experiments, further discussed in Sections 3.1 and 4.1.

In this chapter, we detail all the relevant data acquired in both simulation environments (Section 3.1) and during the measurement campaigns (Section 3.2). This data forms the robust quantitative basis for further RA analysis, which will be carried out by researchers or governing bodies employing data collection portals such as NIKH.

3.1 Modelling approach for exposure assessment

3.1.1 Objectives

EMF exposure limits establish the maximum allowable radiation levels to prevent adverse effects on human health. These limits ensure safety in various contexts, including work and public environments. During the NextGEM project, computational models will be used to simulate and analyse how EMFs interact with environments and human bodies, focusing on the effects of mobile phones (local exposure) and base stations operating in 5th generation (5G) communication systems (whole-body exposure). Both scenarios will be addressed: local exposure in case studies 1 and 3 and whole-body exposure in case study 2. To ensure that the modelling approach is robust and reliable, we will establish quality criteria based on accuracy, reliability, and validity. Several key characteristics must be defined to ensure accurate and relevant results. These characteristics include SAR, energy levels, exposure duration, and temperature effects, amongst others.

3.1.2 Quality criteria

In the NextGEM project, we will adopt the following criteria:

- **Validity**: The model should be validated against experimental data and real-world measurements performed during the NextGEM project. Criteria: Achieve a high correlation coefficient with experimental data.
- **Reliability**: The model should provide consistent results under varying conditions/meshing. Criteria: Perform repeated simulations under different conditions and compare the results to ensure consistency.
- **Accuracy**: The model should accurately predict different exposure levels. Criteria: The model should achieve a low deviation from experimental data.

In cases where experimental data is not available, we will compare results using different computational tools available to consortium partners, such as ERMES and CST Studio. It is noteworthy that both ERMES and CST Studio are well-established electromagnetic computational tools. They have been validated through various peer-reviewed studies, demonstrating their accuracy and reliability in predicting EMF distributions in complex environments. Both tools have been extensively validated across multiple industries, including telecommunications, aerospace, and healthcare. Their validation processes include benchmarking against analytical solutions and experimental data, ensuring high fidelity in simulations [52] and [53].

3.1.3 Scope and expected results

For far-field exposure, the Ray Launching Cassino (RLC) tool will be used. This tool is specifically designed to estimate the channel matrix between a base station antenna and one or more terminals located in urban outdoor

environments (e.g., the Madrid Grid or real city models). It employs a ray-tracing approach, specifically the ray-launching (pincushion) method, which involves generating rays from an antenna while considering its radiation pattern and analysing their reflection, transmission, and diffraction based on surrounding materials. By combining geometric and physical optics, this method effectively characterizes wireless propagation and RF-EMF exposure in complex indoor and outdoor scenarios. It provides accurate approximations with lower computational costs. Another tool used for far-field exposure analysis is the TIMPlan 3D (TP3D) package, developed by TIM. TP3D is designed for radio coverage and channel estimation across macro, micro, and indoor environments. It serves as a universal propagation simulator for all cell configurations, capable of simulating active and passive antennas in both simulated and real scenarios across any frequency, considering the electromagnetic properties of materials. Like RLC, TP3D also relies on ray-tracing technology. The chosen test scenario is the Madrid Grid Scenario (MGS).

For Case Study 1, a finite element method (FEM) in the frequency domain will be used. This approach is ideal when the wavelength is comparable to or smaller than the problem dimensions ($\lambda \leq D$) and when detailed geometries and complex material properties need to be modelled. The simulations will be conducted using ERMES (open-source) and CST (commercial software) for both *C. elegans* and human models. These simulations will numerically determine the maximum SAR (W/kg) under a given radiation level and verify compliance with ICNIRP radiation limits. For Case Studies 2 and 3, TP3D and RLC will be used to analyse the MGS. By the conclusion of the NextGEM project, all advancements and developments will be made publicly available, significantly enhancing EMF modelling capabilities in complex geometries and environments.

3.2 Measurement approach for exposure assessment

3.2.1 Objectives

To assess possible adverse health effects or biological effects, the NextGEM project will assess the exposure to EMF from 5G systems. Measurements will be carried out in the new bands that will be used in FR2 bands (i.e., n258 with carrier set at 26.5 GHz), and the FR1 bands (700 MHz and 3.5 GHz, n67 and n78, respectively) that are already employed in earlier generations. We decided on the measurement devices based on our literature review on measurement devices [54] or devices designed by THUAS and TUD [55] and [56]. We will assess the level of exposure over time, the range, standard deviation, and mean in several microenvironments with wearables for the FR2 band exposure at multiple positions on the body (node sensors placed on a measurement vest). The *in vitro* and *in vivo* experiments in case study 3 in WP7 can be fed with the maximum realistic exposure level encountered in microenvironments accessible either for members of the general public or workers to see whether any biological or health effects are observed on the biophysical properties of red blood cells (RBCs).

3.2.2 Quality criteria

Calibration of the measurement devices will be and has been performed [57] in the lab by means of direct feed to a spectrum analyzer in order to assess the biases and uncertainty budget and to determine the calibration correction factors to be able to perform a relative calibration. The nodes and SDRs will be calibrated in a Gigahertz Transverse Electromagnetic (GTEM) or an anechoic chamber/test dome. Furthermore, a measurement vest will be calibrated while worn to consider the body's influence. The method will be similar to the one applied by Bolte et al. [58] and consists of three types of multiplicative correction factors: calibration correction (based on repeatability, flatness of response, and linearity response), antenna factor, and influence of the body.

The measurement protocol will be similar to earlier personal exposure surveys on exposure to 4G systems, as described by Bolte and Eikelboom (2012) [59] and standardized by Röösli et al. (2010) [60] and Bolte (2016) [61], to ensure optimal repeatability and reproducibility and detect temporal and spatial differences. Therefore, a survey protocol for preparing, wearing, and reading out the measurement vest will be set.

3.2.3 Scope and expected results

Within NextGEM, measurements will be performed to assess the exposure of members of the general public and workers. Experiments will also be conducted *in vivo* and *in vitro*, for which exposure setups and calibration protocols have been generated in WP4. In WP7, several case studies will be performed. Realistic exposure scenarios will be used in the experimental setups in case studies 1-3.

Case Study 1 will focus on the potential effect of exposure on vulnerable populations, i.e. pregnant women and children. To establish a threshold for safe/unsafe situations, we will carry out *in vivo* experiments and electromagnetic numerical computations on adult *C. elegans* of the wild-type strain and a sensitive strain. A collection of scenarios with different EMF frequencies and modulation patterns will be simulated numerically to

obtain the amount of radiation in the critical parts of their body (eggs, reproductive system). The objective is to determine which EMF patterns have an effect on *C. elegans* behaviour and reproduction (if any). Then, we will simulate numerically the distribution of the EMF inside the body of vulnerable populations under 5G and 4G EMF sources and investigate if these patterns are reached or not.

Case Study 2 is devoted to a measurement campaign in real scenarios with operational Next generation NodeB (gNBs) in the FR1 band. The EMF will be evaluated by resorting to MPE techniques applied to the field level measured in real traffic and environmental conditions, both in Line-of-Sight and Non-Line-of-Sight. In addition to standard measurement periods, in compliance with ICNIRP guidelines, long-term (hours to days) acquisitions will be carried out. The final goal is to acquire as much information as possible on the field variability to assess realistic statistical exposure models. Within the task, simulations will be performed to evaluate coverage and field-level in different scenarios and different frequency bands; moreover, the simulations will be linked to measurement campaigns. This information will also provide the rationale for the RF exposure conditions to be tested in *in vitro* experiments on mammalian cell lines, and will be aimed at evaluating the carcinogenic potential of RF exposure under realistic conditions. Furthermore, exhaustive descriptions of exposure assessment protocols that will be employed in Case Studies 1 and 2 will be included in the final version of this deliverable.

In case study 3, the everyday exposure will be assessed using inputs provided by WP3 (Task 3.1, on the measurement systems requirements, to be tested in the lab), by using existing off-the-shelf systems, and by using the developed wearable measurement systems (Task 3.3). In this case study, we will set out a couple of stationary devices for measuring the (long-term) temporal trends in exposure, and we will measure personal exposure using 26.5 GHz wearable nodes attached to the measurement vest developed in WP3 (see also NextGEM deliverable D3.7 section 3). For the frequency bands in the FR1 band (< 6 GHz), we will deploy an adapted commercial software-defined radio device by Adalm Pluto [62], including a newly designed antenna.

The measurement suite consists of a measurement vest with:

- A distributed exposimeter of at least four 26 GHz-nodes attached to a measurement vest;
- Two adapted software-defined radio devices with specially designed antennas to measure the frequency bands in the FR1 band (<6 GHz);
- A GPS-logger, a real-time clock (RTC), an inertial measurement unit (IMU), a temperature sensor, a battery pack, and a logging system with both local storage and
- A wireless transfer module to send data wirelessly (Bluetooth and /or WiFi) at set intervals to a server

Furthermore, a diary is used to note the type of activity or microenvironment, and a digital watch is used to note the start time of a new activity / the entry of a new microenvironment.

The measuring vest will be deployed in case study 3 for two types of measurements: firstly, exposure surveys to assess the exposure in different types of microenvironments, e.g., at home, at work, shopping, elsewhere-inside, elsewhere-outside, and travel [63], [64], and secondly, to assess the maximum exposure at the vulnerable positions on the body, i.e. in superficial blood vessels where the electric field within the RBCs may be maximal. The vest will have 26.5 GHz node sensors at several positions on the body where either the incident field will be at the highest field strength or, depending on the outcome of the modelling exercise, where the incident field on the body may cause the highest internal electric field in RBCs in superficial blood vessels. A third type of survey is the epidemiological survey, in which the exposure and biological effects are concurrently measured by sensors, or the perceived health effects are mentioned in a questionnaire. The vest is especially applicable in a subset of the last type, the ecological momentary assessment, as an epidemiological survey in which one person is under his own control, i.e., responses in lower and higher exposure situations are compared by following this person for several days and concurrently bodily parameters or self-declared well-being will be registered [65] and [66].

The data processing and analysis protocol will also be similar to earlier surveys, considering the calibration correction factors from the calibration step. Also, the exposure could (and should be) expressed using several different metrics. The time-weighted average exposure may not cover the essence of the signal, consisting of modulation, duty cycles, peaks in intensity, or a more or less constant exposure. The main factors describing the signal are a metric for central tendency, most commonly the mean or median; a metric for the variability of the signal in the long term e.g., the standard deviation; and short-term variations e.g., the rate of change metric (RCM) or the number of samples the field strength is above a certain level [67]. RCM is the root mean square of the first difference and describes the variability and the intermittence of short-term changes [68].

