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

D2.1: EMF value drivers towards stakeholders needs on real case studies

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Glossary of terms and abbreviations used

Abbreviation / Term	Description
1G-6G	First-Sixth Generation technology standard for broadband cellular networks
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ALARA	As Low As Reasonably Achievable
CS	Case Study
DMRS	DeModulation Reference Signals
EIRP	Equivalent Isotropically Radiated Power
EM	Electromagnetic
EMF	Electromagnetic Field
EMA	Ecological Momentary Assessment
EPC	Evolved Packet Core
ERMES	Electric Regularized Maxwell Equations with Singularities
FEA	Finite Element Analysis
FR1/2	Frequency Range 1/2
GA	Grant Agreement
gNB	(gNodeB) is a node in a cellular network that provides connectivity between user equipment (UE) and the evolved packet core (EPC)
GPR	Ground Penetrating Radar
GTEM	Gigaherz Transverse Electromagnetic
GUI	Graphical User Interface
HSP	Heat Shock Protein
HW	HardWare
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICT	Information Communication Technology

IEEE	Institute of Electrical and Electronics Engineers
IEEE-ICES	IEEE-International Commission on Electromagnetic Safety
IoT	Internet of Things
IP	Internet Protocol
ISP	Internet Service Provider
KPI	Key Performance Indicator
KOM	Kick-Off Meeting
LOS/NLOS	Line of Sight/Non Line of Sight
LTE	Long Term Evolution (4G mobile communication protocol)
MaMIMO	massive Multiple Input Multiple Output
mmWave	Millimetre Wave
MIMO	Multiple Input/Multiple Output
MPE	Maximum Power Extrapolation
NEC	Numerical Electromagnetics Code
NextGEM	Next Generation Integrated Sensing and Analytical System for Monitoring and Assessing Radiofrequency Electromagnetic Field Exposure and Health
NIKH	NextGEM Innovation & Knowledge Hub
NR	New Radio
PCI	Physical Cell ID
PDSCH	Physical Downlink Shared CHannel
RA	Risk Assessment
RAN	Radio Access Network
RBC	Red Blood Cells (erythrocyte)
RBS	Radio-base Station
RF	Radio Frequency
RT-qPCR	Reverse Transcription quantitative real-time Polymerase Chain Reaction (PCR)

SAR	Specific Absorption Rate
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SOP	Standard Operating Procedures
SRB	Signalling Radio Bearer
SSM	Swedish Radiation Safety Authority
SS/PBCH Channel	Synchronization Signal and Physical Broadcast Channel
SS-RSRP	Synchronization Signal Reference Signal Received Power
UE	User Equipment
URL	Uniform Resource Locator
URLLC	Ultra-Reliable Low Latency Communications
W-LAN	Wireless Local Area Network
WHO	World Health Organization
WP	Work Package
WRC	World Radio Conferences

Executive Summary

The deliverable D2.1: "EMF value drivers towards stakeholders needs on real case studies" is part of the Work Package (WP) 2 "Requirements Analysis, Specification and Design" and lays an early groundwork for all later activities of the NextGEM. The overall goal of this deliverable is to deliver a thorough and clear insight of all the value drivers of Radio Frequency Electromagnetic Fields (RF-EMF) public use in urban, residential, and occupational settings, through the scope of safety and public health. All stakeholders needs and considerations, concerning 5G telecommunications actual implementation schemes, are examined as causal determinants of the aforementioned value drivers and of the design requirements. NextGEM's main goal is to provide a framework for the generation of health-relevant scientific knowledge and data on new scenarios of exposure to EMF in multiple frequency bands as well as to develop and validate tools for evidence-based risk assessment and provide a novel data sharing scheme for the communication and dissemination of all outcomes to the continuously evolving research and dialogue on the matter.

An important contribution of the present document to the entire project is to account for a detailed preconditioning of the design requirements and specifications of all activities, to outline the context on which the NextGEM's novel research approaches are based, describe the challenges, and set the directives of the forthcoming tasks of the project based on the EMF value drivers towards stakeholders needs.

1 Introduction

In terms of technical and creative design, as well as biological study on RF-EMF effects, NextGEM offers a practical and elegant research strategy. A description of these aspects is delivered in this document, with respect to their role in the whole project. The specified Case Studies (CSs) are furthermore described, and the experimental frame of the project is introduced. RF-EMF exposure modelling techniques and examples, measurement details and requirements and design incentives are presented by the partners, regarding the state of the art, and beyond. In addition, possible biological effects of RF-EMF exposure in humans are listed and the need for the NextGEM's umbrella reviews of up-to-date research is explained. NextGEM's novel paradigm of manifold biological research aspects is extensively presented and analysed. The outcomes of the novel research are expected to fulfil the existing gaps of knowledge, and data, in particular areas, and eventually serve as a tool against the general population's misconceptions on 5G and in favour of any possible regulation updates.

The principle of a consistently informed public communication for that matter, is very important, and is apportioned to have led to an urge for a heuristic but more cautious social approach, by means of interactions between the different parts involved. Great significance is attributed to the whole set of the public's contemporary perceptions on 5G safety issues, in relation with other important stakeholders' needs and perspectives, regarding the current and future technological frame. A nodal point of the project effort is considered to be the establishment of a validation and acculturation of the scientific research towards an efficiently risk perception and communication strategy scheme.

The research undertaken by NextGEM is interdisciplinary and multi-levelled and requires careful design, along all stages, from production to delivery. The requirements and specifications are based on real-life scenarios that are already met, but not yet fully examined. The constant changes of the 5G implementation possibilities, imposed by technical and technological progresses in the field, the available advanced biological approaches and tools, and the already existing technical challenges are decisive factors of the NextGEM's design and requirements analysis.

1.1 Mapping NextGEM Outputs

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

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

TASKS	
Task Number & Title	**Respective extract from formal Task Description**
Task 2.1 - Stakeholder mapping, end-user needs analysis and Case Study design through processes of co-design	This task will analyse the EMF value drivers in real- life scenarios and provide detailed and up to date analysis of the current technical landscape in terms of current and future telecommunication technologies. Stakeholder needs and safety requirements will be identified and different appropriate roles for respective partners in Case Study design will be established. The focus of the task is to identify potential health risks in real life scenarios where existing or future EMF exposures exist, reflected in each case study, providing research directives and innovation approaches that are meant to match the derived requirements in the following work packages. Finally, the task will ensure the project's progress beyond the global competitive landscape as the associated research directions (WP3-WP5).
DELIVERABLE	
Deliverable: D2.1: EMF value drivers towards stakeholders needs on real case studies (M06) This deliverable will analyse the detailed specification of stakeholder and end-users needs on existing case studies.	

1.2 Deliverable overview and report structure

Based on the objectives and work carried out under Task 2.1, the document starts with the Executive Summary followed by the introduction of the document in Section 1.

Section 2 includes stakeholder needs for regulatory authorities and public, safety requirements.

Section 3 provides an extensive analysis of the EMF value drivers in terms of current and future telecommunication technologies in real-life scenarios.

Section 4 defines bio-experimentation background and foreseen activities for assessing bio and health-related effects

Section 5 describes health risks in real life scenarios and under the proposed NextGEM case studies.

Finally, Section 6 concludes the deliverable.

2 Stakeholders' needs and safety requirements

Mobile technologies including 5G are taking on an enormous industrial and economic role. In comparison, the amount which is devoted to research into possible health effects of mobile communication technologies is modest. Research data on 5G (3.4-3.8 GHz) and health is only just beginning and there is hardly any research data on the higher frequencies (26-28 GHz). The EU, which had previously funded EMF and health research projects between (2015-2020) with about 22 million EUR, has in its new research and innovation framework programme Horizon Europe, devoted 30 million EUR to fund 4 projects, in which NextGEM is one of these, to investigate new generation of radio-communication, e.g. 5G, and potential health effects to increase knowledge and awareness among the stakeholders.

The requirements for building knowledge and awareness among the stakeholders, with respect to potential human health risk due to the exposure to RF-EMF in real life scenarios, have been analysed. 5G stakeholders have been identified amongst the general population and several sectors such as the telecom industry, governmental institutions, scientific institutions, and agencies. The requirements mainly aim to generate quality data in terms of research outcomes to have a solid health risk assessment for updating the guidelines for exposure limits for both general public and workers; to implement public policy on RF-EMF and to improve awareness on existing and future EMF exposure in the public.

Figure 1: The connected Community [1]

2.1 Identify stakeholders

In general, society as a whole has an interest in correct information about health effects that can result from RF-EMF exposure. However, different stakeholders have different specific needs.

NextGEM distinguishes six types of stakeholders.

(1) **Telecom industry**. The manufacturers and suppliers of network components and user equipment, as well as the providers of telecommunication services, introduce the sources of the RF-EMF into society. The telecom industry wants - and is allowed - to put only safe products on the market.

(2) **General population**, including children, women, the elderly and vulnerable groups, are those who are exposed and who may have or experience health effects.

(3) **Workers** are considered to be a special subgroup that may be exposed to a higher degree than other members of the population because of their specific work.

(4) **Governments** and **health institutions** are responsible for protecting the public and workers from potential adverse health effects from exposure to RF-EMF. To this end, they are empowered to choose what is and is not considered acceptable, to set exposure limits and to enforce those limits.

(5) **Scientific research institutes** and scientific agencies provide the knowledge, including associated uncertainties, necessary to fulfil the role of industry and governments in preventing exposure and protecting people.

(6) Finally, and therein lies one of the spearheads of NextGEM, a special type of 'stakeholder' will be considered: **Educational institutions and (news) media**. They are special because they take part in creating 'awareness'. This last type of stakeholder can also include the first four. This is because communication on the matter is continuously conducted by the industry, by governments, by scientific institutes and bodies, and by citizens (think tanks or action groups, community members, neighbours, family, and acquaintances). All use educational material. One of the results of NextGEM, as a social output, could be one or more modules tailored for the regular education programme.

2.2 Guidelines about RF-EMF exposure to the public

In Europe the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines 2020 and the Institute of Electrical and Electronics Engineers (IEEE) Guidelines are leading in protection of the general population and the workers [2][3]. However, these guidelines only aim to protect from currently scientifically proven short term health effects, i.e. a body core temperature rise where temperature increases more than +1°C, which are all based on the amount of EMF power absorbed or nerve stimulation. Nerve stimulation will not occur if EMF levels remains below the basic restrictions protecting against heating, and neither will electroporation. Electromagnetic radiation from antennas can have a heating effect on the body. Other health effects have not been explicitly demonstrated. The heating effect of RF-EMF, if the electromagnetic field is strong enough, can pose health risks. Accordingly, exposures must be below levels that cause heating. Base station antenna owners and providers of other RF-EMF equipment must adhere to these limits. Competent authorities checks that the exposure limits are not exceeded by taking measurements of the electromagnetic field.

A lot of research has been and is being done regarding RF-EMF and health. A link between exposure to RF-EMF from mobile communication equipment and negative health effects has not been demonstrated and is also unlikely [4]. At the same time, negative health effects cannot be ruled out. The advice is to continue to conduct research, including 5G. The precautionary principle is supported by applying the ICNIRP guidelines, by regularly taking measurements at antennas, and by following the latest scientific results. Most European countries apply the exposure limits of the ICNIRP. ICNIRP is an independent international group of scientists that sets exposure limits for electromagnetic radiation, in forms of basic restrictions (expressed as SAR, W/kg, for RF-EMF) and reference levels (expressed as power density, /W/m²), respectively. A detailed explanation of these terms is provided in [2]. In 2020, the ICNIRP updated their exposure guidelines exposure limits [2]. The guidelines consider vulnerable groups such as children, pregnant women, the elderly and the sick. The total amount of electromagnetic radiation must always remain below the limits expressed as reference levels. The heating properties varies from frequency to frequency, whereby a certain frequency can warm up our body faster than another. Therefore, the limits differ per frequency band Table 2. In the frequency band between 30 MHz and 6.0 GHz, lower frequencies cause more heating of the human body than higher frequencies, due to their difference in penetration depths and hence their influence on body-core temperature. Therefore, the limits for low frequencies are stricter than the limits for higher frequency bands.

Table 2: Reference levels, averaged over 30 min and the whole body, for the general public [2]

Frequency	Application	Reference level (in W/m²)
30 - 400 MHz	broadcast	2 W/m²
700 MHz	**5G**	**3.5 W/ m²**
800 MHz	4G	4 W/ m²
900 MHz	2G, 3G	4.5 W/ m²
1400 MHz	4G	7 W/ m²
1800 MHz	2G, 4G	9 W/ m²
2100 MHz	3G	10 W/ m²
2400 MHz	Wi-Fi	10 W/ m²
2600 MHz	4G	10 W/ m²
3500-6000 MHz	**5G**	**10 W/ m²**

The Council of the European Union has formally recommended in 1999 the ICNIRP guidelines for the general public [5]. Most European countries adhere to these guidelines. Some countries make a different choice based on political or social considerations. Exposure limits applied for workers are different from those applied for the general public. Employees who work near antennas are expected to be well informed about the situation by their employer or client. The European Parliament and the Council of the European Union have drawn up directive 2013/35/EU [6] based on the exposure limits of the ICNIRP at that time for workers who work near antennas.