In order to test the devices and the protocols, a pilot survey will be performed in Delft (the Netherlands), at the Green Village field lab, which has an experimental license to carry out experiments in the FR2-band. As the 5G systems are not working anymore with sector antenna, as the 4G systems did, but with matrix antenna transmitting

focused beams, to be able to detect the maximum exposure, we will use a download device that will attract the beam and generate maximum exposure. The pilot survey will also aim to assess the potential maximum exposure in a real-life setting and environment.

The final survey is expected to be carried out in the second half of 2025. Its goal is to get an impression of the exposure over the body during everyday activities. The 26 GHz band is not expected to be auctioned before 2026 in the Netherlands; however, the FR1 3.5 GHz was auctioned in 2024 and is expected to be used shortly after the auction. The final survey will be either with commissioned workers carrying out activities near a field test location or with commissioned workers and/or volunteers in a country with the 5G systems in the FR1 and FR2 bands rolled out.

4 Collection of data for exposure protocols, conditions and preliminary results from experimental studies within NextGEM

Collecting reproducible and robust data and thus facilitating the advancement of EMF exposure knowledge is paramount for NextGEM, stakeholders, and society. The different areas evaluated within the project established and harmonized quality standards to ensure the data could be considered in UR and Case Studies and fulfil FAIR requirements (Findable, Accessible, Interoperable, and Reusable data). The goal is to create the RA tool and its integration in NIKH, which is the ultimate goal of NextGEM.

4.1 Exposure Assessment and Dosimetry

The title of this section mentions two very important aspects for high-quality research in bio-electromagnetism [69]: 'exposure assessment' refers to the evaluation of levels of RF energy incident on the body, and 'dosimetry' refers to determining the absorption of RF energy within the body. As highlighted in Section 2.1, exposure assessment is very important for RA and is strictly related to the 'dose' that is effectively delivered to the body. The reference dosimetry quantity itself has to be properly identified according to the coupling mechanism between EMF and biological tissues. Several expert committees, such as ICNIRP and IEEE-ICES, thoroughly analysed the scientific literature concerning the effects of RF-EMF exposure on biological systems and established which of these were both harmful to human health[4] and scientifically substantiated. Consequently, guidelines for limiting exposure to EMFs and providing a high level of protection for all people against substantiated adverse health effects were released [1] and [12]. Such guidelines identified relevant dosimetry quantities related to how much biological tissues absorb EMF power, as this is largely responsible for the heating effects for both short- and long-term, continuous, and discontinuous RF-EMF exposures. This represents the solid ground over which the high-quality research carried out in the NextGEM project is built.

The following lists the dosimetry quantities relevant to bio-experiments to be carried out within the NextGEM project.

- **SAR**: the "specific energy absorption rate" is the power absorbed per unit mass [W kg^{-1}]. This is mainly used for frequencies below 6 GHz, where EMFs penetrate deep into tissue (and thus require depth to be considered). SAR is specified over different masses to match particular adverse health effects better; SAR10g represents the power absorbed (per kg) over a 10-g cubical mass, and whole-body average SAR represents power absorbed (per kg) over the entire body.
- $\mathbf{S_{ab}}$: the "absorbed power density" over the area [W m^{-2}]. This is used for frequencies above 6 GHz, where EMFs are absorbed more superficially (making depth less relevant). It must be averaged over a square of 4 cm^2.
- $\mathbf{S_{inc}}$: the "incident power density" over the area [W m^{-2}]. This is used for frequencies above 2 GHz, mainly within the far-field zone, and is, by definition, the power density in the points where the exposed sample is supposed to be, but without the sample. Similarly, to S_{ab}, it must be averaged over a square of 4 cm^2.

A question arises with respect to the possibility of measuring such dosimetry quantities. Indeed, guidelines distinguish between "basic restrictions" and "reference levels". The former is related to physical quantities inside an exposed body, which cannot be easily measured. The latter have been derived from the basic restrictions to provide a more practical means of demonstrating compliance with the guidelines, still providing an equivalent degree of protection. With this respect, S_{inc} is easier to estimate than the other quantities. In any case, a thorough dosimetry analysis is needed to establish a clear link between dose and EMF exposure.

4.1.1 Objectives

The dosimetry measurements and quantifications performed within NextGEM represent the base of the biological experiments on RBCs, cell cultures, the nematode *C. elegans*, and human studies to be performed with fine control and measurement of the dose.

[4] Committees have concluded that there is no evidence for such risks as long as exposures are at or below levels that do not allow tissue heating

4.1.2 Quality criteria

In order to obtain reliable dosimetry, simulations can be used to offer quality criteria and robust data. Simulations greatly simplify and speed up the exposure assessment process, with a very high degree of reliability based on very sophisticated models. Yet, in order for the process to be effectively completed, an experimental validation is needed. Roughly speaking, once the agreement between simulation and experiment is demonstrated, even just in a few cases, all the simulations of that model are trustworthy.

As a first step, the appropriate dosimetric quantity has to be selected according to the frequency range and the specific exposure setup. As a second step, the biological experiment has to be designed so that the selected dosimetric quantity is statistically uniform within the target volume. In practice, a certain degree of non-uniformity is unavoidable and can be quantified by the Coefficient of Variation (CV), defined as the ratio between the standard deviation and the average of the dosimetric quantity computed over all the voxels in the volume of interest. A threshold commonly accepted in the scientific literature [70] is 30%. Finally, simulations have to be validated experimentally.

This is not an easy task since the field distribution *inside* the sample cannot usually be directly measured, so it is necessary to resort to indirect measurements. Indeed, SAR assessment can be determined through temperature rise, considering that it is only appropriate to use the initial rise after the RF exposure is applied. The formula relating the SAR to the temperature increase is:

$$SAR = C_p \frac{\Delta T}{\Delta t}$$

where C_p is the specific heat of the material (e.g., a value of 3250 J/(kg °C) for skin) and $\Delta T/\Delta t$ the ratio of the change in temperature T (°C) to the change in time t (seconds) determined at the instant that the RF source is turned on. In practical terms, such a calculation is performed using measurements at discrete, short-time increments. Such a calculation must use data for no more than the first few seconds of exposure. After this time frame, the formula will no longer be valid due to heat transfer away from the measurement point. A further difficulty with this approach is that the low RF power will cause only a very small and gradual temperature rise, of the order of a fraction of 1 °C or less, so that the sensitivity of the fibre optic probe and the temperature stability of the test laboratory conditions are crucial. Experiments have to be properly designed to measure the temperature on the surface of the sample by means of an infrared camera or inside the sample by means of a fibre optic temperature measurement sensor. For all the currently available exposure systems within the NextGEM project, such validation has been carried out (see D4.7 "Technical report on the results on dosimetry – Final Report"), and the same approach will be adopted for systems currently under design.

4.1.3 Scope and Expected Results

During the second half of the previous century, analytical solutions to the EMF equations for simplified geometrical models of the body exposed to plane wave RF radiation were obtained [71] and [72]. Due to the limited range of idealized models that are amenable to exact analytical solutions and enabled by the steady increase in computing power, numerical modelling came to supplant analytical studies, and nowadays, very sophisticated models of biological systems (see D3.6 "Development of modelling approaches to assess internal and external exposure – Final version" for some examples) are available, and an extremely high level of reliability can be achieved. Numerical simulations provide very accurate results and speed up the design and optimization of exposure systems.

D4.7 described the exposure systems and the related dosimetric analyses currently available for the biological experiments to be carried out within the NextGEM project. Here, it is worth mentioning the criteria followed to carry out numerical dosimetry for the various setups.

In the sub 6 GHz band, the reference dosimetric quantity is undoubtedly the SAR: as mentioned above, basic restrictions are given in terms of SAR, and it is a quantity that can be numerically calculated and experimentally estimated to some extent, as explained in the following sub-section. Exposure systems available at SC and CNR are devoted to *in vitro* and *ex vivo* exposure of human cell cultures. In the case of the cell culture, a cell monolayer is settled at the bottom of the culture dishes. In the case of the *ex vivo* exposure of lymphocytes, the cells are suspended in the cell culture medium. The SAR distribution is then computed in the culture medium, and its statistics are evaluated in terms of the aforementioned CV. It has been computed in both exposure systems and exposure conditions that guarantee a suitable CV level has been selected. The exposure system to be used at UZH is currently under design, and the same approach will be adopted. Additionally, extra SAR modelling will be performed by UCAS to model the exposure of cells in suspension for the experiments performed with human lymphocytes. These will be brought into culture after purification from human blood, and they will be exposed *ex*

vivo. However, these cells do not attach to the bottom of the dish but instead remain in suspension. Additional modelling was necessary to ensure proper dosimetry.

Another activity involving sub-6 GHz RF-EMF is described in D4.7, which is the analysis of exfoliated buccal cells of heavy and light mobile phone users. Human volunteers will be selected based on their mobile phone usage behaviour. The goal is to determine the level of exposure (and any related biological effects) in the general population to their everyday use. The exposure will be assessed using an interview consisting of self-reported usage behaviour and an app on their phone that will record phone data, namely the xMobiSense app, as introduced in Section 2.3.4. Numerical dosimetry will be carried out, in this case, resorting to human bio-models available in the EM simulators and suitably modelling commercial mobile phones, evaluating the SAR also in this case. A standardized procedure for computations has been set up in compliance with IEC/IEEE 62209-1528 [73].

In the mmWave frequency band, a pilot human study will be carried out at SC and will explore the potential effects of a short acute and localized exposure to a 5G signal in the FR2 band. The exposure system has been designed, optimized and characterized by means of simulations in CST Microwave Studio, as detailed in D4.7, section 3.1.3. It is worth mentioning here that it is based on far-field exposure. As such, and due to the smaller wavelength, the reference dosimetric quantities to be considered are S_{inc} and S_{ab}. Numerical dosimetry has been carried out, and the aperture between the antenna and the part of the body exposed (at the wrist level, with the forearm placed on a wooden plank) has been characterized and set up to achieve the most uniform exposure possible in terms of S_{inc}, with a CV below 30%. The antenna is placed underneath the plank, below the aperture. The results of numerical dosimetry are reported in D4.7. Additional details are provided in Section 0.

A prior related study will be conducted at UZH premises, exposing blood samples *ex vivo* at 3.5 GHz. The exposure system is currently under design, and no data is available yet. Still, the basic principle will be the same: numerical dosimetry will focus on S_{inc} uniformity as a far-field-based exposure system. It is useful to recall that it is calculated in the absence of the target, thus simplifying the computational models and dividing the analysis into two steps: first, calculate the power density distribution without the target and then compute the power density absorbed by the target.