For exposures in frequency bands above 6 GHz, the mmWaves, EMFs are absorbed more superficially. The absorbed EMF power is not described by the specific absorption rate (SAR) in W kg^{-1} of the tissue, but by the absorbed power over area (W/m^{-2}), for short term exposures, when there is not sufficient time for heat diffusion to occur, the absorbed energy density J/m^2 is used. As the penetration gets more superficial with increasing frequency the heating occurs predominantly in the skin and tissues just below such as blood vessels.

2.3 Monitoring networks of RF-EMF exposures in Europe

Sensor technologies for monitoring purpose are continuously used in different environments to unobtrusively measure and monitor various types of exposures and provide real time feedback or access to data on demand. The exposure from RF-EMF is measured in both spatial and temporal distribution to validate the regulatory limits as well as to appease public uncertainty and anxiety about the ever-increasing use of wireless technologies. Currently more than 1400 stations across Europe provide exposure measurement data for RF-EMF [7] as demonstrated in Table 3.

Table 3: Active EMF monitoring networks in Europe from [7].

Country	Starting date (year)	Number of stations	Frequency Range
Hungary	-	-	100 kHz – 7 GHz
Spain (Catalonia)	2005	336	10 Hz – 3 kHz 900 MHz / 1800 MHz / 2100 MHz (bands) 100 kHz – 8 GHz
Spain (Sandander)	2014	40	900 MHz /1800 MHz / 2100 MHz / 2400 MHz (bands)
Spain (Vitoria Gasteiz)	2017	6	900 MHz /1800 MHz / 2100 MHz (bands)
Romania	2015	150	100 kHz – 7 GHz 925 MHz - 960 MHz 1805 MHz – 1860 MHz 2110 MHz – 2170 MHz
Serbia	2017	90	100 kHz – 7 GHz 925 MHz - 960 MHz 1805 MHz – 1860 MHz 2110 MHz – 2170 MHz
France/Belgium	2020	102	80 MHz – 6 GHz
Greece (NOEF)	2015	500	100 kHz – 7 GHz / 100 kHz – 6 GHz
Greece (Pedion24)	2007	246	100 kHz – 3 GHz

In the 5G allocation, the usage of mmWave (i.e., FR2 band) is forecasted and only partially implemented in some EU countries; one of the reasons of this is the reduced data and availability of monitoring sensor technologies, which could be used to provide data to better improve the public acceptance of these systems.

2.4 Knowledge and knowledge gaps from scientific studies on mmWave effects

A recent review pointed out that only a few studies have addressed the question of heating of skin and skin cells from RF-EMF at 6 GHz of higher frequencies [8]. Several of these studies are furthermore relevant for exposure s to radar installations, and not to mobile communication, making exposure comparisons difficult. For instance, during use of mobile communication devices, both antennas and devices will be continuously in very close proximity of the user's body, so the exposure may not occur in the far field. Also, Simko and Mattsson [9] mention that additional research on effects on the skin is necessary. Apart from acute skin damage from tissue heating (burns), also less acute effects (such as inflammation, tumour development, etc.) appearing after prolonged and repeated heating of superficial structures (the skin) should be investigated. This would imply that thermal effects occur that are not due to acute but to chronic damage.

Additional recent reviews [9][10][11] show no scientifically proven health effects at frequencies above 6 GHz at the low-level RF fields such as used by 5G networks [10]. These conclusions were based on experimental research performed *in vitro*, and, most frequently, *in vivo* studies.

Though there are a number of studies reporting biological effects and health effects, Karipidis et all [10] mentions that, based on 107 experimental studies that investigated various bioeffects including genotoxicity, cell proliferation, gene expression, cell signalling, membrane function and other effects, reported bioeffects were generally not independently replicated and the majority of the studies employed low quality methods of exposure assessment and control. Wood et all [11] reports a negative correlation between effect size and quality score from a meta-analysis of 107 *in vitro* and *in vivo* studies at low exposure levels, mostly in the range of 30 to 65 GHz. Though most of the studies with a high effect size are in the range of 40 – 55 GHz, this negative correlation is still in effect for this range. They conclude that their study does not confirm an association between low-level millimetre waves and biological effects. [9] showed that even though out of 94 publications 80% of the *in vivo* and 58% of the *in vitro* studies showed response to exposure, there was no consistent relationship between power density, exposure duration, or frequency, and exposure effects. Some publications mentioned the occurrence of non-thermal effects, but this cannot be sustaintiated as no clear explanation was offered and only a few studies applied appropriate temperature controls. Also due to contradictory information from *in vivo* and *in vitro* studies, no clear evidence on possible exposure effect associations is available.

For experimental studies not finding conclusive evidence for effects has been attributed to quality issues in experimental designs, particularly regarding dosimetry (and incident EMF) and temperature control [10]. Also, the modulation may cause different effects, although ICNIRP (2020) does not make a distinction between continuous and discontinuous (e.g. pulsed) EMFs, as there is no evidence that they result in different biological effects [12][13] is still a source of debate for mmWaves, since there is a lack of relevant studies. Therefore, future experimental studies with millimetre waves should improve the control of local heat developments on small surfaces of skin or the eye, for instance by application of better types of thermal probes (thermocouples are better than fibre optic probes) and optimal size of the probe (smaller probes are more accurate) [14]. Simko and Mattsson [9] states that there is a need for exact dosimetry with consideration of the skin for relevant frequency ranges, including the consideration of short intense pulses (bursts). They propose the following future studies:

- Studies on inflammatory reactions starting from the skin and the associated tissues.
- *In vivo* studies on the influence of a possible tissue temperature increase (e.g., nude mouse or hairless mouse model).
- *In vivo* dose-response studies of heat development.
- Use of *in vitro* models (3D models) of the skin for molecular and cellular endpoints
- Clarification of the question about non-thermal effects (*in vitro*).

Availability of epidemiological data is limited, as the 5G network is only recently deployed in some countries, and not yet in others. And if so, mostly the FR1 bands are used, with less contributions from FR2 bands. Therefore, no population exists that has been at risk for a substantial time. The current epidemiological evidence is from people exposed to radar frequencies above 6 GHz, but radar uses different intensities and modulations and is very far from the body. Many of these studies cannot be used for any risk determination regarding 5G, because the radar systems used frequencies outside the range 20 to 40 GHz, or because the studies did not state which radar systems or frequencies had been used [5]. Anyway, available epidemiological studies showed little evidence of health effects including cancer at different sites, effects on reproduction and other diseases [10]. Until now no studies on associations between non-thermal effects or on non-specific physical symptoms on possible exposure to 5G signals have been published, although epidemiological research on 4G effects showed effects at the Wi-Fi frequencies [15][16].

In order to monitor populations for potential long-term effects or to study effects among electrosensitive groups, for instance, for non-specific physical symptoms in Ecological Momentary Assessment (EMA) [17][18], we need body worn sensors capable of measuring the incident field strength for 5G FR1 and FR2. A number of off the shelf wearables are available for the 3G, 4G and 5G FR1 bands [19][20], and also stationary equipment has been deployed [21]. For FR2 bands, though for stationary measurements for legal compliance several protocols and measurement devices have been developed [22], there is a need for new wearables or measurement vests with multiple sensors to be able to correct for influence on the body during shading or reflecting of the 5G signals [16]. This should be developed for the FR2 bands. Also, there is the need to develop and test new study protocols as the protocols for 4G surveys [23] have to be changed to appropriate measurement protocols for 5G FR1 [24].

2.5 Limitation of risk assessment, evaluation, and communication on existing or future EMF exposure in the general public

Risk assessment tells us "How risky is an agent", in our case the RF-EMF.

Risk assessment is a qualitative and/or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards. The term "health effect" should not be confused with the term "biological effect". In any case, the exposure to RF-EMF may cause some noticeable or detectable physiological change in a biological system which is not necessarily hazardous.

There is no evidences of adverse health effects at exposure levels below the basic restrictions as described in the ICNIRP (2020) guidelines [2] and no evidence of an interaction mechanism that would predict that adverse health effects could occur due to radiofrequency RF-EMF exposure below restriction levels [25][26].

Figure 2: Risk Assessment Phases

Risk management answers: "What shall we do about it and what are we willing to accept "[27].

Risk management is a process with several steps: identification of hazard, characterization, classification, reduction, monitoring and communication of the measures needed to protect public health (Figure 2). Without reliable data and accurate sources of information based on high quality studies (clinical trials, systematic reviews, meta-analysis, epidemiological (cohort, case-control, *in vivo* and *in vitro* studies) we cannot make a solid risk assessment and management. All evidence must be based on criteria of quality, validity, relevance and must be classified on weight of evidence [25]. Risk management must include all the proposed regulatory measures that reside on the conclusions of risk assessment, as well as, the considerations of legislative and technical feasibility, social, economic, and political enforcement tools, and of course, engineering criteria and the limits of science. Meanwhile, there are some limitations on **evaluation** and **communication** of the effects of RF-EMF exposure. It must deal with many shortcuts (restrains) related with dosimetry, ethical problems concerning the studies on human exposure, absence of a clear and plausible causal mechanism, difficulty in extrapolating results to humans, misinterpretation of studies, etc. Choosing the risk reduction measures is the most difficult problem because it is related with acceptability, public perception, and the uncertainty margins of the research. The value drivers of the risk perception on RF-EMF exposure [28] must be identified, to facilitate the adoption of the risk reduction measures and promote the principles of good faith and trust in the scientific community and of course the regulatory public health authorities (EU, WHO, ICNIRP).

The citizens' needs and concerns about RF-EMF are being undercut by misinformation that undermines public regulations and communication actions and consequently the efforts to establish safe limits of exposure to RF-EMF. We need to understand why there are people against science and what we can do about it [28]. The acceptability is a variable related to risk perception and it is prone to misinformation and disinformation (i.e., 5G and coronavirus, anti-vaccine, etc.) conspiracy theories, hoaxes, and falsehoods. Claims of dubious veracity frequently go viral on the internet. In the long term, the only lasting "vaccine" against this onslaught of poisonous fictions is to improve our societal critical-thinking skills. Conspiratorial thinking contributes to the rejection and dissolution of science. On the other hand, good faith, and acceptance of science, are strongly associated with the perception of a consensus among scientists. The WHO "infodemic" declaration [29] claims that there is an overabundance of information, some accurate, and some not, that makes it hard for people to find trustworthy sources and reliable guidance when they need it. Falsehood diffused significantly faster, deeper, and more broadly than the truth in all categories of information [30].

There are many factors regarding the policy making decisions based on risk evaluation that we must identify, some of them are: different drivers' perceptions, diverse needs and concerns, lack of availability of conclusive evidence, impact of social media, protests of activist groups, regulatory discrepancies in limits of public exposure to RF-EMF and legal court interpretations of precaution principles. But misinformation is also affected by science sidekicks (lack of data, inadequate measurements, human errors, publication bias, citation misdirection, etc.) [31]. We cannot forget that science is inconclusive, is not exact and can never provide "the perfect solution". Therefore, we must be fully aware of the limitations of the risk assessment methodology. When one refers to risk assessment, not everybody agrees on what it consists of, as it often generates confusion, misunderstanding and controversy about its scope and purpose. There is a frequent discrepancy in the interpretation of the results of such scientific studies as those of complex biological systems interacting with EMF.

In our case, the novel 5G technology has not been welcomed by everyone, citizens have perceived that EMF from 5G network base stations are potential health risks, which has been shown by the protests in Korea, United Kingdom, and Switzerland. Authorities such as the WHO made statements that EMF from 5G network base stations would not cause substantial adverse health effects, as their levels were well within the regulated exposure limits; however, the public high-risk perception remains. Dread and unknown risk considerations are natural candidates to be regarded as drivers of inter-individual differences in risk perception of 5G. Some people may perceive high levels of unknown risk because 5G is a novel technology with potentially uncertain consequences [28].

How people take decision on risks? People often rely on simple heuristics to form their perceptions when they make decisions on RF-EMF risk perception, so risks can be misjudged, sometimes overestimated, or underestimated. We need to impose a better understanding of the factors that determine which heuristics people rely on, when evaluating hazards and risk perceptions [32]. But it is crucial to recognize the importance of "trust" in risk perception as a mechanism for the reduction of complexity that forces citizens to deal with a vast amount of confusing and difficult to understand information. We must provide the knowledge and tools that can improve risk understanding communication by adding **new drivers** that reduce individual concern, facilitate quicker policy acceptance and institutional support levels.

From a psychobiological point of view, risk perception allows us to quickly identify important threats that must be encountered through immediate action. It has been shown that perception and acceptance of risk are influenced by sociocultural factors like news media or social groups among others. There are quite a few studies which have assessed risk perception related to RF-EMF, so it is important that public agencies that are responsible for regulating health policies should gain a full understanding of the mechanisms behind the formation of perceptions about such new technologies in the general population. NextGEM will study the factors that have contributed to such an increased risk perception.

Risk management has become increasingly politicized, and polarized views and overt conflict have become pervasive. Consequently, distrust in risk evaluation and risk management plays a central role in this perspective. The conflicts and controversies surrounding risk management are not due to public ignorance or irrationality, but instead are seen as a side effect of our remarkable form of participatory democracy, amplified by powerful technological and social changes that systematically break trust. Recognizing the importance of trust and understanding the factors that destroy trust has vast implications for how we approach risk management. The competent authorities who promote and regulate public health and safety, need to understand how people think about, and respond to risk. Without such understanding, well-intended policies may be ineffective. The risk assessment must reflect legitimate citizen concerns that are, sometimes, omitted from expert risk assessments. Therefore, risk communication and risk management efforts are destined to fail, unless they are structured as a two-way process. Each side, experts and public, has something valid to contribute and must respect the insights and intelligence of the other [33].