An exposure system has been designed to be used at CNR for *in vitro* studies on cell cultures and *in vivo* studies on *C. elegans*. It is a reverberation chamber and is aimed at creating a rich scattering environment: the field uniformity is not achieved by exploiting far-field conditions but by using a random distribution of the field with the proper statistics. In this case, SAR has been adopted as a reference dosimetric quantity for two main reasons: on the one hand, far-field conditions are not achieved in this case, thus not properly adhering to the defined concept of "incident field"; on the other hand, one aim of the experiments to be carried out within NextGEM is to verify effects evidenced in previous telecommunication generations which proved to be SAR dependent. In addition, even with such shorter wavelengths, when resorting to microdosimetry at the cellular monolayer level, the concept of local, as opposed to whole body, exposure can be retained. Consequently, numerical dosimetry has been carried out regarding SAR (see D4.7), showing excellent compliance with the 30% rule.

4.2 *In vitro*

Most of the experimental studies regarding the biological effects of RF-EMF available in the literature refer to *in vitro* investigations due to their key role in advancing knowledge about mechanistic processes and the possible relationship between RF exposures and human diseases [48]. Moreover, *in vitro* mechanistic studies have recently received increased emphasis from the International Agency for Research on Cancer [74], which highlights their importance in corroborating evidence and providing biological plausibility to other types of studies, provided that the quality of the study design, exposure assessment methods and biological assay validity are assured [74]. To generate reliable data from *in vitro* studies and thus provide relevant results for the health risk assessment, particular attention has been devoted within WP4 to the study design by setting quality criteria and adequate procedures to expose cells to RF-EMF and to analyse the induced effects. Appropriate dosimetry simulations and experimental validations are a minimal requirement to know the exact SAR level experienced by biological samples, detailed in the previous subsection. Within NextGEM experiments, the experimental design includes the relevant cell model based on the research question, negative controls, sham controls, temperature control, positive controls, blind exposure or analysis, the appropriate number of independent experiments, and statistics.

4.2.1 Quality criteria

Quality criteria allow the obtaining of data that could fit the RA tool and allow the comparison with future data produced by the consortium or others. Certain measures are taken to ensure the quality of the tests performed to achieve these biological tests. These include:

- To ensure consistency and compliance of the experiments with good laboratory practices, NextGEM has developed standardized protocols (Standard Operating Procedures or SOPs), which include detailed procedures for the RF exposures and biological assays used for the experiments under WP4.
- Dosimetry simulations and experimental validations. Appropriate computational simulations and experimental validation determined the exact SAR used in the experiments.
- Sham control is achieved by positioning samples in an identical exposure system but with no field and allowing to rule out any effect of the environmental conditions inside the exposure chamber.
- Temperature monitoring can be performed continuously during treatment or, at least, in preliminary experiments aimed at characterizing the temperature profile of the exposed samples to rule out any thermal effect, using fibre optic thermometers, infrared cameras, or other tools that do not perturb the field.
- Negative control is obtained by positioning cell cultures in a separate standard incubator, which provides information about the background level of the endpoint under evaluation.
- Positive control is achieved by using well-known treatments inducing the effect under investigation and serves to provide evidence that the biological assay is properly carried out and thus able to detect the effects of RF-EMF exposure, if any.
- Blinding procedures at the exposure administration and/or assay procedure step allow for minimizing experimenter bias in the sample analysis.
- Appropriate number of independent experiments and statistics. This is critical to properly analysing the results. The number of experiments should be based on a power analysis, determining the adequate number of independent experiments necessary to draw a conclusion.

4.2.2 RF-EMF exposure of red blood cells (RBC) and their components at 3.5 GHz

4.2.2.1 *Objectives*

To explore the effect of the modulated signal and of the carrier frequency 3.5 GHz in the far-field mode on at least 5 of the following parameters from those listed below[5]:

- Changes in the state of water in RBCs (free-to-bound water)
- Changes in the intracellular pH
- Changes in haemoglobin (Hb) oxygenation in solution
- Kinetics of the interaction of Hb in solution with oxidized glutathione (dithiol exchange, S-glutathionylation). In case changes are found, responses of these two parameters to EMF will be tested on intact RBCs.
- Ca^{2+} entry into the cells and its extrusion
- Function of NO synthase and NO production
- Reduced thiols abundance (non-protein and bulk) in RBCs
- Deformability of RBCs
- Aggregability and sedimentation rate of RBCs

A harmonized signal has been set up by UCAS and will be generated by a signal generator suitably designed by TUD. The goal of these experiments is not directly related to the RA. However, a better understanding of the molecular mechanisms of interaction between the biomolecules and intact model cells with the EMF will contribute to RA in the future after validation of the observed mechanisms in more complex systems such as intact cells, organs and human studies. Time- and dose-dependence of exposures and the SARs in our studies are chosen to address the thresholds, reversibility, and durability of possible effects as well as the possible thermal component of the responses.

4.2.2.2 *Quality criteria*

An exposure system designed to expose Hb solutions and RBCs to RF-EMF inflow is under construction and validation. The related numerical dosimetry is currently in progress. Energy absorption is assessed by detecting

[5] Explanations of the selection of parameters and the expected impact of microwave EMF on them can be found in D4.1 and the Scope and expected results section.

changes in temperature in the plasma-like buffer and blood in the exposure unit using fiber-optic temperature sensors (FISO Technologies Inc., Quebec, Canada) during exposure to EMF.

Responses of the biological parameters of interest to the changes in temperature without application of the EMF are performed to discriminate between thermal and non-thermal effects as well as possible.

SOPs include step-by-step protocols, the choice of positive and negative controls, and the temperature sensitivity of the parameters tested by now. At present, intracellular Ca^{2+} was shown to be the most temperature-sensitive parameter amongst those listed above, along with the dissociation-association of protons from Hb, which alters the protein conformation and its oxygen affinity. S-glutathionylation of Hb thiols is also sensitive to the changes in temperature.

Sham exposure is included in the protocols when the cells are placed into the exposure setup and the RBC circulation protocol is initiated (shear stress-induced), but the experiment was performed without the EMF generator turned on. The order of performing sham and real exposures is chosen randomly.

Temperature monitoring is performed in the sampling chamber during or in separate sets of experiments.

Each experiment will be repeated at least 6 times to assess the presence of the effect and the non-parametric or parametric statistical model used to evaluate its statistical significance—associations between the parameters measured during the study.

4.2.2.3 *Scope and Expected Results*

At present, UZH partners have received the exposure setup prototype to be used at 3.5 GHz from the HUJI partners and the generator of modulated and unmodulated signals from TUD. Dosimetric evaluation is pending, and the exact SAR values are not available. The optimal power suggested for exposure by the partners currently is 12 mW, corresponding to 10.72 dBm. Using the new exposure setup UZH partners plan to assess the changes in the intracellular GSH in RBCs and S-glutathionylation of haemoglobin in response to RF-EMF exposure with or without modulation first as these parameters will be measured later in blood samples of volunteers exposed to 26 GHz in a pilot human study (case study 3). HUJI partners focus on the impact of RF-EMF on the state of water in haemoglobin solutions and on the ability of RBCs to aggregate.

(1) Changes in hydration shells of Hb molecule.

In our previous studies, we assessed the properties of water within hydration shells of Hb in Hb solutions and intact RBCs using dielectric spectroscopy [75] and [76]. We have found that water dynamics in hydration shells of Hb depend on the oxygenation of Hb and its concentration in solutions or the cytosol [75] and [76]. It has also been shown that the ability of Hb to bind water changes with the alteration of Hb macromolecular conformation (e.g., transition from T to R state). Earlier on, the changes in haemoglobin structure and O_2 affinity in response to irradiation with 0.91-2.5 GHz were reported using circular dichroism and fluorescence spectroscopy [77]. Our data indicate that 20-40 min of exposure of hemolysates (native haemoglobin aqueous solutions) to 3.5 GHz caused an increase in electric conductivity (σ) and a decrease in dielectric strength ($\Delta\varepsilon$) as follows from dielectric spectral characteristics, which is indicative of the conformational changes in the Hb molecule.

(2) Changes in the potential of hydrogen (pH) associated with the changes in Hb conformation.

Hb is a powerful buffer, and oxygenation of hemes is associated with releasing protons as the Hb conformation changes from the R to the T state (a phenomenon known as the Haldane effect [78]). So far, we could not detect significant changes in pH in aqueous Hb solutions exposed to 3.5 GHz EMF over 20 min. Heating results in the changes in Hb conformation that impact the dissociation of O_2 and protonation of thiols, carboxylic, and amino groups. Possible changes in the intracellular pH following EMF exposure will be detected using flow cytometry, which will apply BCECF-DA as a marker of intracellular pH. Calibration with nigericin/KCl solutions allows quantitative detection of pH using this method.

(3) Effect of EMF/heat on dioxygen (O_2) affinity of haemoglobin.

The interaction of O_2 with Hb heme groups is an exothermic reaction, and rising temperature is, therefore, decreasing O_2 affinity [79]. Thus, heating may result in O_2 release from Hb and an increase in deoxyhemoglobin abundance using co-oximetry. Deoxygenation induced by equilibration of haemoglobin solutions with the atmosphere of N_2 or treatment with sodium dithionite $Na_2S_2O_4$, or oxygenation by pure O_2 are used as controls. Edani20 has its own set of internal controls (calibrators) used before each measurement.

(4) Kinetics of S-glutathionylation reaction

Within the NextGEM project it has been observed that S-glutathionylation reaction is sped up with an increase in temperature. Our pilot studies in a near-field setting demonstrated that modulated EMF of 3.5 GHz slows down the reaction kinetics. These results will be verified using a new exposure system employing a far-field radiation approach to provide a well-controlled EMF exposure to the investigated sample. A 5G compliant modulation signal frame adopted throughout the NextGEM consortium will be employed (note: due to some instrument limitations, a 50 MHz band will be used for these systems as compared to 100 MHz used in other setups) for both the 3.5 GHz (direct SDR output) and later for 26 GHz (using a custom developed up-conversion module at the output of the SDR).

Positive control includes a diamide-treated Hb sample where S-glutathionylation is facilitated. DTT-treated Hb samples serve as a negative control. Two detection techniques (western blotting and mass spectrometry) are used to detect S-glutathionylated Hb adducts. Sham-exposed samples with the EMF generator off will be compared with EMF-exposed samples. Temperature will be controlled by the water jacket and monitored in the sampling chamber (outside the exposure system). As mentioned above, thiol-disulfide exchange may only occur when reduced thiol is in dissociated form ($-S^-$). Exposure to radiofrequency EMF was predicted to cause the shifts in pKa of thiol groups due to the redistribution of surface charge and, hence, may influence the S-glutathionylation reaction [80].