2.6 Practical insights in public policy regarding EMF for research institutes and governing authorities

In order to implement public policy on RF-EMF, governing authorities (want to) rely on sound knowledge of, firstly, the actual level of exposure of the public, and, secondly, above which levels of exposure there is an actual or possible health risk.

At the European level, and also in the individual member states, there are scientific committees that advise on this: SCHEER in Europe and, for example, SSM's Scientific Council on Electromagnetic Fields in Sweden and the Health Council in the Netherlands. The advice of these committees in Europe is based mostly on the ICNIRP Guidelines, considering at least the effects of excessive heating due to exposure to radiofrequency EMF. For well-known risks due to high exposure levels, there is sufficient information available to derive exposure limits. However, for exposure levels below the exposure limits, there are suspicions or indications of possible health effects. Due to the uncertainties about these possible health effects governments seize the precautionary principle and the ALARA ("as low as reasonably achievable") principle.

In 5G, there are higher frequencies and other beam techniques applied. This leads to different exposure patterns [34][35]. And for the sake of enforcement, but also for scientific experiments, a detailed knowledge of that exposure in practical circumstances is indispensable. This also applies to taking measures.

The occupational hygiene strategy is followed in the Netherlands to keep employees healthy. In short, this strategy is the order in which a company must take measures to ensure that the work can be done as healthily and as safely as possible.

- **Step 1**: Replace the source with a source that does not pose any danger or is less dangerous;
- **Step 2**: Apply technical measures, work processes, equipment and materials that prevent or limit the risks;
- **Step 3**: Take collective protection measures at source or take organizational measures;
- **Step 4**: Provide personal protective equipment for employees who are or may be exposed to electromagnetic fields.

In addition, a measure from any step may only be taken if the earlier step is not reasonably technically, operationally, or economically possible. It is important that employers and employees have information material that meets requirements, such as trustworthiness, but also legibility [36].

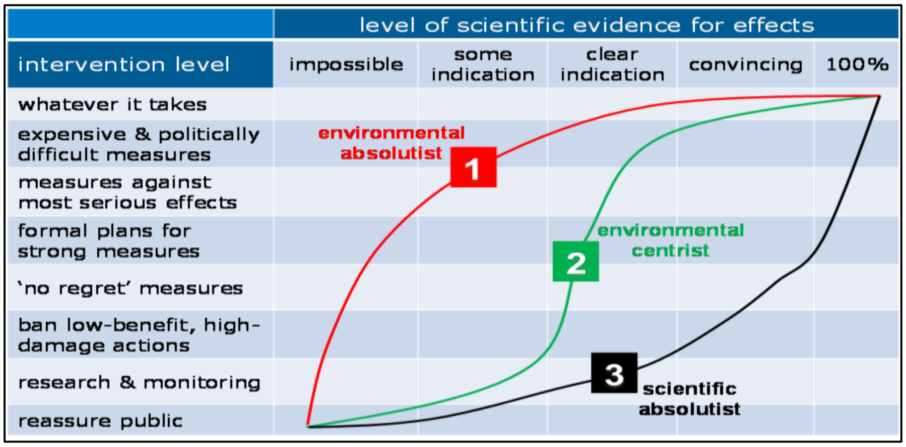


Figure 3: Type of intervention versus the level of scientific evidence for several types of stakeholders [37].

In the case of unknown health risks, stakeholders have to deal with the actual knowledge on the level of scientific evidence. The attitude of the people making the risk assessment determines which choice they make in the degree of intervention that goes with their assessment of the strength of the scientific evidence (Figure 3) [37]. In societal discussions between stakeholders, they have to agree on the level of scientific evidence. For example, in a discussion of "formal plans to take rigorous action," an environmental absolutist will never agree with a scientific absolutist on how to interpret the strength of the evidence.

The implementation of the Council Recommendation (1999/519/EC of 12 July 1999 on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz)) and the Workers Directive (Directive 2013/35/EU) varies among the European member states (Figure 4) [37][38]. The groups are classified as: Group 1 (purple): legal limits derived from EU recommendation; Group 2 (pink): no legal limits or limits less strict than in EU recommendation; Group 3 (yellow): stricter limits than in EU recommendation (from [37], updated in 2020).

Member states differ in policies regarding RF-exposure [37] and also in risk communication and type of public administration [39]. These factors and aspects are important in making practical guidelines. This brings us to the need of constant regulations updates, based on well documented novel research especially on the biological aspects of the issue.

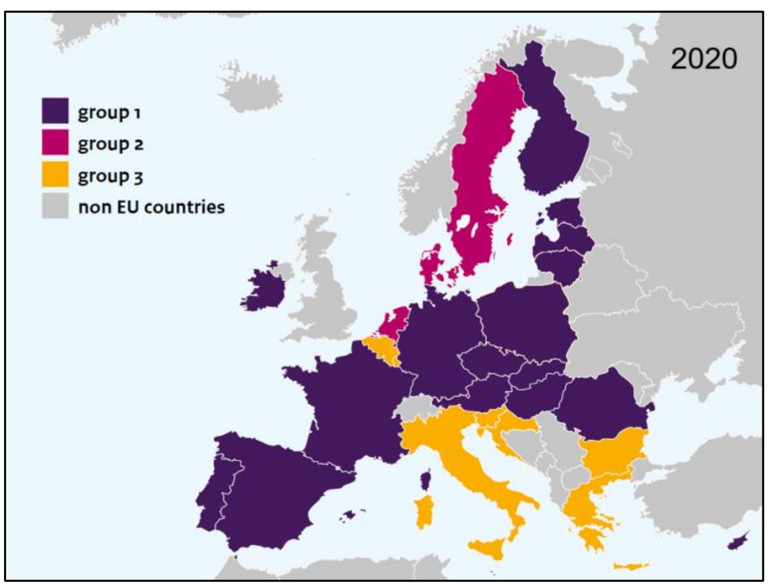


Figure 4: Overview of limits for exposure of the general population to radiofrequency EMF in the EU.

3 Analyse the EMF value drivers of the current and future telecommunication technologies in real-life scenarios

From their conceptual discovery in the end of the 20th century to their first usage as a means of information transport, RF-EMF have been pervading every aspect of the modern connected society as defined by International Telecommunications Union (ITU) in Figure 5. In this section the current technologies employed in the design and usage of current communication systems with a focus on the challenges arising from their planning, deployment and measurement are reviewed. An outlook of what lies ahead, i.e., beyond 5G is then presented. Furthermore, the technologies for characterizing the RF-EMF, their distributions in real life scenarios are presented, so as to introduce the readers to some of the challenges the NextGEM project is tackling. In addition, this section presents the tools from a simulation and experimental perspective capable of providing specific information to the regulatory agencies, system providers and ultimately to the public on what is the RF-EMF field intensity at specific location and even how those fields distribute inside the body. Moreover, a brief review on the underlying (complex) hardware to enable the characterization of these fields is given, highlighting the challenges and thus absence of experimental surveys, of continuous field monitoring in real life use scenarios.

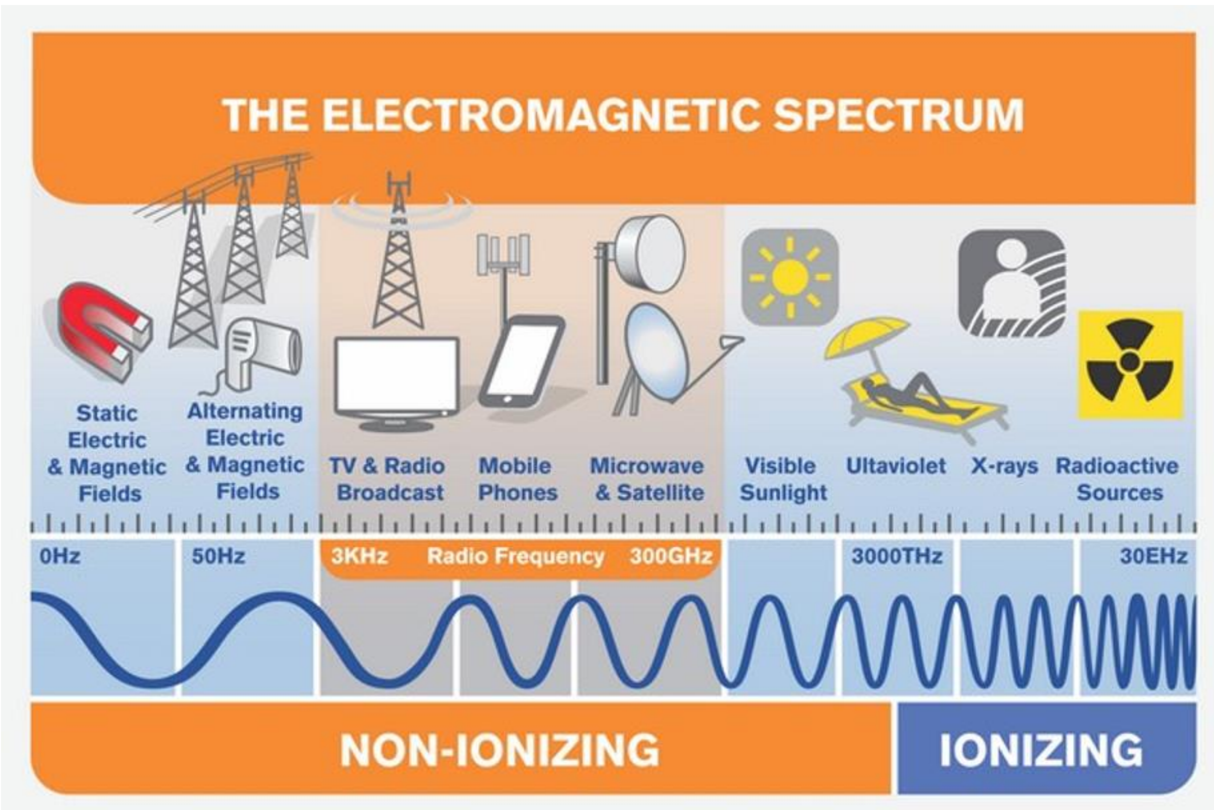


Figure 5: The Electromagnetic Spectrum (ITU)

Development of 5G has represented a huge engineering challenge. New technical solutions based on sophisticated strategies able to share the resources available in the communication channel among the users with unprecedented efficiency have been conceived and implemented, and, after a path full of difficulties, nowadays technology is mature for the full deployment of 5G. On the other hand, the advanced technological solutions introduced in 5G posed a number of new challenges with reference to measurement techniques and architecture modelling and mapping. The aim of this section is to analyse the current technical landscape, and to review the novel techniques proposed to measure 5G signals EMF levels and 5G architecture models.

3.1 Analysis of the current technical landscape in terms of current telecommunication technologies

As of 2022, 5G technologies have been widely adopted in both user equipment (e.g., smartphones) and network devices (e.g., routers). This adoption is being carried out in stages (*Releases*) since the first deployment of 5G-capable networks in late 2018, with each stage widening the range of deployment, accompanied with new specifications. Currently, the Release 16 focuses on enabling these technologies in areas that have a commercial interest for enterprises, such as Internet of Things (IoT) and Ultra Reliable Low Latency Communications (URLLC), while the previous Release 15 was more limited to mobile broadband enhancements. However, the key enabler of all applications in 5G, is the advancement in wireless connectivity capabilities, mainly implemented at the radio access network (RAN) level. The current range of frequencies of 5G has been increased to 52.6 GHz as of Release 16, allowing higher capacity, and is expected to reach 71 GHz in Release 17. This is complemented with the ability of 5G networks to use different bands for a different coverage/capacity ratio as depicted in Figure 6. Low frequency bands provide high coverage but low capacity, while mid-band frequencies provide both sufficient coverage and capacity. Millimetre wave (mmWave) frequency bands technology can deliver very high throughput and low latency, enabled by a considerable increase in usable bandwidth, but at the cost of limited coverage. Mid-band frequencies can be the preferred choice for 5G network operators as they can sustain very high throughput (performance) and at the same time allow the deployment of 5G capabilities (e.g., increased spectrum) on existing 4G infrastructure. The latter has been instrumental in facilitating the fast adoption of 5G in a relatively short period of time.