(5) Ca^{2+} entry and extrusion

Alterations in the abundance and function of Ca^{2+}-permeable ion channels in response to EMF exposure were reported in different cell types, including neurons, as summarized in several reviews [81], [82] and [83]. Affected by 0.8-0.9 GHz RF-EMF are voltage-gated ion channels as well as channels exerting mechano-sensitivity. So far, we have seen a temperature-dependent pattern of regulation of the intracellular Ca^{2+} in red blood cells. However, we could not confirm any robust responses of the intracellular Ca^{2+} to the exposure to EMF within the 20 min (kinetics were performed from 2 min to 20 min exposure time).

(6) Reduced thiols abundance (non-protein and bulk) in RBCs

Exposure to RF-EMF was reported to cause oxidative stress in nucleated cells [84], [85] by several research groups. Data on the possible changes in the redox state of RBCs upon exposure to EMF are largely missing. We have shown that exposure to 3.5 GHz for 20-40 min is associated with a modest increase in the intracellular free reduced glutathione levels in intact red blood cells. We did not observe any changes in methaemoglobin levels in response to EMF exposure. We are currently working to assess the reversibility of the effect and its association with the changes in the abundance of reduced thiols in proteins (haemoglobin). We also plan to evaluate the temperature dependence of the changes in reduced glutathione in red blood cells. Depletion of reduced glutathione is used as a negative control (chlorodinitrobenzene or diamide treatment). Loading with an ethylated permeable form of reduced glutathione is a positive control in the case of glutathione detection, which is performed using Ellman's reagent.

(7) Deformability of RBCs

RBCs show an impressive ability to deform when passing through the capillaries that are smaller in diameter than the cells as well as when filtering through even more narrow splenic slits [86]. Reduced deformability results in compromised O_2 delivery to the tissues and fast clearance of non-deformable cells from the circulation. Deformability is a function of RBC membrane surface-to-volume ratio, membrane elasticity, and cytosolic viscosity. Any of these parameters may be affected by the EMF exposure. We plan to assess deformability upon shear stress at various osmolarities and different shear stress intensities (0.1-30 Pa) using the Lorrca Maxsis analyser after sham or real exposure to EMF. An increase in temperature from 25 to 40°C was shown to cause an increased number of non-deformable cells by the HUJI colleagues using the microfluidic method to assess single-cell deformability at a shear rate of 4 Pa. We plan to reproduce these data using the Lorrca Macsis settings at the UZH. Both groups will explore the impact of 3.5 GHz on the ability of red blood cells to deform at low shear rates. Glutaraldehyde-fixed cells are used as a model to produce non-deformable cells.

(8) Aggregability and sedimentation rate of RBCs.

Erythrocyte aggregation is a physiological phenomenon in blood under low-flow conditions or at stasis that accelerates under inflammatory states [87], [88] and [89]. In turn, aggregation of RBCs in whole blood accelerates their sedimentation. Our previous studies have shown the high sensitivity of RBC aggregation to the state of the cell membrane and plasma protein concentration [90] and [91]. Specifically, an alteration in the surface charge of cells causes significant changes in their ability to aggregate [92]. Due to this, charge distribution on the cell surface can be altered under EMF exposure; we expect that RBC sedimentation studies may provide a method for monitoring the sensitivity of RBCs to EMF exposure.

4.2.3 Exposure of human neuroblastoma cell cultures to 4G LTE signal at 1950 MHz

4.2.3.1 *Objectives*

Currently, the human population is exposed to RF-EMF emitted by wireless technologies based on multiple standards, from 2G GSM to 3G systems based on technologies such as the wideband code-division multiple access (WCDMA), and the 4G mobile service, which relies on a fully digital Internet protocol-based technology called Long Term Evolution (LTE) operating in the frequency range from 800 MHz to 2600 MHz. Moreover, despite the recent transition from 4G to 5G networks, 4G LTE is still the most frequently used signal in wireless communication [93], [94]. Despite that, only a limited number of investigations on the effects of RF-EMF address the 4G signal. These experiments investigate cancer-related endpoints in human neuroblastoma (SH-SY5Y) cells exposed to a 4G LTE signal at 2 different SAR levels. Moreover, the effect of a combined RF exposure protocol with menadione (MD), a well-known cytotoxic agent, is also considered. The latter protocol aims to explore the possibility that RF exposure can modify the effect of another stressor in co-exposure experiments and thus account for a more realistic scenario in which humans are exposed to different agents.

4.2.3.2 *Quality criteria*

To ensure the quality of the experimental activities and, thus, the reliability of the final results, the following specific measures have been considered:

a) Appropriate numerical and experimental dosimetry evaluations to assure homogeneous SAR distribution inside the cell cultures;
b) Appropriate temperature measurements by using a fibre optic thermometer to rule out any thermal increase inside the cell cultures during the RF exposure;
c) Preliminary experiments to optimize the cell culture conditions for SH-SY5Y cells;
d) Preliminary experiments to set the assay procedures to analyse the effects on ROS formation, apoptosis, and cell cycle after RF exposure and co-exposure;
e) Preliminary experiments to identify the proper menadione concentrations to be used for positive control treatment and co-exposure protocols;
f) Blinding procedures at the step of the assay procedure to minimize the experimenter bias in the sample analysis. The researcher involved in the assay procedure and sample analysis was not aware of the exposure/treatment of the samples at hand;
g) At least three independent experiments were carried out;
h) Each experiment included negative, sham, and positive controls.

Specific SOPs have been developed. These will be routinely applied to execute the experiments to ensure consistency among the independent experiments and cope with the experimental variability that greatly affects the final results. These SOPs have been included in D4.3.

4.2.3.3 *Scope and expected results*

The primary goal of this activity is to investigate the effects of a 3 hours-long, 4G LTE, 1950 MHz RF-EMF exposure in the absence and presence of a chemical treatment to mimic a real-life situation of exposure to multiple agents. Human neuroblastoma cells (SH-SY5Y) have been chosen because it is one of the most used biological models in bioelectromagnetic studies. ROS formation, apoptosis induction, and cell cycle progression are being investigated at SAR levels of 0.3 and 1.25 W/kg in the absence and presence of MD, a chemical agent inducing DNA damage via ROS formation and apoptosis. A waveguide-based exposure system was employed, which allows the exposure of cell cultures to uniformly distributed electric fields and simultaneously to two SAR levels. In co-exposure, two MD concentrations, a lower (5 μM) and a higher (20 μM), were used. This approach will allow the identification of a possible SAR-dependent effect and assess whether RF-EMF can modulate the effect of MD in different ways depending on its concentration. A detailed description of the exposure setup is reported in D4.7, whereas the experimental procedures and results of the experiments will be presented in D4.8.

4.2.4 Exposure of cell cultures to 5G signal at 26.5 GHz

4.2.4.1 *Objectives*

5G technology operates on different frequency bands: (i) below 1 GHz to provide coverage in rural, suburban, and urban scenarios (including for Internet of Things devices), (ii) between 1 and 6 GHz to offer a mixture of coverage and capacity, and (iii) above 6 GHz up to the millimetre waves (mmW) to exploit the massive amount of raw bandwidth and potential multigigabit-per-second (Gb/s) data rates [94]. While there is abundant scientific literature dealing with the evaluation of biological effects of low-level (i.e., below the limits set for protection against acknowledged effects) EMFs at frequencies below 6 GHz, there are currently very few studies in the mmW band.

The primary goal of this activity is to investigate the effects of 5G RF-EMF exposure at 26.5 GHz. Due to the low penetration depth of RF-EMF at 26.5 GHz, human keratinocytes (HaCaT) have been chosen as the skin cell model, and UVB radiation was chosen as the agent for co-exposure

4.2.4.2 *Quality criteria*

To ensure the quality of the experimental activities and, thus, the reliability of the final results, the following specific measures have been considered:

a) Appropriate numerical and experimental dosimetry evaluations to assure homogeneous SAR distribution inside the cell cultures. This was carried out by UCAS;
b) Appropriate temperature measurements, by using a fibre optic thermometer, to rule out any thermal increase inside the cell cultures during the RF exposure;
c) Preliminary experiments to optimize the cell culture conditions for HaCaT cells;
d) Preliminary experiments to optimize the assay procedures to analyse the effects on ROS formation, apoptosis and cell cycle after RF exposure and co-exposure;
e) Realization and optimization of a setup for exposure to UV radiation;
f) Preliminary experiments to identify the proper UVB treatment to be used for co-exposure protocols;
g) Preliminary experiments to identify the proper chemical treatment to be used for positive control;
h) Blinding procedures at the step of assay procedure to minimize the experimenter bias in the sample analysis. The researcher involved in the assay procedure and sample analysis was not aware of the exposure/treatment of the samples at hand;
i) At least three independent experiments were carried out;
j) Each experiment included negative control, sham control, and positive control.

Some specific SOPs for these investigations on HaCaT cells have already been developed, while others are under development. These will be routinely applied to execute the experiments to assure consistency among the independent experiments and cope with the experimental variability that greatly affects the final results.

4.2.4.3 *Scope and expected results*

ROS formation, apoptosis induction, cell cycle progression and transcriptomics will be investigated after 3 and 24h exposure at SAR levels of 0.4 and 1 W/kg. For co-exposure, two doses of UVB radiation, a major environmental skin stressor classified as a human carcinogen (Class 1) by IARC, will be administered after RF-EMF. A reverberation chamber-based exposure system is employed, allowing cell culture exposure to the uniformly distributed electric field. This approach will allow the identification of a possible SAR-dependent effect and assess whether RF-EMF can modulate the effect of UVB radiation. A detailed description of the exposure setup is reported in D4.7.

4.2.5 Cell cultures exposure to multiple frequencies and signals

4.2.5.1 *Objectives*

Daily exposure to EMFs in workplaces and for the general public consists of multifrequency exposure to signals with different characteristics. An example is the usage of mobile phones operating under different modes (e.g., switching between 3G and 4G modes) with WiFi and 5G networks. Therefore, it is evident that the effects not only of a single frequency/signal, but also of multiple exposure scenarios are worthy of investigation. In this context, a critical role is played by the possibility of reproducing combined exposure conditions with high accuracy and reliability. To this aim, carrying out *in vitro* studies evaluating the influence of either single signals or more than one signal simultaneously is particularly attractive.

The primary goal of this activity is to investigate the effects of exposure to RF-EMF under different frequencies/signals. The SH-SY5Y cell model will be employed in this case as it is one of the most used biological models in bioelectromagnetic studies. It has been used in NextGEM to evaluate the effects of 4G exposure alone.