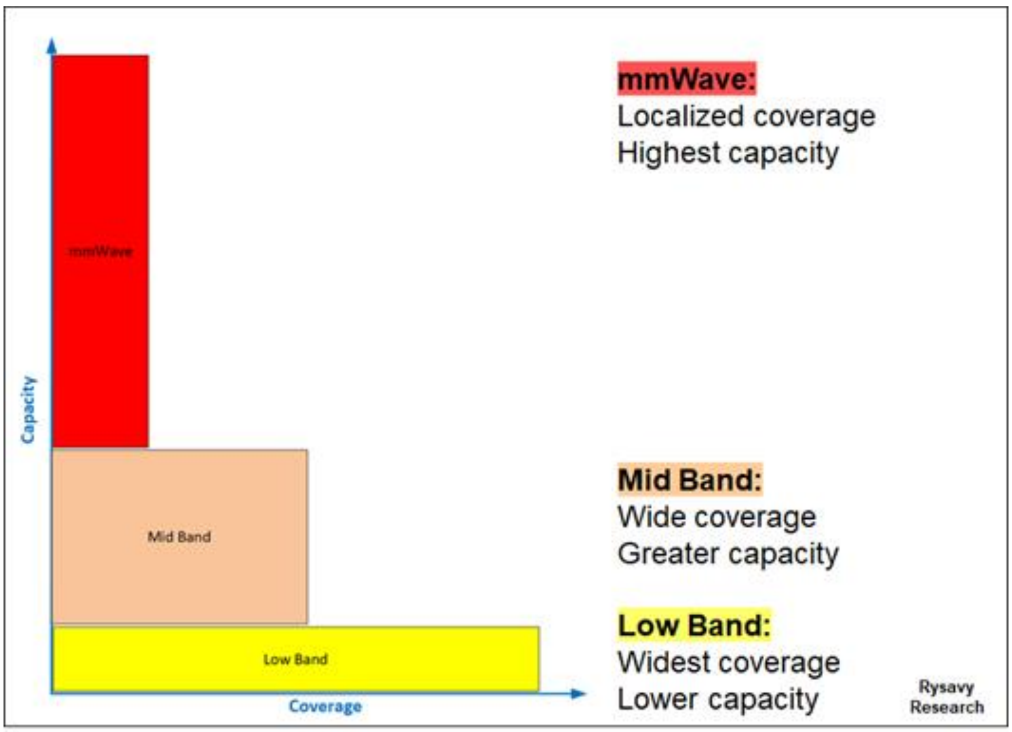


Figure 6: Coverage/Capacity ratio per band frequency [40]

The next iteration of 5G features and standards, Release 17, reached functional freeze (system design) in March 2022, with the general rollout yet to be announced. Some of the most important enhancements of Release 17 are [41]:

- Further enhanced multiple input/multiple output (MIMO)
- Coverage enhancements
- Spectrum expansion
- URLLC enhancement

3.2 Novel techniques to measure 5G signals EMF levels in real conditions

Estimation of the field level radiated by cellular systems has been the object of intense studies, and techniques for 2G, 3G and 4G signals are part of international standards and are routinely used [42]. However, application of these techniques to 5G signals is not straightforward due to some specific characteristics of the 5G signals. One of the main problems in the assessment of EMF exposure is related to the large variations of the field levels since the radiated power changes over time with data traffic variation. Particularly, in the absence of 5G users only the SS/PBCH channel (Synchronization Signal and Physical Broadcast Channel) is transmitted. Measurements in these conditions give a quite low field level, that however, is not representative of the field level in presence of data traffic. Another characteristic of 5G gNB, a node in a cellular network that provides connectivity between user equipment (UE) and the evolved packet core (EPC), is that the always present channel, i.e. SS/PBCH, is transmitted using beams (called 'broadcast beams') that are less direct compared to the beams used to transmit users' data traffic (called 'traffic beams'). This prerogative of 5G gNBs leads to issues and challenges related to EMF measurements in 5G technology which are discussed in [43], in which it is noted that due to massive MIMO and beamforming existing measurement methods can lead to significantly overestimated results when applied to 5G networks.

Measurement strategies specifically developed for 5G have been proposed by many research groups. Direct estimations using channel power measurement, even when possible, suffer from the highly variable power radiated by the gNB, making the result strongly dependent on the level of traffic data in the measurement period. In order to overcome this problem, the research has been focused on Maximum Power Extrapolation (MPE) methods, that allow to estimate an upper bound of the field level in the worst traffic conditions. The value obtained by the MPE procedure is an unrealistic upper bound, since it assumes that all the resources of the communication system are dedicated to only one user. With the intention to obtain a realistic value this quantity must be scaled by a proper correction factor with respect to the stochastic nature of the problem. Accordingly, the estimation of a realistic 5G field level requires two steps, i.e. the MPE procedures and the estimation of the scaling parameter.

In [44], two different potential methods for the extrapolation process, called "frequency selective method" and the "SS demodulation-based method" are described. The first one is based on frequency domain and requires some preconditions. One of these is that resource elements outside the SS/PBCH blocks are never transmitted with higher power and higher antenna gain due to beam forming compared to the nonzero resource elements used in SS/PBCH blocks. The second one does not require this precondition. Furthermore, it is possible to separate the exposure due to different cells.

In [45] a procedure using spectrum analysis with water-falling technique was proposed and experimentally tested [46][47]. A procedure based on the use of the PDSCH/DMRS as reference signal was proposed and experimentally tested in [48] and [49]. Measurements using SS-RSRP as reference signal were carried out in [50][51]. More recently, procedures that avoid the use of reference signals have been developed and experimentally tested [52][53]. Anyway, techniques based on the demodulation of the signal require very expansive instrumentation, still require homogenization and validation in all real scenarios (NLOS, full traffic, etc), and usually lack of uncertainty assessment (an attempt of filling this gap can be found in [16]). Measurements of FR2 signals follow the same strategies developed for FR1 [54][55][56][57]. Regarding the estimation of the scaling factor for a realistic conservative RF exposure assessment, a statistical model for 5G was proposed in [58]. Further statistical models have been described in [59] considering BSs fully loaded and different configurations of active UEs per cell, and successively in [60], and more recently in [61]. Besides statistical approach, a deterministic approach has also been proposed in [62]. Both statistical and deterministic models have to be validated in real scenarios.

3.3 Numerical modelling of EMF distributions inside the human body and animals

There are several commercial/open-source electromagnetic Finite Element Analysis (FEA) software brands on the market, including MagNet, COMSOL, ERMES, JSOL, NEC, MAXWELL, ANSYS Multiphysics, OPERA, FLUX and others. In Table 4, a comparison of Electromagnetic Simulation Codes (and antennas) is shown.

Table 4: List of Radiation Pattern Simulation Software [63]

Name	License	Area of application
AWR Analyst	Commercial	3D structurers (including 3D Antennas), Waveguides, 3D filters, PCBs, Multi-Layer PCBs, LTCC, HTCC, On-Chip Passives, Printed Antennas. Integrated into Microwave Office
AWR Axiem	Commercial	PCBs, Multi-Layer PCBs, LTCC, HTCC, On-Chip Passives, Printed Antennas. Integrated into Microwave Office
Bempp	Open source	An open-source computational boundary element platform to solve electrostatic, acoustic and electromagnetic problems.
COMSOL Multiphysics	Commercial	General Purpose. A low/high frequency electromagnetics code associated with antenna, RF identification and high-speed digital applications.
CST Microwave Studio	Commercial	CST Studio Suite is a high-performance 3D EM analysis software package for designing, analyzing and optimizing electromagnetic (EM) components and systems. Common software based on the finite integration technique (FIT)
Elmer FEM	Open source (GPL)	General Purpose includes 2D and 3D magnetics solvers, both static and harmonic. 3D solver is based on the Whitney AV formulation of Maxwell's equations.
EMAP	Commercial	EMAP is a family of three-dimensional electromagnetic modeling codes developed at the University of Missouri-Rolla and Clemson University. Each code has different capabilities, but they all have a common easy to understand input file format. EMAP2 is a scalar FEM code, EMAP3 is a vector FEM code, and EMAP5 is a vector FEM/MoM code.
ERMES	Open source	ERMES is a finite element code in frequency domain which implements in C++ a simplified version of the weighted regularized Maxwell equation method.
FEKO	Commercial	For antenna analysis, antenna placement, windscreen antennas, microstrip circuits, waveguide structures, radomes, EMI, cable coupling, FSS, metamaterials, periodic structures, RFID
FEMM	Open source	A finite element package for solving 2D planar and axisymmetric problems in electrostatics and in low frequency magnetics.
FEniCS	Open source	Some elementary problems implemented in FEniCS include the scalar potential solution to closed- and open-boundary electrostatic problems, as well as the cutoff and dispersion analysis of a hollow rectangular waveguide. More advanced topics considered include the implementation of radiation from an infinitesimal dipole, and near-field-to-far-field transformations.

Name	License	Area of application
FreeFEM	Open source	This module illustrates how to implement waveguide boundary conditions in Maxwell equations. So far it is done for 2D planar case in Cartezian and Axial (m = 0) cases. Waveguides modes and waveguides port are hardcoded.
gprMax	Open source	gprMax was designed for modelling Ground Penetrating Radar (GPR) but can also be used to model electromagnetic wave propagation for many other applications.
HFSS	Commercial	For antenna/filter/IC packages, Radome, RFIC, LTCC, MMIC, Antenna Placement, Wave guides, EMI, FSS, Metamaterial, Composite Material, RCS-Mono and Bi development.
JCMsuite	Commercial	Nano- and micro-photonic applications (light scattering, waveguide modes, optical resonances).
Momentum	Commercial	For passive planar elements development, integrated into Keysight EEsof Advanced Design System.
NEC/NEC2++	Open source	Antenna modeling, especially in Amateur Radio. Widely used as the basis for many GUI-based programs on many platforms (including popular distributions such as 4nec2 and EZnec on Windows, xnec2c on Linux, and cocoaNEC for Mac OS X). Version 2 is open source, but Versions 3 and 4 are commercially licensed.
OpenEMS	Open source	OpenEMS is a free and open-source electromagnetic field solver employing the FDTD method. It uses Matlab or Octave as a scripting interface. openEMS is licensed under the GNU General Public License, Version 3 or later. https://openems.de/start/index.php
Sim4Life	Commercial	A full Wave Solvers (P-EM-FDTD) enable accelerated full-wave, large-scale EM modelling (> billion voxels) with Yee discretization on geometrically adaptive.
VSimEM	Commercial	Simulating electromagnetics, and electrostatics in complex dielectric and metallic environments. Phased array antenna systems, radar equipment, and photonics.
XFdtd	Commercial	RF and microwave antennas, components, and systems, including mobile devices. MRI coils, radar, waveguides, SAR validation.

Most of these software (particularly FEKO, ERMES and Sim4life are use-ready for conducting studies of the EMF distributions inside the human body. More specifically, ERMES (Electric Regularized Maxwell Equations with Singularities) is an open source and versatile tool which can be used in a wide variety of situations. This finite element formulation produces well-conditioned matrices which can be solved efficiently with low-memory consuming iterative methods. Also, thanks to the null kernel of its differential operator, it can operate indistinctly in the quasi-static and the high frequency regimens. Since it is provided in NextGEM by partner CIMNE, it can be customized according to project needs. One important aspect of the *in vivo* experiments will be to define the electrical properties of the nematode

C-elegans. These parameters are vital for the NextGEM project, if we want to reproduce numerically the *in vivo* experiments. After setting properly the initial and boundary conditions, ERMES will be able to estimate the external and internal field levels within the C-elegans. The numerical results obtained will be used within the *in vivo* experiments (including locomotion, RNAseq, various biological parameters.) in order to elucidate how RF-EMF can (or not) affect an *in vivo* specimen. The results obtained will serve as a basis to establish the course of subsequent experiments within the case studies. Other solvers, such us, FEKO or SIM4Life, could be also used during case studies in order to compare the numerical results obtained on ERMES.

3.4 Human healthy working environments based on field testing and measurement surveys

Whilst numerous EMF measurement surveys with wearables have been performed during daily activities and in microenvironments (e.g., [64][65][66][16]), not so many surveys have been performed in working environments. There are numerous reports on occupational measurements and models, but mostly performed to check for compliance with the legal limits in the European Directive (2013/35/EU), and thus performed with high grade spectrum analysers and three axial antennas. As these systems tend to be expensive, heavy and bulky they are not capable of being used as wearables. Commercially available wearables tend to be less accurate and though some types show a very stable repeatability, their measurement uncertainty is too high for legal compliance [20]. Though workers in potential high exposure professions are equipped with so called warning wearables which produce an alarm if an action value might be exceeded, these do not usually log the measurement data. A recent review [67] on studies on occupational exposure mentions that new sources of occupational exposure such as those in fifth generation telecommunication systems or energy transition will require further assessment as no measurement data are currently available. In addition, most measurements have been performed for legal compliances and therefore only the maximum exposures at the workplace per frequency per publication are listed as an indication of worst-case conditions. Further, spatial averaging was hardly taken into account, giving a conservative estimate of exposure. Measurement uncertainty is also rarely addressed.

Concerning epidemiological research, the development of wearables for occupational exposure, that do not hinder work activities on the one hand and are capable of measuring the exposure in a consistent and repeatable way on the other hand, is strongly recommended. And of course, measurements with wearables can be used to improve work protocols in such a way that the actions are performed so that they lead to the lowest exposure. Figure 7 shows how spatial mapping of the (working) environment can be used to map hotspots.

Also, occupational safety is a very important issue, in which wearables combined with GPS can contribute in several ways, such as early warning systems, mapping out exposure hot spots in space and time, and improving work protocols by comparison of exposures of different workers performing the same tasks.

Figure 7: Example of spatial mapping of electromagnetic exposure from base stations in the 900 MHz (brown), 1800 MHz (yellow), and 2100 MHz (green) bands. Only exposure above 0.05 V/m was shown, highest brown peak is 1.8 V/m.