4.2.5.2 *Quality criteria*

These activities started in September 2024, and to ensure the quality of the experimental activities and, thus, the reliability of the final results, the following specific measures will be considered in this case:

a) Appropriate numerical and experimental dosimetry evaluations to assure homogeneous SAR distribution inside the cell cultures;
b) Appropriate temperature measurements, by using a fibre optic thermometer, to rule out any thermal increase inside the cell cultures during the RF exposure;

c) Blinding procedures at the step of assay procedure to minimize the experimenter bias in the sample analysis. The researcher involved in the assay procedure and sample analysis was not aware of the exposure/treatment of the samples at hand;
d) At least three independent experiments will be carried out;
e) Each experiment will include negative, sham, and positive control.

Specific SOPs for these investigations on SH-SY5Y cells have already been developed. These will be routinely applied to execute the experiments to assure consistency among the independent experiments and cope with the experimental variability that greatly affects the final results.

4.2.5.3 *Scope and expected results*

The exposure will be carried out for 3h by using a 1950 MHz LTE signal and 2450 MHz WiFi at 0.3, and 1.25 W/kg SAR levels and cell cycle progression will be investigated. The waveguide-based applicator, used for the exposure to a 4G signal, will allow the exposure of cell cultures to the uniformly distributed electric field and simultaneously to two SAR levels.

This approach will allow the identification of a possible SAR-dependent effect of RF exposure under one of the realistic multiple frequency/signal scenarios. Moreover, the obtained results will be compared with those of 4G exposure alone obtained on the same cell model with the same SAR levels.

A detailed description of the exposure set-up is reported in D4.7.

4.2.6 Cell cultures exposure to 5G signal at 3.5 GHz

4.2.6.1 *Objectives*

This study aims to provide more insight into the potential mechanistic side of cancer at the cell level. While 5G has already been rolled out in certain countries, research performed on 3.5 GHz frequencies (and especially representative modulated frequencies) is needed.

Furthermore, in many previously performed studies, flawed study design has been at the basis of many difficulties in coming to a useful RA of RF-EMF in general, leaving many gaps in knowledge, with studies of differing quality that show diverging effects, making it difficult to conclude that is applicable to real situations, which is an important aspect in RA for stakeholders and decisionmakers.

4.2.6.2 *Quality criteria*

In order to achieve this, certain measures are taken to ensure the quality of the biological tests performed. This includes SOPs, which ensure the quality and reproducibility of the experiments. Additionally, we make use of a validated exposure system (the sXc3500 exposure system from the IT'IS foundation) in order to expose our cells at 5G-NR modulated RF-EMF at a defined SAR ascertained by appropriate computational simulations and experimental validation. Furthermore, this system allows us to expose our cells in a blinded manner, which prevents conscious or unconscious bias of the researcher in the execution of the experiment. Samples are only decoded after the analysis is finished.

Another important aspect is the use of the right controls, either the sham control (non-exposed, in the same condition otherwise as the exposed condition, in the second waveguide of the exposure system), positive controls (a chemical inducing a certain response from the cell depending on the endpoint, such as methyl methanesulfonate used for the micronucleus assay, ethyl methanesulfonate for the comet assay and menadione for the oxidative stress assays), or an incubator control, which should, in principle, have a similar outcome as the sham control, to see if placing the sample inside the exposure system induces a particular effect.

We also use duplicates in each experiment and perform each experiment multiple times (n=3) to ensure that the effect is reproducible and statistically significant. Furthermore, we make sure to perform multiple measurements (sample size) per sample.

We also have a fibre-optic temperature sensor, which is placed inside one sample in both sham and exposed waveguides (for contamination reasons, this sample is not used in any other analysis but is purely used to track any potential temperature increases that might emerge from exposure to RF-EMF). The topic of the effects emerging from heating vs. the so-called non-thermal effects remains a hotly debated topic. Still, since the limits put forward by ICNIRP, most thermal effects should be able to be avoided in real exposure scenarios. This temperature probe thus ensures that we are exposing our cells to a non-thermal dose.

HaCaT cells were chosen within the NextGEM project because with the advent of 5G, especially in the FR2 band, the penetration depth of the fields we are exposed to decreases, making the skin one of the main targets. HaCaT

is a spontaneously immortalized human keratinocyte cell line, making it an ideal 2D model for *in vitro* tests. To have a point of comparison between 26.5 GHz and 3.5 GHz, HaCaT cells were selected as a general model.

4.2.6.3 *Scope and expected results*

With the HaCaT cells exposed to 3.5 GHz, we investigate a wide variety of endpoints, going from genotoxic and cytogenetic endpoints (DNA and chromosomal damage) to oxidative stress, apoptosis, and cell cycle analysis.

- Genotoxicity and cytogenetic endpoints: In the NextGEM project, we examine the potential for RF-EMF exposure to induce DNA damage, either through chromosomal damage (*in vitro* micronucleus assay) or DNA double-strand breaks (*in vitro* comet assay). DNA damage is one of the main factors in the development of cancer. This is investigated using standardised signals at 3.5 GHz. Exposures at 3.5 GHz were performed at multiple SAR levels (0.4 W/kg and 1 W/kg) for a duration of 24 hours. For the comet assay, cells were fixed directly after exposure, while for the micronucleus assay, cells were allowed to rest in cytochalasin B for another 24 hours, in order to ensure a cell division to obtain binucleated cells for scoring.
- Transcriptomics: To our knowledge, this is the first full transcriptome study on 5G frequencies, and it might give additional insight into the mechanistic effects of RF-EMF and how the cell reacts to them. Although this approach makes it possible to study processes other than carcinogenesis, these cancer processes will be studied as part of NextGEM. This experiment was performed by using 3.5 GHz and 26.5 GHz signals. Exposures at 3.5 GHz were performed at multiple SAR levels (0.4 W/kg and 1 W/kg) for durations of 1, 3 and 24 hours, and cells were harvested directly after exposure.
- Epigenetics: One of the regulators of transcriptomics is the methylation status of certain regulatory elements in the DNA. Because epigenetic changes help determine whether genes are turned on or off, they influence the production of proteins in cells. And where transcriptomics looks at the RNA transcripts formed; epigenetics looks at the methylation of certain regions in the DNA. This way, it is possible to get a more complete view of how certain genes are regulated when exposed to RF-EMF. Here, we also do a whole epigenome study of exposed vs. non-exposed cells, allowing a more complete view of potential cellular interactions with RF-EMF. Exposures at 3.5 GHz were performed at multiple SAR levels (0.4 W/kg and 1 W/kg) for durations of 1, 3 and 24 hours, with various resting times after exposure, in order to observe if any effects as a result of exposure would be permanent or transient.
- Oxidative stress: Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and a biological system's ability to detoxify these reactive intermediates or repair the resulting damage. This imbalance can lead to the formation of peroxides and free radicals, which damage cellular components such as proteins, lipids, and DNA. Oxidative metabolism generates ROS, potentially causing base damage or double-strand breaks in DNA. The base damage primarily occurs indirectly due to ROS, like superoxide radical (O_2-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2). Additionally, some ROS function as cellular messengers in redox signalling, and oxidative stress can disrupt normal cellular signalling mechanisms. An increase in oxidative stress has been linked to many disease outcomes, cancer being one among them. Exposures at 3.5 GHz were performed at multiple SAR levels (0.4 W/kg and 1 W/kg) for durations of 1, 3 and 24 hours, with various resting times after exposure, in order to observe if any effects as a result of exposure would only appear after exposure ends.
- Cell cycle analysis and apoptosis: The final aspect of the cellular metabolism NextGEM will look at is the cell cycle and the ability of RF-EMF to influence the rate of apoptosis (programmed cell death). One of the major aspects of many types of cancer is the ability of cancerous cells to divide more than they should be able to, eventually ending up in tumours. Because of this, the disruption of apoptosis and an increased proliferation rate could also indicate that direction. Exposures at 3.5 GHz were performed at multiple SAR levels (0.4 W/kg and 1 W/kg) for durations of 1, 3 and 24 hours, with various resting times after exposure, in order to observe if any effects as a result of exposure would only appear after exposure ends.

With this approach, we look at a wide variety of (cancer-related) endpoints to provide additional insight into the potential action of RF-EMF at the cell level.

4.2.7 Lymphocytes exposure to 5G signal at 3.5 GHz

4.2.7.1 *Objectives*

After establishing our results in an *in vitro* cell line, we will carry out research using primary cells taken directly from humans. Cell lines, including HaCaT, are widely used in research to model human health effects, but they have limitations: these cell lines often have mutations and lack the complexity of whole organisms, as they do not fully replicate the intricate interactions between different cell types and tissues. HaCaT cells, specifically, are immortalized keratinocytes, which means they may exhibit genetic and phenotypic differences from normal human

skin cells, potentially affecting the accuracy of experimental results. This does not mean these are bad models for research purposes, but their findings will most likely need to be validated in other systems as well.

While still not perfect, primary lymphocytes should give us a better proxy for a realistic, live human cell. By picking a different cell type (lymphocytes in this case), we also try to see whether or not the effect RF-EMF has on cells is universal or different depending on the type of cell.

4.2.7.2 *Quality criteria*

The sXc3500 (see 4.2.4.2.) will be used to expose the lymphocytes *ex vivo*. Similarly, the same quality parameters as in 4.2.4.2 will be used (standardized protocols, accurate dosimetry in a specialized exposure system, proper controls, temperature measurements, a reasonable sample size, replicates, and repeats) to ensure the quality of the data we gather from our experiments.

UCAS will perform dosimetry to certify the SAR for cells in suspension (which will be the case for the lymphocytes).

4.2.7.3 *Scope and expected results*

- Using lymphocytes exposed *ex vivo* to the modulated 3.5 GHz signal, we are studying a wide range of parameters, from chromosome damage to analysis of the expression of selected genes. Genotoxicity and cytogenetic endpoints: In the NextGEM project, we look at the potential of RF-EMF exposure to induce DNA damage, either through the induction of chromosomal damage (*in vitro* micronucleus assay) or DNA double-strand breaks (*in vitro* comet assay). DNA damage is one of the main factors that are important to cancer development. We will perform both the *in vitro* micronucleus assay and the *in vitro* comet assay using a method similar to that used in our HaCaT cell line to look at these endpoints. This is investigated using standardised signals at 3.5 GHz. Exposures at 3.5 GHz were performed at 1 W/kg for 24 hours. For the comet assay, cells were fixed directly after exposure, while for the micronucleus assay, cells were allowed to rest in cytochalasin B for another 24 hours, in order to ensure a cell division to obtain binucleated cells for scoring.

- Transcriptomics: The regulation and metabolism of the cell are governed by the genome and how these genes are transcribed into RNA (and subsequently into proteins). As such, transcriptomics can give us an understanding of how the cell reacts to its environment, including external factors. We will use lymphocytes to perform a transcriptomics analysis through RT-qPCR, focusing on the genes identified in previous *in vitro* studies with HaCaT cells. By comparing the gene expression profiles between the lymphocytes and HaCaT cells, we aim to validate and extend our understanding of these genes' functions in response to RF-EMF in a more physiologically relevant cell type. Exposures at 3.5 GHz were performed at 1 W/kg for 24 hours. RNA was extracted right after exposure ended.

D4.3 provides more information on the cell culture procedure and experimental protocols. D4.7 and D4.3 provide a more detailed description of the exposure system and the exposure protocols used.

4.3 *In vivo*

4.3.1 *C. elegans* exposure to 5G signal at 26.5 GHz

4.3.1.1 *Objectives*

In the NextGEM project, we use the nematode Caenorhabditis elegans (*C. elegans*) as an *in vivo* model to evaluate the effects of a 5G-modulated signal on health parameters and transcriptomics. *C. elegans* presents several experimental advantages but has not been investigated much concerning electromagnetic field (EMF) effects. It is a small worm-like organism, ~ 1 mm long, with a life and reproductive cycle of about 3 weeks and 3 days, respectively, and without bioethical requirements, allowing experiments to be carried out faster and cheaper than mammal systems. Moreover, it presents 60-80% genome homology with humans, which allows for analysis of transcriptomic data regarding key genes.

4.3.1.2 *Quality criteria*

To ensure the quality of the biological tests performed, we provided the SOPs for maintaining, analysing, and experimenting with *C. elegans* within NextGEM. We used the validated exposure system at the CNR premises, which allowed us to stabilize a comparison of the data produced for *in vitro* cell cultures and *C. elegans*, increasing the robustness and reliability of the experiment. The dosimetry and, thus, SAR values during exposure and the 5G modulation have been appropriately simulated and experimentally validated by UCAS and CNR, respectively.

Another important aspect is using the right controls. A non-exposed control known as sham will be kept in the same incubator as the exposed worms, thus maintaining the same environmental conditions as the ones exposed to RF-EMF. A second non-exposed negative control will be kept in a different incubator and should, in principle, have a similar outcome as the sham control since neither is exposed to RF-EMF. Several experiments also call for positive controls in the form of certain chemicals inducing an expected response from the *C. elegans,* depending on the endpoint.

We used 600 worms in each experiment and performed each multiple times (n=3) to ensure that any effect was reproducible and statistically significant. Furthermore, we performed multiple measurements for each sample in the different experiments.

We also have a fibre-optic temperature sensor, which is placed inside one sample in both sham and exposed waveguides (for contamination reasons, this sample is not used in any other analysis but is purely used to track any potential temperature increases that might emerge from exposure to RF-EMF).

A wild-type strain of *C. elegans*, representing a healthy individual, was chosen. We assessed different generations to evaluate whether effects are seen at different ages. Additionally, a cuticle-sensitive strain will be explored to understand if such a parameter is important for any exposure effects.

4.3.1.3 *Scope and expected results*

C. elegans exposed to 26.5 GHz is measured on a wide variety of endpoints, from individual health (such as survival, developmental health, length, and motility) to biological mechanisms (such as oxidative stress and total antioxidant capacity) and transcriptomic endpoints (investigated by RNA sequencing) to elucidate any effects at the genetic level.

- Organismal health: *C. elegans* is a 1-mm-long, transparent, and free-living nematode. It exhibits a rapid life cycle (3 days) with development stages well-defined in terms of development time and length of the nematode at each stage. We monitored the survival rate and growth of the nematodes by measuring their body length.
- Reprotoxicity: We evaluate two generations of *C. elegans* after exposure to 5G, including counting the progeny in each generation. After the exposure, reprotoxicity does not seem to be affected by the wild-type strain after 5G exposure.
- Reactive oxygen species (ROS) and Total Antioxidant Capacity (TAC). *C. elegans* exposed to 5G will be analysed for reactive oxygen species and TAC. The experiments are not completed.
- Transcriptomics: RNA is extracted from *C. elegans* after 5G exposure and from nonexposed controls. Gene expression is quantified, and the differences between conditions are assessed. *C. elegans* is a widely used genetic model organism, so its genome is fully sequenced and well annotated, and the gene functions and families are well understood. Therefore, when examining gene expression patterns, we can elucidate the effects of 5G on functions rather than individual genes. After analysis, there seems to be no significant change in gene expression in the wild-type strain after 5G exposure.

For a detailed description of the *C. elegans* maintenance and experimental protocol, SOPS are provided within NextGEM.

4.4 In humans

Two studies involving human volunteers are planned in the NextGEM project. The first is a pilot study in which volunteers will be either real or sham exposed (in a double-blind manner) to a standardised modulated 5G signal as specified in NextGEM, at 26.5 GHz, with the aim of exploring RBCs characteristics. The second study will involve the collection of buccal cells from volunteers, who are either frequent or occasional mobile phone users during oral communication, with the aim of evaluating the occurrence of cytogenetic responses (micronuclei formation) and changes in selected gene expression with the help of modelling and a mobile phone app to aid in the exposure assessment.

4.4.1 Pilot study under 26.5 GHz controlled exposure

4.4.1.1 *Objective*

The objective of the blood testing following the sham or real exposure of healthy human volunteers is to explore the possible responsiveness of RBCs to RF-EMF (controlled exposure to a modulated 5G signal at 26.5 GHz for

45 minutes). This is a pilot experiment that follows prior experiments on whole blood, suspensions of RBCs, and RBC components such as Hb exposed to the modulated signal *ex vivo*, as described in D4.1.

4.4.1.2 *Quality criteria*

Standardised protocol

To ensure the quality of the pilot experiments in humans, and, thus, the reliability of the final results, the following specific measures have been thoroughly described in the protocol of the study, approved by the ethics committee of Université Libre de Bruxelles (ULB-Erasme), Belgium.: characteristics of the population, exposure source, exposure conditions, endpoints, methods of analysis, sample size, controls, exposure assessment, double blinding process, and data protection (pseudonymization and registration of the human samples – blood - in a certified biobank).

The protocol received approval from the relevant ethics committee, and an informed consent form will be co-signed by the study volunteers and the investigator before inclusion in the study.

Exposure conditions

- Background EMF: The test will take place in a specially equipped test room within a container allowing to control background EMF levels (50 Hz: <0.05 μT; average RF < 0.1 V/m in the range up to 6 GHz)
- Double-blinded
- Randomization of real and sham exposures to avoid bias

Exposure characterization

The exposure system has been designed, optimised, and characterised by means of simulations in CST Microwave Studio, as detailed in D4.7, section 3.1.3, so as to obtain a uniformity of the Incident Power Density on the exposed region that is lower than 30% in terms of CV. A suitable coating of an absorbing material was applied to the interior of the wooden box in order to prevent unwanted exposure or interference. The reliability of exposure simulations was ensured by proper implementation of both the radiating antenna (PE9851B/2F-15 horn antenna from Pasternack) and the wooden box, according to laboratory-tested physical properties of the material, treated wood to prevent swelling due to humidity. Simulations were experimentally validated by exposing a skin phantom manufactured and characterised in the laboratory (based on a recipe of PvP in water mixed with agar), confirming an excellent agreement between theory, simulations, and measurements (Figure 2).

The final output of the simulations is represented by design curves (Figure 3) of average IPD and CV at 26.5 GHz as a function of the distance of the antenna from the top of the box for an input reference power of 1W. Such curves allow to properly set up the system according to the selected exposure level.

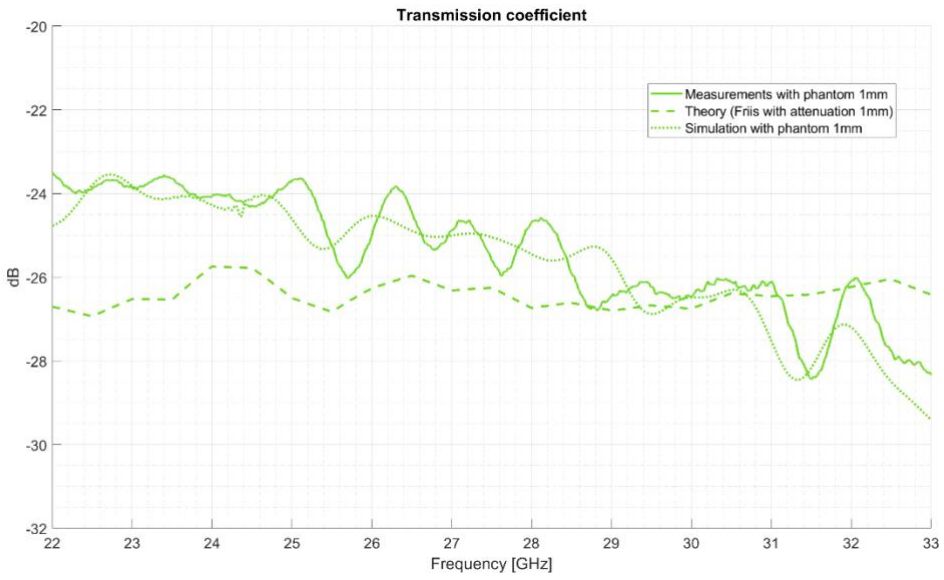

Figure 2: Transmission coefficient trough an exposed skin phantom: comparison between theory, simulation and measurements.