Modelling environmental human exposure: In particular the availability of wearables will be of great importance for the following issues, to be addressed throughout the NextGEM project. Modelling of the expected environmental field strength based on the 5G network layout at Delft Campus requires a modelling methodology, apart from the spatial layout and transmitter specs, in several scenarios regarding number and location of users with respect to the base stations and can be performed by raytracing and wave field modelling methods. The actual exposure modelling for realistic scenarios is highly statistical as there will be five types of exposures generated: there will be a broadcast signal from the base station; downlink data transmission in narrow beams aimed from base stations to the user device (in NLOS this results in a RF-EMF hotspot at the user device); a traffic signal from the base station in narrow beams and hotspots aimed at and around other, nearby user devices; data transmission from a user's own device; environmental data transmission uplink from other users.

Measurements of the environment: In order to acquire a realistic picture of the actual exposure in real life scenarios apart from own measurements at the test locations, also measurements in other countries in which the 5G FR2 network is up and running need to be used for comparison. Based on these measurements and models the requirements, sensitivity and threshold, and accuracy for the wearable sensors can be determined.

Measurements for comparison of devices: The sensors need to be calibrated for a list of errors: mechanical errors; design of hardware and software filters; anisotropy; and influence of the body [16]. Various measurements by golden standards and spectrum analysers will be performed at the lab with a Gigahertz Transverse Electromagnetic (GTEM) cell and the dome technology to calibrate and compare them to of-the-shelf devices and self-developed wearables. Based on a modelled exposure pattern, the optimal positioning on the body and the necessary number of the sensors will be assessed, and tested in the lab, and at the test location with real time 5G signals at the Green Village. As the body influences the measurements by shielding and reflection also here a calibration is in place.

3.5 Characterization techniques of the radiated power in dynamic operation of 5G mmWave antennas in real scenarios

EMF levels measurement of 5G signals transmitted in real scenarios can be performed using two different means, namely:

- **Direct channel power measurements**, often known as frequency selective approaches, where the power is measured across the spectrum band of interest and integrated.
- **Code-selective measurements**, where cell-specific synchronization or reference signals are used to measure the received power and information related to the stochastic nature of the signal and the power ratio between the synchronization signals and the data carrying ones are used to scale the measure power to the one a user in that location would experience.

In both measurement approaches, a high sensitivity receiver interfaced with an omnidirectional antenna is used to acquire the signals/power at a specific location.

With a direct channel power measurement, instruments providing a frequency scanning heterodyne architecture can be used, see Figure 8. This approach implies that each sub-portion of the RF spectrum of interest is sequentially down-converted (shifted to lower frequency and digitized).

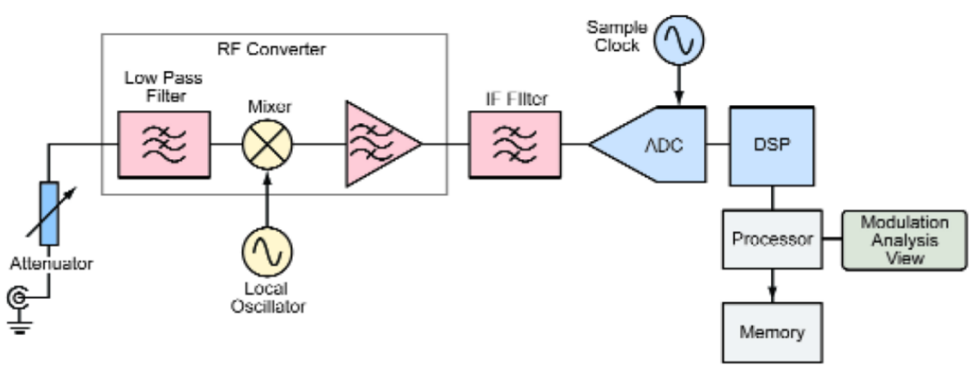


Figure 8: Typical vector signal analyser architecture

While this approach allows to compute the total effective power in the observed band, it does not allow to observe the entire portion of the spectrum used by telecom providers in a single time frame. When, instead a code-selective approach is chosen, the instrument needs to be able to digitize the entire spectrum used by the telecommunication provider at once and to employ high speed computing to identify the various reference signals and apply a power scaling procedure, i.e., based on the antenna HW information and stochastic information related to the nature of the signal, see Figure 9.

The approaches and the instrument architecture briefly sketched above are provided to inform the reader of the current state-of-the-art techniques and HW solutions used by telecom providers and regulatory agency to quantify the power in real scenarios in given moment of time and traffic conditions.

When shifting to the higher FR2 band, an extension that occurs for the first time in 5G systems (i.e., mmWave), code-selective instruments can employ an external downconverter to enable the detection of the higher frequency carrier used in this band. This can often be done to keep the digitizer portion compatible between FR1 and FR2 and optimize the front-end downconverter.

Nevertheless, also single box solutions are present. This simple description is meant to provide the reader with the impact on system complexity, cost and operator skills requirement, that the deployment of mmWave 5G system has introduced.

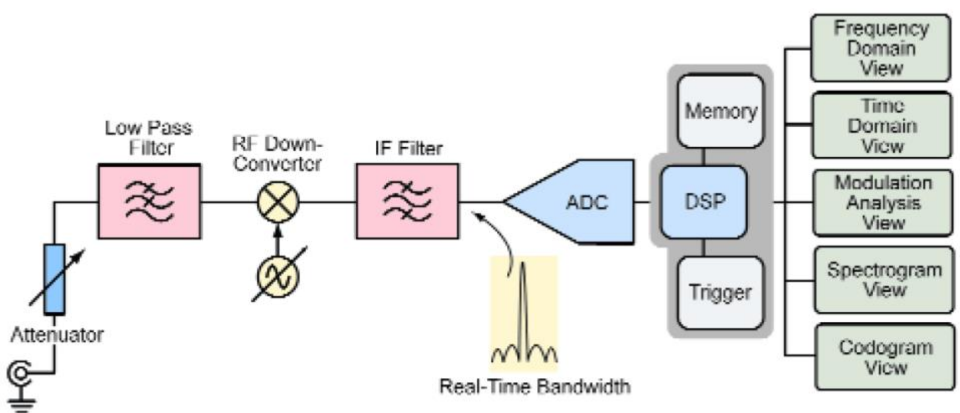
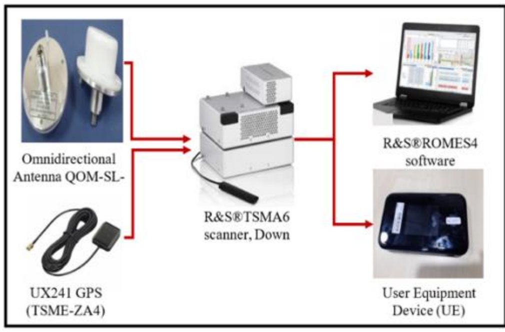


Figure 9: Real-time spectrum analyser architecture

From the antenna interface perspective, low gain (i.e., omnidirectional) antennas are often employed. The reason is to allow to capture the energy received in a spatial location from all the antenna stations operating. The low antenna gain increases the sensitivity requirements of the receiver. When a direct power measurement is employed the energy from the various sources operating in the same frequency slot are summed and no identification of the power received versus sources is possible. In Code-selective measurements the decoded Physical Cell ID (PCI) information can link the received power to a given source/antenna, despite the higher cost/complexity of this approach it allows to distinguish the source (i.e., gNB) of the received power and thus the operator transmitting it

The current available sensor technologies for measurements of mmWave 5G signal is being presented in scientific publications as [55] and [68]. The proposed measurement setups are composed of off-the-shelf high-end instrumentation from high-frequency measurement equipment vendors, as shown in the Figure 10. These test-benches are expensive and require experienced operators to collect and process data. For this reason, they are not applicable to continuous monitoring sites.



Setup	Equipment	Description
Transmitter @28 GHz	Signal generator SMB100A from Rohde & Schwarz, Munich, Germany	Signal generator up to 20 GHz. The transmitted power has been set at 14 dBm
	Frequency multiplier FDA-K/28 from Farran Technologies, Cork, Ireland	Frequency multiplier connected to the signal generator to increase the CW transmitted signal up to 28 GHz
	Ka-band pyramidal horn antenna, model SAR-2013-28KF-E2 from SAGE Millimeter, Inc.	The antenna offers 20 dBi nominal gain and a typical half power beamwidth of 14 degrees on the E-plane and 16 degrees on the H-plane
Receiver @28 GHz	Spectrum analyzer N9952A 50 GHZ FieldFox from Keysight Technologies, Santa Rosa, CA, USA	Portable spectrum analyzer up to 50 GHz (see Figure 6 for reference)
	Ka-band omnidirectional antenna Model SAO-2734033045-KF-C1-BL from SAGE Millimeter, Inc.	The antenna model is equipped with a low noise amplifier (LNA) of 30 dBi

Figure 10: (left) Measurement setup from [55], (right) measurement equipment used in [68].

When considering low-cost deployable equipment in the 5G below 6 GHz range, as presented in [21], see Figure 11, we can identify all the technological developments required to enable deployable low-cost measurement nodes for RF-EMF monitoring, i.e., volume, usage of low cost dedicated components and capability to be deployed in real life environmental conditions.

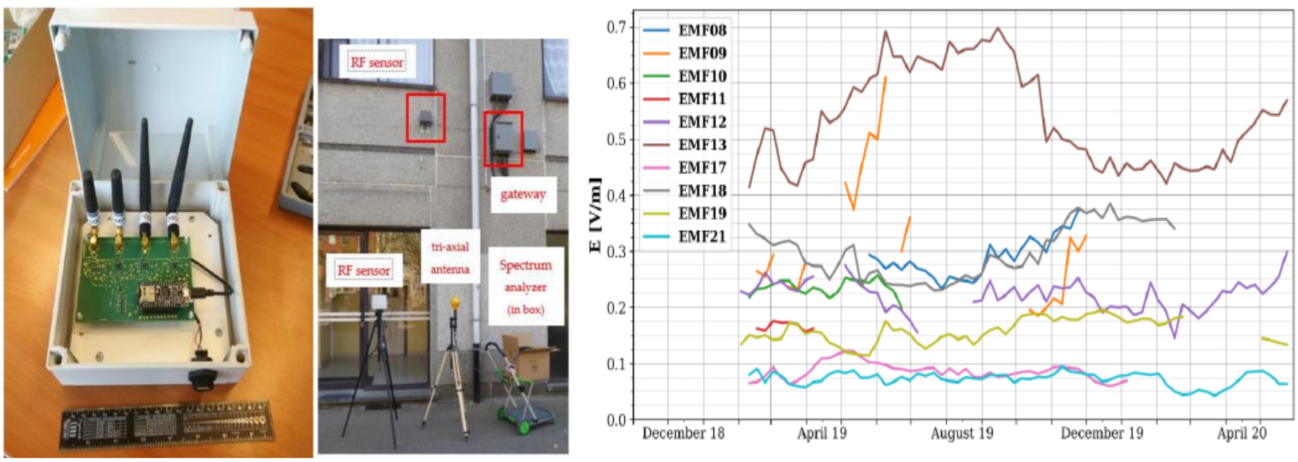


Figure 11: (left) The RF-EMF sensor in its casing (right) Weekly average electric field strength as measured by the fixed RF-EMF sensors in the 900 MHz frequency band. EMF08 (dark blue) and EMF09 (orange) were not validated in situ [21].

For the above case to develop deployable sensors, different technology blocks should be developed:

- Low loss FR2 frequency selective filters
- High dynamic range rms detectors
- Low power converting and processing units
- Antennas providing medium level gain to improve sensitivity

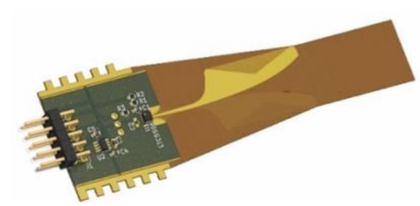


Figure 12: Vivaldi antenna PCB equipped with receiving node and ADC.

These sensor topologies then must be scaled in the form of a non-coherent detection array to cover the same sensing area covered by the omnidirectional antennas used in high-end setups. The development of these sensors will be based on the FR2 detecting unit cell developed at TU Delft as presented in [68], shown in Figure 12.

A specific set of quantifiable requirements of the sensor will be derived from a state-of-the-art analysis of the current high end equipment, providing the “reference standard” and tuning those performance parameters to the use case scenarios selected in the NextGEM project. The frequency bands minimum detectable level will be also targeted to provide a comparison ground with the test performed in the *in vitro*, in silico and emulative studies carried out in the project.

3.6 5G Architecture modelling and mapping for indoor and outdoor urban planning

Activities planned for 5G Architecture modelling and mapping are devoted to analyse the EMF distribution over large areas (e.g., whole towns) in order to properly evaluate actual human exposure. This analysis is conducted with a befitting simulation approach by evenly considering coverage, and performance throughout the design process. Activities involve the definition of simplified outdoor and indoor real scenarios, for which the radiation distribution analysis is appropriately utilised to evaluate the KPIs (Key Performance Indicators), regarding the endpoints required for the design and deployment of a mobile telecommunications network. The novel challenges introduced by the 5G technology are well considered and analysed to adhesively complement the effort to define concrete quantification methods and metrics of network design.

The simulation activities planned in NextGEM are in close relationship with the measurement activities planned in the case studies. Experience acquired from simulations is therefore eligible to be used as an integration tool for activities performed in other activities of the NextGEM Project, if required. The overall experience acquired from simulations and measurements will be used as a base of experience for the forthcoming 6G technology.