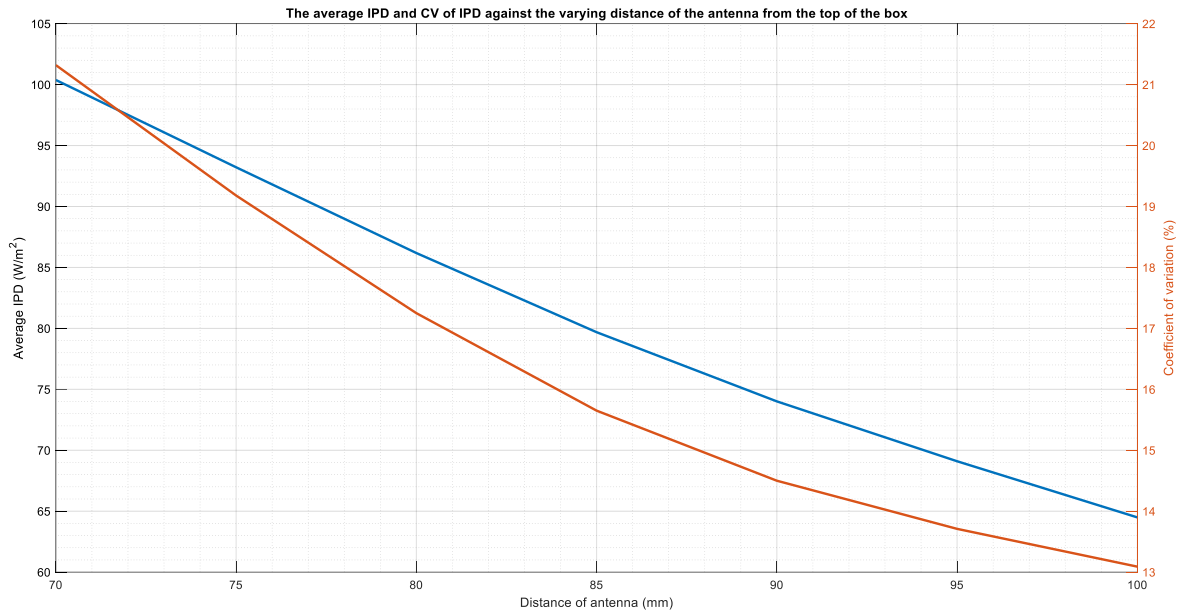

Figure 3: Average IPD and coefficient of variation (CV) as a function of the distance of the antenna from the top of the box. The input reference power is 1W, and the frequency is 26.5 GHz.

4.4.1.3 *Scope and Expected Results*

Results of the pilot study will provide a proof-of-principle dataset on the possible non-thermal responses of RBC indices, morphology, and redox state (intracellular reduced glutathione, S-glutathionylation of proteins, and nitric monoxide production) to the modulated 26.5 GHz exposure. Results will also serve as a basis for case study 3. The temperature dependence of the selected parameters was tested *in vitro* at 3.5 GHz to discriminate between the non-thermal and thermal effects of the signal used. Some of the parameters (Ca^{2+}-levels, which influence morphology, S-glutathionylation) show temperature dependence in the range of +2 to +40 °C. It is not clear if subtle transient changes in temperature may result in detectable alterations of any of them. *Ex vivo* tests are being performed, in which changes in the intracellular GSH are followed in blood samples exposed to the modulated and non-modulated signal at 3.5 GHz. The *ex vivo* investigations on the possible non-thermal responses of blood cells to the RT-EMF aim at understanding the possible molecular mechanisms of interactions of biomolecules with the EMF. This understanding is of key importance in the evaluation of the potential health risks. However, it is not directly associated with RA.

4.4.2 Heavy and light mobile phone users

4.4.2.1 *Objective*

Volunteers in Belgium will be recruited through various methods and asked to self-report their mobile phone call usage via a short LimeSurvey. Those using their phones for less than 10 minutes daily will be classified as "light" users, and those over 2 hours as "heavy" users to ensure clear group separation. Due to the unreliability of self-reported phone use, additional exposure assessments will be performed. Eligible participants (based on age, Android phone use, and call time) will be contacted to confirm inclusion criteria and schedule two appointments. The first visit includes signing the informed consent form (ICF), a detailed interview, personal and medical information, installing the xMobiSense app, and collecting buccal cell samples. The second visit, about a week later, will involve reviewing phone usage data, retrieving and uninstalling the app, and collecting a second buccal sample.

The primary objective of this study is to assess whether specific biological markers, previously identified in *in vitro* studies, are also detectable under real-world human exposure conditions. In this context, exposure is limited to the everyday use of mobile phones and environmental factors within typical living environments. To bridge the gap between highly controlled laboratory experiments and realistic exposure scenarios to RF-EMF, we have developed this comprehensive study protocol.

The first biological endpoint focuses on examining gene expression in exfoliated buccal cells collected from volunteers categorized as either high or low mobile phone users. Gene expression analysis will be performed using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) targeting genes previously identified in *in vitro* studies. These *in vitro* experiments employ cell lines and utilize near-complete transcriptome analyses through

TempO-Seq to identify potential gene candidates indicative of RF-EMF exposure. Candidate genes will be selected based on distinct expression patterns observed under *in vitro* conditions. While gene expression changes following RF-EMF exposure have predominantly been examined in *in vitro* contexts [95], [96] or in *in vivo* rat models with restricted gene subsets [97], [98] and [99], human studies have been limited. Notably, Karinen et al. (2008) [100] explored gene expression in human skin post-specific RF-EMF exposure; however, to the best of our knowledge, no study has investigated gene expression following everyday exposure scenarios of RF-EMF.

The second biological endpoint examines potential genetic damage through micronucleus assays in the same cohort as the previously mentioned gene expression analysis. Micronuclei—small, DNA-containing structures separate from the primary nucleus—are recognized as biomarkers for various pathologies, including cancer, and recent studies highlight their active role in tumorigenesis [100] and [101].

To evaluate potential associations between mobile phone usage and biological effects, 60 human volunteers will be recruited—30 light users (≤10 minutes/day, with a preference for close to 0 minutes/day) and 30 heavy users (≥2 hours/day). Participants will initially self-report their mobile phone usage habits through a LimeSurvey (used to apply to become a participant in the study). To ensure objective classification and enhance data reliability, exposure assessment will be conducted via a dual approach:

Because purely self-reported data regarding phone use has been shown to be unreliable [102], exposure modelling will estimate RF-EMF exposure levels based on usage patterns collected with the help of the xMobiSense Android application and dosimetry modelling based on device specifications. Exposure modelling at the inner cheek will be done by Prof. Fulvio Schettino (University of Cassino) using a Samsung Galaxy J model, adjusted to represent the phone types used. Pseudonymized phone data will be shared for this purpose.

The xMobiSense app, previously validated in epidemiological studies [103] and [104], will monitor actual mobile phone use and associated RF-EMF exposure in real time, as well as give some rudimentary data, such as the state of the phone (e.g., An incoming/outgoing voice call (call time); On/Off WiFi connection; On/Off mobile data), the connected network type (2G/3G/4G/5G/Wi-Fi), The GPS data, the use of headsets and the loudspeaker, the values of the accelerometers and the proximity sensor, both used to predict the laterality of the mobile phone with respect to the head or body during calls, the battery level of the phone and the received power levels such as the received signal strength indicator (RSSI) for WiFi, GSM (2G) or CDMA cells, the reference signal received power (RSRP) for LTE (4G) cells, the received signal code power (RSCP) for WCDMA (3G) cells and the data for Synchronization Signal reference signal received power (SS-RSRP), the Secondary synchronization Signal Reference Signal Received.

Additionally, structured interviews will capture information on smartphone usage behaviour, such as call duration, use of hands-free devices, and phone positioning during calls. Subsequent measurements or controls will be incorporated to further objectify exposure metrics and confirm group classifications.

Buccal samples will be stored for five years post-study, allowing future analysis if new genes or assays emerge.

4.4.2.2 *Quality criteria*

The study will implement stringent quality criteria across all phases of the research process to ensure the validity, reliability, and reproducibility of the experimental results. These criteria are designed to minimize bias, reduce variability, and enhance the accuracy of biological measurements and exposure assessments.

- **Clear Inclusion/Exclusion Criteria**: Volunteers will be selected based on well-defined criteria to exclude confounding factors. The exclusion and inclusion criteria used are.
    - Inclusion criteria: Inclusion criteria (asked in the initial LimeSurvey), between 18 and 45 years of age, an Android phone user, perceived use of a mobile phone for oral communications (mobile phone at the ear), more than 2 hours/day for inclusion in the "heavy" user group, less than 10 minutes/day for inclusion in the "light" user group (ideally no oral communication at all)
    - Exclusion criteria (additional information asked during the initial contact): Long-term diseases (currently or recovering) (cancer, COPD, Alzheimer's disease, Parkinson's disease, etc.), a mobile phone use for oral communication between 10 minutes and 2h/day, use of illegal recreational drugs (e.g. cannabis, heroin, cocaine, etc.), smoker or former smoker, history of exposure to harmful materials which may be confounding factors in this study, if data is unable to be retrieved for either the exposure assessment or the biological outcomes (due to sample insufficiency or incompatibility of the mobile phone with the app). Volunteers will be included in the study according to their date of completion of the LimeSurvey. Once the 30 participants have been obtained, gender balance will be prioritized, and volunteers will be excluded in order of the date

of submission of the LimeSurvey and, finally, if the informed consent form could not be signed or if the volunteer withdrew consent during the study.

- **Balanced Demographics**: Age, gender, and other lifestyle factors will be matched across high and low mobile phone user groups to mitigate potential confounders.
- **Selection**: The initial self-selection based on their self-reported mobile phone use will provide us with two distinct study populations based on usage behaviours, confirmed or not by the data collected with the mobile phone app. One will serve as the control group against the high mobile phone users.
- **Informed Consent**: All participants will provide informed consent, ensuring ethical compliance
- **Harmonised Collection Protocols**: Buccal cell collection will follow standardised procedures, including instructions on pre-collection behaviour (e.g., no eating or drinking 30 minutes prior to collection).
- **Validated Assay Methods**: RT-qPCR assays and micronucleus tests will use validated protocols with appropriate positive and negative controls.
- **Reagent Quality Control**: All reagents will be sourced from reputable suppliers, and batch-to-batch consistency will be monitored.
- **Blinded Analysis**: Laboratory personnel will be blinded to participants' exposure categories to prevent bias.
- **Technical Replicates**: Multiple samples from the same person at different time points (taken during the two visits) will serve as technical replicates to assess intra-assay variability.
- **Biological Replicates**: Sampling from different volunteers will ensure biological variability is appropriately accounted for.
- **Internal Reference Genes**: For gene expression analysis, multiple validated reference genes will be used for normalisation to avoid bias from variable gene expression.
- **Validated Tools**: The xMobiSense app has been previously validated in epidemiological studies, ensuring reliability for exposure data collection. This app also provides us with a more objective measure of mobile phone usage time (in terms of call time), since past studies have proven that self-reported data is often biased.
- **Consistency Checks**: Data from the app will be cross-referenced with self-reported usage and interview information.

4.4.2.3 *Scope and Expected Results*

This study is exploratory in nature, aiming to investigate the potential biological effects of everyday exposure to RF-EMF from mobile phone use. The primary objective is to assess whether certain biological markers previously identified in *in vitro* studies can also be detected under realistic human exposure conditions. By focusing on real-world scenarios, where individuals are exposed solely through the daily use of mobile devices and their immediate environments, the study seeks to bridge the existing knowledge gap between controlled laboratory experiments and actual human exposure.