3.6.1 Scenario Simulation

Manhattan Grid: For early simulation purposes, a simplified scenario such as the Manhattan Grid [69] or the Madrid Grid is a simple and regular environment allowing an easy verification of the evaluation metrics used to calculate coverage. Within the scenario each building is represented as a three-dimensional geometry; it shows a geometric regularity of the buildings, each one represented as a parallelepiped having a rectangular base and a randomly variable height in a defined range (see Figure 13). The streets between the buildings are straight and have the same dimensions (e.g., streets 40 m wide and 10 Km in length). The analysis of the scenario allows to consider the influence of the materials behaviour in the calculation of the radio coverage and the main processes of electromagnetic interaction.

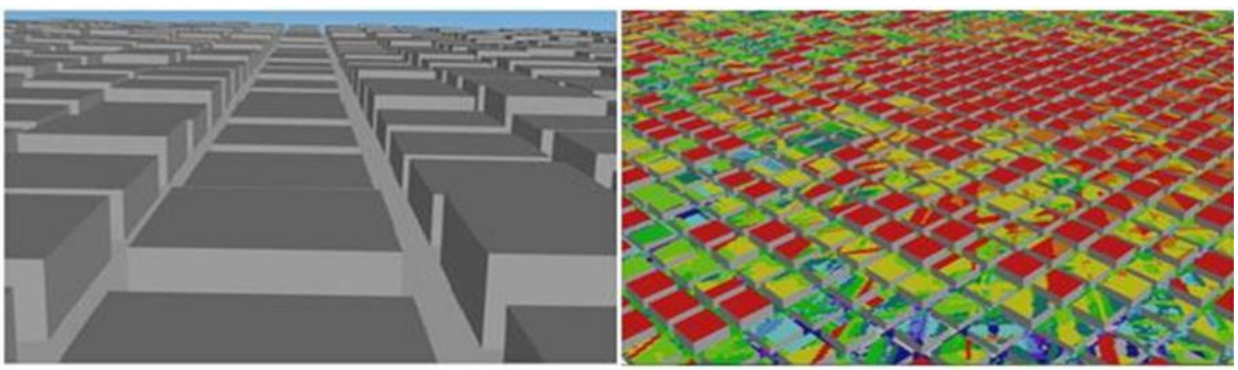
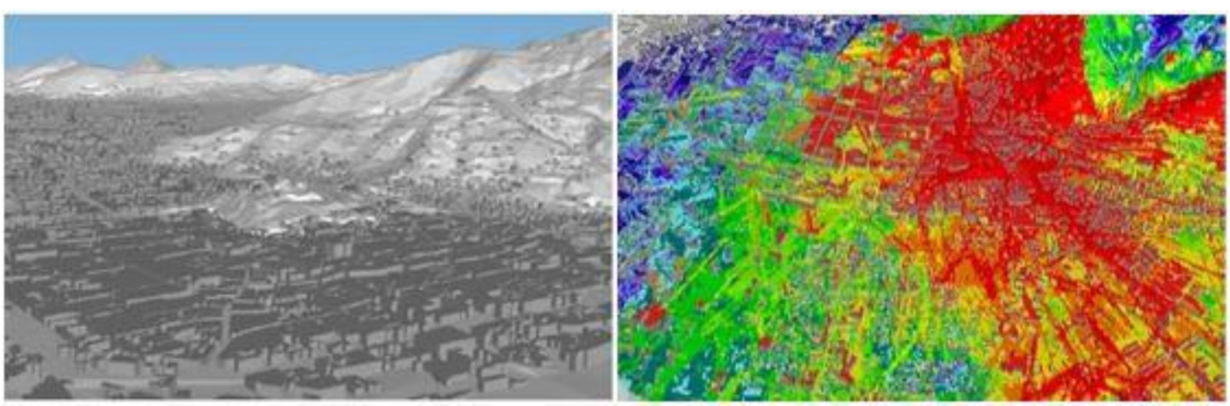


Figure 13: Examples of Manhattan Grid



(a) (b)

Figure 14: Example of a Real Scenario representation: a) a picture of three-dimensional model b) coverage simulation

Real scenario: It is possible to get an accurate three-dimensional representation of a real scenario starting from two-dimension images, like a whole city, using different and specific techniques, like stereoscopic aero photogrammetry that is based on the physiological principle of the three-dimensionality perception in human vision. The stereoscopic reconstruction process allows the fusion of two, or more, different images, taken in succession by the aircraft in flight, into a single three-dimensional view. In fact, our eyes see the same object from two different positions, the positions of the eyes themselves and the brain combines the two images and processes the depth. Figure 14 shows a reconstructed model of a real town including details, orography and surrounding environment, including – as in the example - the mountains. Each element of the model can be characterized in its specificity: each building is represented through a specific object with its own characteristics, such as shape, size and electromagnetic properties of the materials. The orography is represented too allowing a complete evaluation of the real scenario.

Indoor modelling: To assure adequate coverage, capacity, or roundtrip delay for subscriber/verticals in need of ad-hoc applications or performance, indoor deployments of mobile radio station for office/home/factories will become increasingly common in 5G. Therefore, in the project activity, simulations will be devoted to indoor scenarios to analyse the propagation characteristics inside buildings. The simulated indoor environment could be a simplified ideal structure: an example can be seen in the right side of Figure 15, where each small square room has certain dimensions (e.g., 5 m x 5 m). The different materials included in the model are distinguished by the colour assignations (e.g., in grey are the walls made of concrete and in red the ones made of bricks) and the proper EM characteristics will be associated to each material. Additionally, an example of coverage can be observed. According to the objectives and case studies of the project the indoor models could be detailed and adapted to better fit the analysis requirements. At the left side of Figure 15, it is possible to see an example of a more detailed indoor structure of three identical floors where windows cover a portion of the outside wall and internally there are brick, glass frame, and plasterboard walls at different heights. Moreover, the indoor coverage can be considered in an actual urban environment (i.e., a real scenario) so as to address the interaction between the macro-outdoor coverage and the indoor coverage (see Figure 16 as an example).

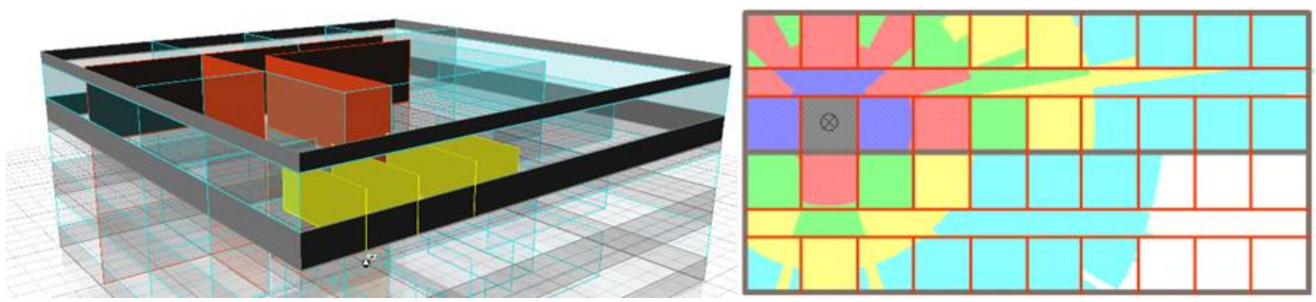


Figure 15: Indoor models for simplified structures and indoor coverage simulation

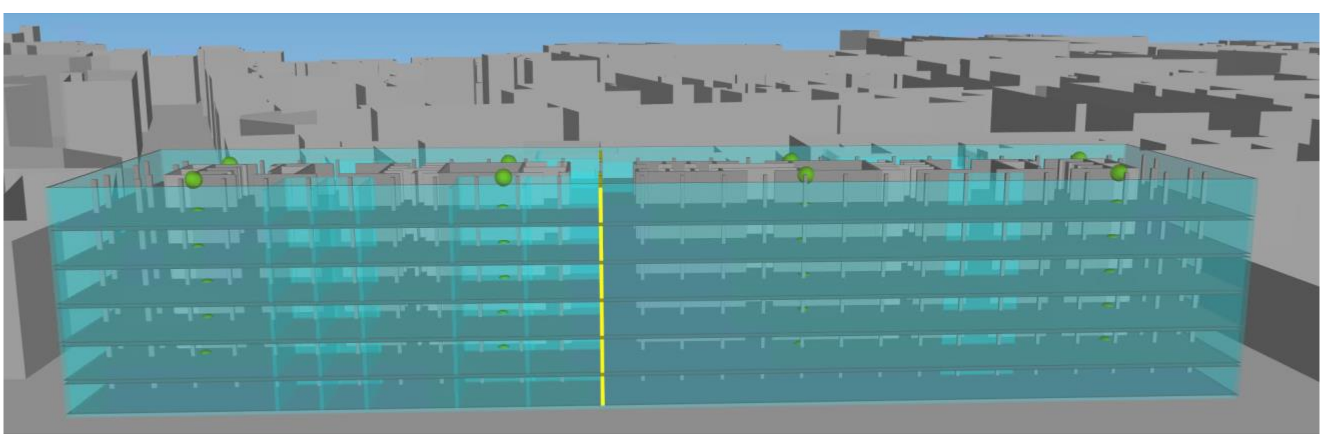


Figure 16: Examples of an indoor representation of a building in a real urban environment

5G Base stations representation: One of the major innovations introduced by 5G technology is the use of Active Antennas (or equivalently beamforming Antennas or Massive MIMO Antennas). An active antenna is an antenna able to change its radiative characteristics over time, based on the service requirements. MaMIMO antennas for 5G can make use of different radiation patterns for signalling (SSB) and for traffic for a better quality and optimization of the service. Within the activities of the NextGEM project both static and sweeping beam broadcast radiation patterns will be considered for coverage determination while envelope radiation patterns will be used for quality of service and exposure evaluation. It is a common practice to represent the radiation pattern of an antenna by making use of the main azimuth and elevation conical cuts of the radiation pattern; that requires the reconstruction of the radiation pattern's surface by interpolation and extrapolations. An analysis of different coverage distributions due to the usage of a reconstructed radiation pattern from 2-D cuts and three-dimensional representation of the radiation pattern will be performed too. The study is completed with the analysis of the effect on coverage, performance, and exposure as a function of deployment and distribution of transmitters over in the scenario.

3.6.2 Optimized outdoor urban planning and 5G design architecture

To optimize the outdoor urban planning, the following key aspects are required about the definition for the evaluation of coverage, service, and exposure in 5G design architecture. In particular, MaMIMO antennas for 5G deployment has introduced a further degree of freedom in the design of a mobile communication network. For technologies prior to 5G, the coverage, performance, and exposure were determined by the configuration of each transmitting point like transmitted power, antenna radiation pattern, antenna tilt and power control. MaMIMO antennas have separated the concept of the coverage from the concept of service quality introducing, furthermore, statistics in the spatial distribution of radiation making efficient the management of interference [61][42]. That requires to generate a new family of KPIs to describe coverage, performance and exposure considering the statistics generated by MaMIMO. The NextGEM project's objectives include the definition and analysis of a new model pattern for KPIs.

Measurement methodologies: The EMF assessment procedure of a radio-base station (RBS) requires verifying that the maximum exposure to which the population is exposed, i.e., the exposure under maximum traffic-load condition, does not exceed the permitted limits. As with previous technologies, different methodologies of *extrapolation to the maximum power* (MPE) are available for NR-5G, the applicability of which depends on the available measurement equipment and scenario conditions.

MPE based on reference-signal measurement: When the equipment allows decoding the NR-5G frame, the MPE can be done by measuring the received power associated to Resource Element of a certain reference-signal, typically within the Synchronization Signal Block, and by extending it to the whole time-frequency grid. This procedure is very similar to that used with LTE, but the peculiarities of NR-5G makes it challenging as it requires considering the different radiation patterns through which the SSB and the payload are transmitted. When an equipment capable of frame decoding is not available, the above procedure is still usable in the case it is possible to measure the SSB level with a spectrum analyser, as an example in zero-span mode. In [49][57][42][53] a deep analysis of the extrapolation approaches and experimental applications of the methodologies for MPE can be found. A similar approach can be also adopted by measuring the signal associated to a traffic channel instead of a reference-signal channel; in this case it is required to stimulate the base station to radiate in full buffer conditions and, if MaMIMO antennas are used, to steer a beam toward the measurement point by assuring the condition remains constant for the whole measurement time. The methodology briefly described here is applicable in Line-of-Sight (LOS) conditions – de facto, the most relevant case for the purpose of EMF exposure assessment.

MPE based on traffic measurement: When no equipment capable of NR-5G frame decoding is available, or zero-span technique is not feasible, the MPE can be achieved by measuring the channel power over the whole NR-5G band, by assuring the base station works full buffer and, if MaMIMO antennas are used, a beam is steered toward the measurement point (Figure 17). In principle, this modality can be adopted also in a NLOS scenario. In any case, it requires the generation of full buffer traffic to fill the NR-5G time-frequency grid, so that the maximum exposure condition is realized and to direct the whole radiation towards the measurement point. In practice, the only active UEs in the cell must be those used for generating full-buffer traffic toward the measurement point and this might not be easily feasible in an in-field scenario and a maturely deployed technology. Alternatively, artificial traffic may be generated for measurement purpose if the base station manufacturer provides this feature in its antenna system.

Considerations on MPE methodologies: The application of the MPE methodologies can fail in the case:

- NLOS conditions: the determination of the gain of the broadcast and traffic beams may be hardly achieved. That could preclude the application of the MPE methodologies as described in [42].

- Assuring full buffer conditions may be hardly achieved depending on the real traffic load condition of the network
- Steering just one beam in one direction may be hardly achieved in real traffic network conditions
- Performance-maximization algorithm determines one or more serving beams (e.g., multiple beams in spatial diversity) instead of a single beam steered toward the UE.

Long-term measurements: MPE approach assumes that a UE is served full buffer and full time; this situation does not correspond to a real usage scenario drawn by power control mechanisms, spatial diversity, and high throughput capacity. Beside extrapolation to the maximum power, EMF exposure assessment may require measuring and recording field levels over prolonged time to characterize the Signalling Radio Bearer (SRB) behaviour during operation. Long Term measurement are required since:

- they are likely to be necessary whenever a procedure for estimating the transmitted power based on *cell counters* needs to be validated. In this case, special "traffic patterns", synchronized with the system reporting-interval, need to be implemented in a way that does not require human intervention. Therefore, the test bed shall implement both the traffic stimulation sub-system and the measurement recording sub-system, so that the data collected over several hours or days could be post-processed at a later stage.
- a characterization of the traffic profile generated by real users' distributions is required. When spatial diversity is adopted, there is not a direct correspondence between the power transmitted by the base station and the power measured where it is radiated; therefore, MPE methodologies could not correctly represent the real exposure scenario, especially in real traffic conditions.

Measurement campaigns are foreseen both in FR1 and later in FR2.

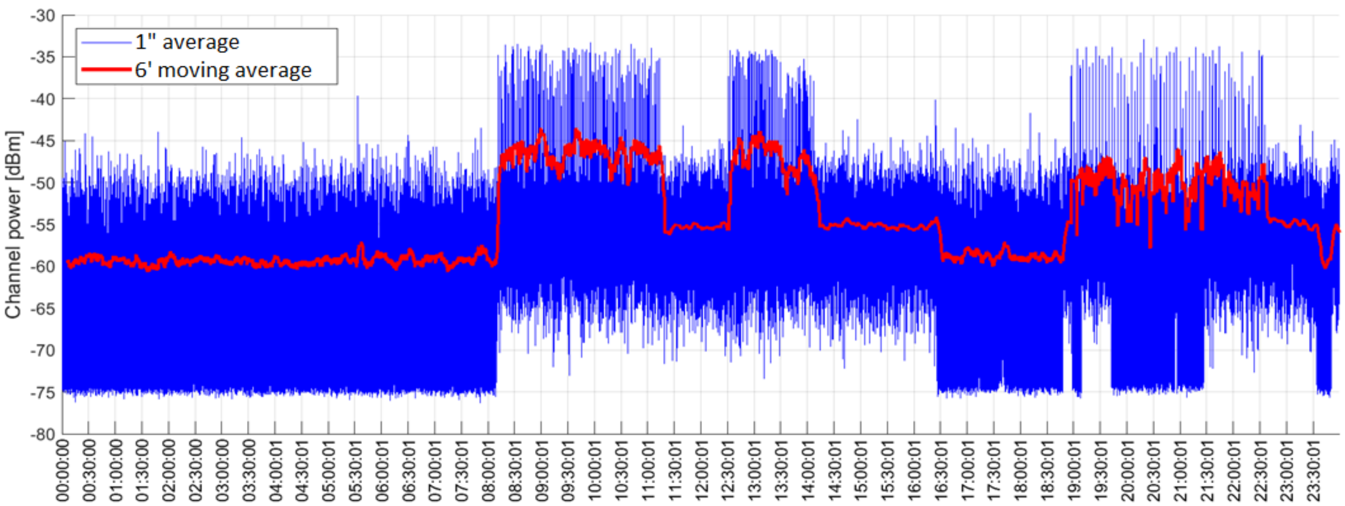


Figure 17: Channel power over the whole NR-5G band

Statistical approach: Unlike passive antennas, where the changes of the radiation-distribution are due only to the power control mechanisms acting in the time, MaMIMO antenna systems introduce the spatial diversity. For the time necessary to deliver the payload, a multiplicity of traffic beams is generated and steered toward the UEs requesting service [61]. Radiation distribution follows service-request distribution and, due to the high performance of the 5G-NR in delivering payload, the traffic could be bursty. With respect to MPE, a different approach is then required to describe the EMF, with a high grade of statistics to follow the variations of the radiation in time and space. It is in the aims of the experimental activities to get information from long term measurement campaigns, supported by statistical analysis, to characterize the EMF radiation distribution and exposure generated by MaMIMO antennas.

3.6.3 Towards 6G

A new generation of mobile radio systems is usually developed every ten years; despite that currently the 5G is in its initial and partial deployment, research activities already started on the new beyond 5G/6G system, aiming to a full standardized set of specifications around year 2030, namely 10 years after the initial 5G roll-out.

The conceptual view of what could be the new 6G telecommunications approach is reported in the Figure 18. This figure is from the European Project named “Hexa-X” [70]. Hexa-project is financed by the European Commission in the framework of the 5G-PPP cooperation, considered as the “flagship” of the research activities in Europe towards the introduction of the new telecommunications’ system.

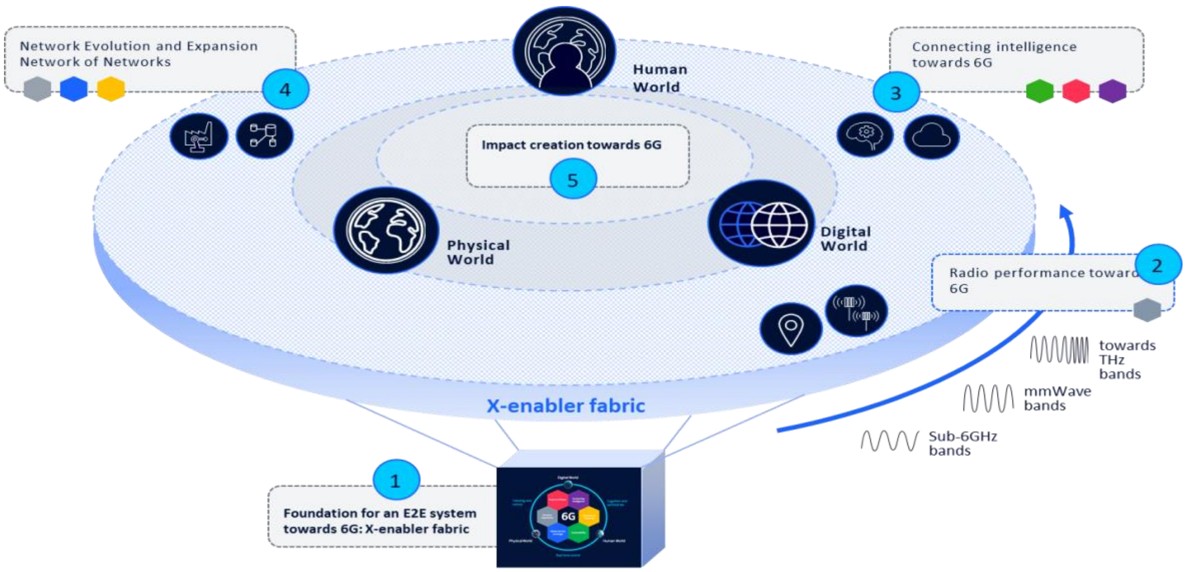


Figure 18: The view on 6G from Hexa-X project [70].

As it can be seen from the figure, 6G is deemed to merge the “physical”, the “digital” and the “human” world, aiming in particular to the tight interaction between the actual reality and the digital replica of it. Having 5G as a foundational background, 6G targets the full trustworthiness of the telecommunications, where trustworthiness is intended as a general objective encompassing sustainability, digital inclusion, efficiency, and more widely an attempt to implement a system answering urgent needs of the customers, and not simply a technological challenge of the current limits of the physical laws.

While it is still too early to identify new technologies for 6G, rather it is the time when “use cases” and “applications” are envisaged. In this context, all of them, especially from an operator’s viewpoint, need to answer the fundamental requirement of human centricity, answering the needs of sustainability previously mentioned.

In terms of frequency bands, it is still too premature to predict which new frequency bands the 6G system will adopt. World Radio Conferences (WRC) in the next years will allocate them according to the availability and the needs. A possibility that is currently under study is to adopt THz communications for very specific use cases.

4 Experimental approaches for identifying safety requirements and assessing biological and health-related effects of EMF

During the last several decades, a large amount of *in vitro* and *in vivo* studies has been carried out to address the effects of RF exposure. In most cases, no effects have been detected but, when present, they have been mainly associated to thermal increase in exposed samples. However, some studies suggested that exposure can affect a variety of biological functions at levels where the RF does not produce any heating of cells and tissues. **Oxidative stress** is emerging as a plausible cellular mechanism due to RF-EMF exposure, as pointed out in several *in vivo* and *in vitro* studies [71]. Most of the investigations so far have been devoted to test the effects of signals associated to 2G/3G networks, considering both continuous wave and modulations applied by the communication standards [72]. Fewer studies have addressed 4G signals, while 5G and its related modulations have not yet been investigated. Moreover, few studies have been devoted to investigating the effects of RF combined with other agents (combined exposures) [73] and the combination of different signals (multiple exposures) by employing 2G and 3G standards [74].

In vitro studies have been carried out mainly on mammalian cell cultures, but erythroid precursors and red blood cells (RBCs) components have also been investigated to some extent since blood cells may respond to the exposure when passing through the dermal microvasculature and thus transducing the signal to the peripheral tissues [75][76][77]. Moreover, the micronucleus test on exfoliated oral cells has long been used to monitor human genetic damages related to environmental and occupational exposures, lifestyle factors, dietary deficiencies, and various diseases. Several studies applied this technique to explore the potential adverse effects of RF from mobile phones, but the results were controversial [78][79][80][81], since most, if not all, of the studies have a number of shortcomings that preclude firm conclusions, including the absence of dosimetry and other important quality criteria.

For a better understanding of the biological effects and molecular mechanisms of EMF (3G, 4G and 5G), exposure in realistic scenarios, including effects from exposure **combined with other agents** and **multiple exposure** to different RF frequencies and signals, are required to investigate *in vitro* with cell lines and primary human cells, *in vivo* with *C. elegans*, and ex vivo with RBC and human lymphocytes, based on harmonized exposure and experimental protocols. Such studies focusing on complex exposure conditions have previously not been performed and extend significantly beyond the State of the Art.

A set of well standardized experimental activities will be implemented in the NextGEM, corresponding to the need of producing reliable data on the biological effects of RF-EMF exposure along the different lines of evidence of *in vitro*, *in vivo*, and human studies. The quality of the experiments in terms of both electromagnetic and biological aspects is the primary requirement which will accompany all the activities carried out in NextGEM. The lack of this requirement will prevent any trustworthy result and thus frustrate one of the main goals of NextGEM that is to provide new insights into the process of health risk assessment and safety requirements due to RF exposure in the new real-life scenario.

NextGEM will provide a large set of data obtained from *in vivo* (animal model and humans), *in vitro* and ex vivo experimental studies in an integrated approach. Procedures assuring studies of good quality will be defined and rigorously followed through the experimental activities. This will provide increased knowledge on the effects of RF-EMF exposure, co-exposure, and multiple exposure useful for the health risk assessment and for the transfer of appropriate information to the interested stakeholder (consumers, industry, and regulators).

4.1 *In vitro* experimental studies between RF fields and living cells for cancer-related endpoints

In 2011, the International Agency for Research on Cancer (IARC) of the WHO has classified RF-EMF as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer, associated with wireless phone use. This classification category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. The IARC Working Group performed a critical analysis of the available literature (human, animal and mechanistic studies) published between 1978 and 2011 and dealing with different RF-EMF exposure categories: 1) occupational exposure to radar and to microwaves; 2) environmental exposures associated with transmission of radio, television and wireless telecommunication signals; 3) personal exposures associated with the use of wireless telephones. In the case of personal exposure to RF-EMF from wireless telephones, the evidence of carcinogenicity was overall evaluated as limited for glioma and acoustic neurinoma, and inadequate to draw conclusions for other types of cancer. For occupational and environmental exposure, the evidence was overall considered as inadequate [82]. In all cases, the judgement was developed on the basis of epidemiological and animal studies.

Over the years, several groups of experts have been issued from the scientific community, at national and international level, to evaluate the alleged health effects of RF-EMF by integrating the different evidence streams of epidemiological, animal, and *in vitro* studies) (ICNIRP, ANSES, SCENIHR, SSM, among the others) [82]. In the vast majority of these documents, evidence on adverse health effects of RF-EMF, at current exposure levels, is considered as weak or insufficient. A precautionary position is generally taken with respect to long-term effects, and the need of additional research is always highlighted. With this respect, reviews of the available scientific evidence on cancer-related hazard due to RF-EMF exposure with clear and transparent criteria in the selection procedures and for studies assessment; and absence of conflict of interests are highly recommended. Moreover, scientific data respecting the same criteria, needs to be collected in the case of the new exposure scenario deriving from the deployment of the recently introduced telecommunication frequency and signals such as 5G that is perceived by some citizen groups as a more significant threat to public health than previous generation systems, although, in this case, RF-EMF will only be present when and where it is needed. Several studies have investigated potential cellular mechanisms that can operate at RF exposure levels found in the everyday environment, and several cellular endpoints have been analysed, as presented in a recent meta-analysis by Halgamuge and co-workers [83] which included data from *in vitro* studies published between 1990 and 2015 and investigating effects of weak RF-EMF from mobile phones.