Given the exploratory nature of this research, no definitive outcomes are presumed. Instead, the study aims to identify potential biological markers, provide preliminary data for future research, enhance understanding of real-world exposure effects, and validate or refute laboratory findings.

Given the complex and multifactorial nature of RF-EMF exposure, observed effects (if any are present at all) may be subtle and require further investigation. It is also possible that no significant biological changes will be detected, which would still provide valuable information for understanding the biological plausibility of RF-EMF effects at everyday exposure levels.

5 Harmonization Protocols

The outcomes of the work in the NextGEM project will lead to a better understanding of the 5G NR exposure situations, the dosimetry in organisms and cell cultures during exposure, the possible biological effects of exposure, and the requirements for appropriate RA. With this in mind, the project has carefully developed and implemented protocols for umbrella reviews, exposure assessment, dosimetry, experimental studies, and RA models that go significantly beyond state-of-the-art and will provide a substantial knowledge increase for relevant stakeholders.

The protocols are harmonized between the various partners within NextGEM, meaning that all involved actors have been part of the development and implementation. Furthermore, the protocols are open for all partners in the project and will also be available via NIKH for other stakeholders, making it possible to perform replication studies, which is a prerequisite for attaining a large enough database to use in future RAs. These features are possible to offer since NextGEM has a deliberate and well-thought-out data collection framework and a system for integrating all relevant data into the NIKH framework. These aspects are further outlined below.

5.1 Data Collection Framework

5.1.1 Objective

Data collection within NextGEM aims to gather information that can be used to support or refute hypotheses, draw conclusions, and contribute to the broader body of knowledge and RAs regarding the potential effects of RF-EMF exposure on biological processes and health.

5.1.2 Quality criteria

Ensuring a high quality of data collection is crucial to obtaining reliable and valid results. For this reason, NextGEM partners have defined quality criteria to be followed during data collection. These quality criteria are reflected in additional metadata as described in D1.6. Data collection must also be relevant and consistent with the project's hypotheses. For data collected in experiments involving human volunteers, ethical considerations must be strictly adhered to, ensuring that data collection methods comply with ethical standards, including informed consent, confidentiality, and respectful treatment of human subjects. Thus, data collection must also be documented, including methods, tools, and any changes made during the research. It is also important to ensure that data is collected in a format that is accessible, understandable, and usable for subsequent analysis.

5.1.3 Scope and Expected Results

Different types of outputs will be generated during experiments using exposure protocols, such as literature reviews, technical (measurements and numerical simulations), and biological data from *in vitro*, *in vivo*, *ex vivo* and human studies. Other documents, e.g. study protocols, will also be stored and preserved.

The NextGEM Data Management Plan (DMP) aimed to standardize how outputs are managed within NextGEM under the FAIR principles and follow the rules "As open as possible, as closed as necessary". The FAIR data principles encompass four essential elements. Firstly, data must be findable, requiring adequate metadata, a unique identifier, and registration in a searchable resource. Secondly, accessibility is a key, with metadata and data being readable by humans and machines and stored in a trusted repository. Thirdly, data should be interoperable, sharing a common structure, while metadata employs recognized terminologies. Finally, reusability is emphasized, necessitating clear usage licenses, provenance, and alignment with community standards.

The first step in data management is to clearly identify the characteristics of outputs that are going to be generated in NextGEM. This involves gathering the following information for each output:

- Title
- Re-use of existing data: yes or no
- Origin, e.g., laboratory testing, simulation, literature review, open-source tools, *in situ* EMF measurements
- Purpose of the output and relation to the objectives of the project
- Resp.: partners in charge of the output
- WP: generated in which work package(s)
- WP use: used in in which work package(s)
- Format of the outputs, preferably a non-proprietary format
- Size

- Location of the ongoing document / raw datasets, e.g. partner local server, NextGEM repo or any other locations used to store ongoing document or raw datasets
- Back-up frequency of the ongoing document / raw datasets
- Location of the final outputs, e.g. partner local server, NextGEM repo, the NIKH, Zenodo or another external repository (e.g. GitHub)
- Destroyed at the end of the NextGEM project? Yes or no
- Duration (preservation): if "no" in the previous question, provide the number of years (as an example, it is 20 years in Zenodo)
- Ethics issues? Yes or no
- Privacy level/accessibility: Open / Open after embargo / Restricted (contact) / Closed
- Stakeholders to whom access will be granted

In terms of output preservation, all open, open after embargo, and restricted outputs will be stored on Zenodo or other dedicated repositories (e.g., software code) that will preserve outputs for at least 20 years. To make the outputs findable, the required metadata will be assigned to all these outputs via the repository. Metadata will then be automatically extracted and inserted into NIKH. Further information is available on the current interim version of the DMP (D1.6).

5.2 Integration of collected data in the NIKH framework

The integration of collected data into the NIKH framework is essential for ensuring a harmonized approach to data management and analysis within the NextGEM project. As mentioned above, the NextGEM DMP aims to standardize the management of outputs generated during the project, ensuring that data adheres to the FAIR principles. A crucial aspect of the data management plan is the clear and detailed identification of the specific characteristics of each research output. The diverse and specific kinds of datasets and the manner in which they are collected from various sources require a uniform integration into NIKH.

The NextGEM project involves extensive data collection from a variety of experimental studies to assess the effects of RF-EMF exposure on biological systems. These data sources include exposure assessment from modelling and measurement data, numerical and experimental dosimetry, *in vitro* studies, *in vivo* studies and human studies. Each source provides unique insights into the biological impacts of RF-EMF, contributing to a comprehensive understanding of its effects.

5.2.1 Integration into the NIKH Framework

Integrating the collected data into the NIKH framework involves a structured and detailed methodology to ensure that data from diverse sources is harmonized, validated, and made accessible for comprehensive analysis. This framework provides a unified platform for data storage, sharing, and analysis, adhering to the FAIR principles. The methodologies of data collection within the NIKH framework are designed to facilitate seamless integration and management of data. One of the primary repositories used is Zenodo, which allows for the storage and sharing of research outputs in a secure and accessible manner. Zenodo supports the FAIR principles by providing a platform where data can be easily found, accessed, and reused with standardized and comprehensive metadata.

Additionally, NIKH's data spaces play a crucial role in integrating data from the local spaces of NIKH participants. These data spaces enable the seamless transfer and sharing of data across different institutions and platforms, ensuring that all participants can contribute to and access the shared repository. The use of data spaces within NIKH involves several steps, including the uploading of data to the local data space, the assignment of metadata, and the integration of this data into the central NIKH repository. This approach ensures that all data is standardized, validated, and securely stored, facilitating easy access and use by all project partners. The integration process follows a structured approach. A comprehensive analysis of the methodologies employed in the integration process is provided in the following subsection.

5.2.2 Data Standardization and Harmonization

The integration process begins with the standardization of all collected data. This involves converting raw data into predefined formats and protocols to ensure consistency and interoperability within NIKH. Standardization includes converting data into standardized common file formats, such as CSV, JSON, XML, or specific scientific formats, applying consistent naming conventions, and structuring the data to facilitate easy integration and analysis with standardized schemas to represent data structures consistently across different datasets. Harmonization ensures that data from different sources and types can be seamlessly combined and compared.

Validation and Quality Control: Each dataset undergoes rigorous validation checks to confirm its integrity and reliability. This process includes cross-referencing the data with existing datasets, performing technical verifications, and subjecting the data to peer review to validate the methods and findings. Quality control measures are essential for maintaining high standards of data reliability and usability.

Comprehensive Metadata Assignment: Detailed metadata is attached to each dataset, providing essential information on data origin, collection methods, experimental conditions, and potential use cases. This metadata ensures that data is findable and accessible and provides sufficient context for interpretation and reuse. Comprehensive metadata includes details such as the dataset's title, description, origin such as laboratory testing, simulation, literature review, or in situ measurements, experimental conditions, and any ethical or privacy considerations and policies. The desired rich metadata annotation is accomplished with custom standardised metadata schemas and project-specific ontologies.

Data Acquisition and Upload: Collected data from various studies (exposure assessment, *in vitro, in vivo*, human studies) is first aggregated and uploaded to the participating institutions' local data spaces. This initial step ensures that all raw data is centrally located and ready for further processing. Local data spaces facilitate the initial organization and preparation of data before it is integrated into the central NIKH repository.

Secure Data Storage and Access Control: Validated data is submitted to the NIKH repository, where it is stored securely and made accessible according to predefined access levels. Data is categorized based on its sensitivity and usage rights, with classifications such as open, open after embargo, restricted, or closed. This ensures that data is protected while also being accessible to authorized users for collaborative research.

Use of the Zenodo Repository: Zenodo is utilized for long-term storage and accessibility of research outputs, supporting the FAIR principles. Zenodo provides a platform where data can be easily found, accessed, and reused, with comprehensive metadata ensuring standardization.

NIKH's Data Spaces: Additionally, NIKH's data spaces play a crucial role in integrating data from the local spaces of NIKH participants. Data spaces enable seamless transfer and sharing of data across different institutions and platforms. The integration process includes uploading data to local data spaces, assigning metadata, and integrating this data into the central NIKH repository. This ensures that all data is standardized, validated, and securely stored, facilitating easy access and use by all project partners.

Connector Manager Operations: The Connector Manager handles all requests related to data spaces within the NIKH framework. This includes managing operations such as metadata upload, data exchange, and asset transfer, ensuring that data is uploaded, stored, and accessed in a structured and secure manner. The Connector Manager also facilitates collaboration by streamlining data management processes and ensuring data integrity throughout the integration process. This involves the creation of access policies and contract definitions that bind these policies with the respective assets. Additionally, the Connector Manager facilitates file sharing between connectors, encapsulating complex processes such as contract negotiation and acceptance into simplified function calls. The use of containerization technologies (e.g., Docker, Kubernetes) also allows for scalable data management.

6 Conclusion

This deliverable confirms the need for standardising and harmonising exposure protocols to collect data for use by different stakeholders in future risk assessments. The chosen protocols for the different studies undertaken within NextGEM are described in detail.

This deliverable feeds into the effort of all NextGEM partners. It explicitly outlines how the studies' scope is reached and how identified relevant quality controls are implemented. This will ensure that many previous shortcomings found in the published literature can be overcome so that improved studies can be performed and replicated by others outside of the NextGEM consortium.

The work within NextGEM, ranging from umbrella reviews to dedicated experimental studies yielding data using harmonized protocols, will influence and provide a solid framework for developing and implementing the RA Tool into the NIKH. In this manner, Deliverable D5.7 provides the basis for the solid research to be conducted.

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