With this respect, NextGEM Project will generate relevant scientific knowledge and data on RF EMF exposure and health with particular attention to mechanisms of carcinogenesis, and more importantly will contribute to promote public awareness among concerned groups. NextGEM will focus on *in vitro* studies that can provide essential information on specific cell properties, and allow a more rapid, cost-effective, and well-controlled approach to molecular and mechanistic studies than conventional laboratory animal models [84]. The importance of *in vitro* experimental studies has been recently recognized by the International Agency for Research on Cancer (IARC) who has given new emphasis and highlighted the crucial role of mechanistic studies. They could provide strong evidence in case of consistent findings demonstrated across a number of different systems and in different species, can corroborate evidence and provide biological plausibility to other types of studies. Given the increasing emphasis on mechanistic data, the IARC also recognizes the importance of evaluating the quality of the study design, exposure assessment methods and biological assay validity [85]. This is a very critical point that applies particularly in the case of investigations aimed at evaluating the cellular mechanisms of RF-EMF exposures for which a multidisciplinary approach is required, covering both biological and electromagnetic aspects.

NextGEM will focus on two well standardized cell models to investigate the effects of RF-EMF on **oxidative stress**, **apoptosis**, **genotoxicity**, and **cell cycle** which are among the most critical cellular parameters that act through highly regulated molecular pathways to maintain cellular homeostasis. Oxidative stress occurs when the production of oxidants overrides the antioxidant capability of the cells. As a result, the oxidants react with macromolecules like proteins, lipids and nucleic acids giving raise to alteration in cellular functions related to several diseases including cancer. The study of the genotoxic effects plays a key role owing to its direct linkage to carcinogenesis. Apoptosis is a highly conserved cell death program responsible for the removal of damaged, dysfunctional, or no longer necessary cells to promote homeostasis and survival of organisms [86]. The cell cycle is tightly controlled by many regulatory mechanisms that either permit or restrain its progression. Cell cycle dysfunctions induce an un-controlled cellular proliferation leading to carcinogenesis [87]. Moreover, alteration in the aforementioned cellular parameters are key features of carcinogens [88]. Such endpoints will be analysed to evaluate the effects of RF-EMF exposure alone, in combination with other physical/chemical agents and under multiple frequencies, in a wide range of frequencies and signals related to 4G (1950 MHz) and 5G (26.5 GHz) technologies. This approach is chosen to analyse the effects of RF-EMF exposure in a realistic scenario in which general population and workers are subjected to a very complex exposure.

For the planned investigations to be reliable, replicable in independent laboratories, informative, and thus to provide meaningful foundation for the process of health risk assessment, experiments will be carried out by rigorously controlling the biological materials and the RF exposures. Particular attention will be given to the methodological quality, and detailed advice for the proper procedures is provided in [89][90][91]. The design and realization of the experimental set up for *in vitro* exposure is a primary requirement. A schematic representation of the main steps in designing and realizing an experimental set up for *in vitro* studies is presented in Figure 19.

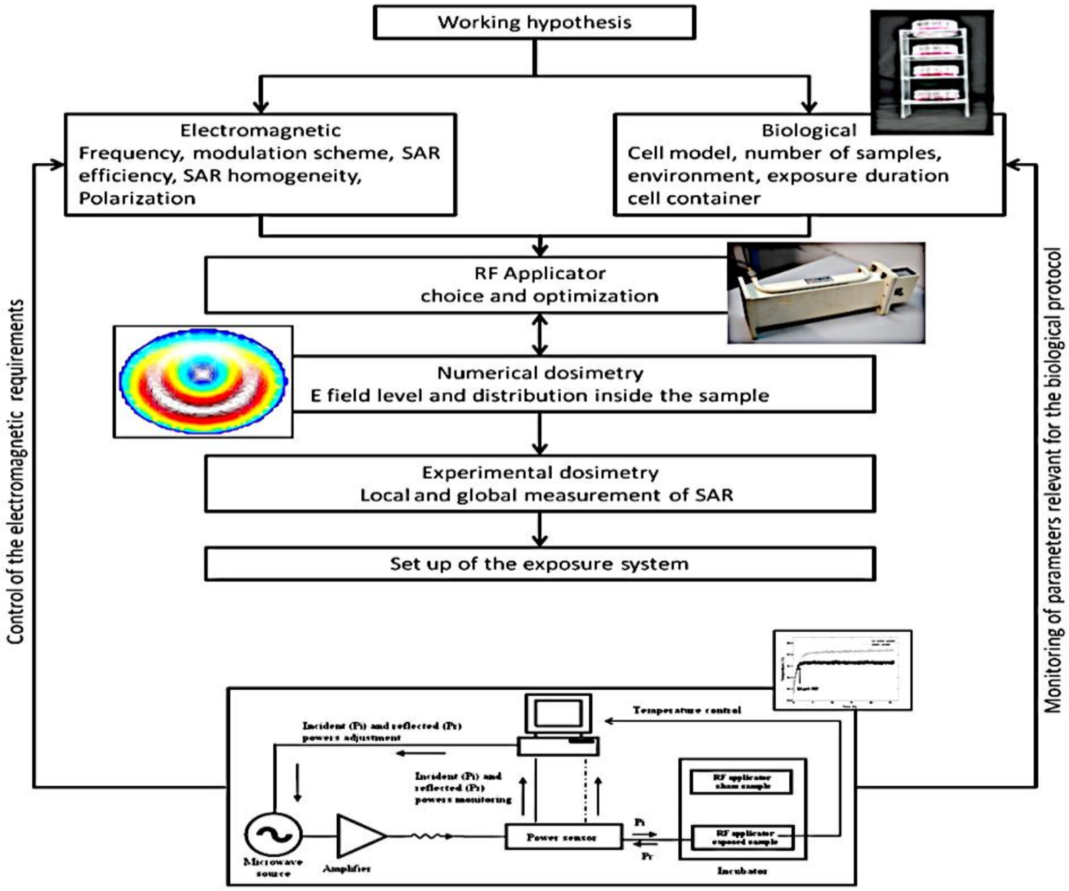


Figure 19: Schematic representation of the main steps in designing and realising an experimental setup for *in vitro* studies

The standardization of the cell models will be achieved by controlling the materials, such as cells and culture media which interact and determine the properties of the total system. Authenticated stocks of cell lines and reagents will be purchased from recognized manufacturers, and master and working banks will be established. Mycoplasma infection will be assayed periodically, and cells at defined passages will be used for the experiments. Negative control samples (cell cultures placed in standard cell culture CO_2 incubator) provide information on the background level of the endpoint under examination.

Then, five relevant quality criteria that are the inclusion of a sham and a positive control, an accurate dosimetry evaluation, a rigorous temperature control, and a blind procedure will be satisfied [84].

- The sham control sample (cell culture placed in a RF exposure device identical to the one employed for the exposure but with zero RF field) represents the true control of the experiment, considering the microenvironment in the exposure device, and the experimental conditions that could affect the cellular endpoint under examination.
- Monitoring the specific absorption rate (SAR, W/kg) distribution pattern, or power density of the incident field (W/m^2) by means of numerical and/or experimental dosimetry within the cell cultures, is of paramount importance and allows avoiding undesired temperature increase that can cause local heating within the sample.
- Positive control provides evidence for a correct assay procedure assuring that the methodology is adequate to detect the effect of a well-known damaging agent.
- Temperature, as a confounding variable, is monitored by using non-perturbing probes and, if needed, active cooling with either forced air or water.
- Blinded experimental conditions prevent any kind of bias in the analysis of experimental data. They are achieved by coding samples and breaking the code after the data are analysed.

To ascertain replicability of the experiments and full transparency, standard operating procedures (SOPs) for the above-mentioned variables of in vitro experiments, will be set up for the experiments carried out within NextGEM.

4.2 *In vitro* and human studies on EMF exposure with different cellular and molecular techniques to ensure a safe electromagnetic environment

Analysis of gene expression changes following an exposure, i.e., exposure to RF-EMF, is a promising approach to determine biomarkers of exposure and/or effects which can provide insight into the interaction mechanism of RF-EMF. The focus of *in vitro* studies is as mentioned earlier on the effects related to carcinogenesis. Different cell models (SH-SY5Y, human neuroblastoma and HaCat cells, as a skin model), and primary human cells (lymphocytes, RBC, and buccal mucosa cells) will be investigated depending on the frequency, signal modulation and biological target. A large battery of assays will be employed to address the above listed endpoints at cellular and molecular level, including cytogenetic and epigenetic assays. Different -omics approaches will be used to identify genes and proteins as potential exposure marker candidates.

The studies to be conducted under NextGEM will specifically aim at assessing the most critical possible biological effects of 5G EMF. We aim at contributing to the state-of-the-art with studies focusing on EMF exposure effects under realistic conditions (for both intensity (SAR) and modulation used in 5G-NR). Initially we will focus on well-evaluated biology parameters *in vitro,* such as genetic damage, apoptosis, and oxidative stress, on cell lines. This will be combined with (epi)genetic screening in order to investigate the genes (and the expression thereof) underlying the observed effects. This will allow us to further study mutagenesis and other endpoints, based on the gene expression profiles. Candidate genes identified in the *in vitro* studies will be further investigated under more realistic experiments, e.g. by exposing ex vivo lymphocytes from human donors instead of cell lines and in an exploratory human study.

In this exploratory study, we will pursue the objective of investigating potential effects of mobile phone use on micronucleus formation and gene expression levels in exfoliated buccal cells collected from 30 high and 30 low mobile phone users (oral communication). In the case this exposure estimate is deemed to be too inaccurate a metric, different exposure scenarios, such as acute exposure (making a phone call) prior to the taking of the sample can be considered. Gene expression analysis will be conducted by RT-qPCR on genes of interest selected based on the results of the *in vitro* studies. Interviews will be conducted to obtain information on participants' behaviour when using their mobile phones. The mobile phone models used in the last 10 years will also be requested. Average SAR at the level of the inner cheek (on the mobile phone side and on the other side) will be modelled. Great care will be needed in the selection of the participants and in establishing the protocol and questionnaire given to the participants to ensure a reliable study population of this exploratory study. Further consideration is currently being given to the feasibility of carrying out exposure recordings to confirm belonging to the two groups defined on the basis of self-reported data. A measurement protocol will need to be developed for this purpose.

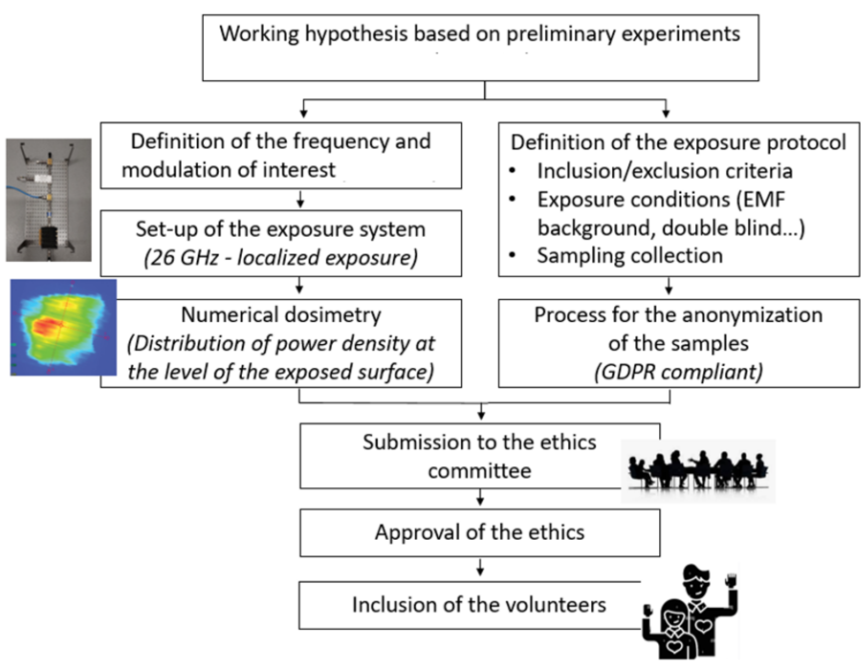


Figure 20: Schematic representation of the main steps in designing a human study

Moreover, the changes in the dynamics of water within the hydration shell around hemoglobin solution under exposure mimicking 5G signals (mmWaves) will be explored. A protocol will be set up for the detection of changes in the protonation of thiols and amino probes. Based on the results, a pilot study on healthy volunteers (Figure 20) will also be conducted after exposure to 5G carrier frequencies and modulation envelopes, a signal similar to the one that should be deployed in Europe, reproducing real conditions as closely as possible. Such investigations are innovative as detailed analyses of the alterations in red blood cell properties have not been done under controlled reproducible conditions. *In vitro* studies on red blood cells and whole blood will include the acting frequencies (0.9-3 GHz range bands) as well as the 26 GHz band that is not yet broadly deployed world-wide and identify the parameters that respond to irradiation as well as the duration of exposure that is causing the effects. The human study involving healthy volunteers will be performed using the 26 GHz EMF with modulation. As this frequency is scarcely implemented in Europe, this is proactive work, the results of which will form part of the risk analysis to ensure a safe evolution of the electromagnetic environment for citizens.

The exposure system, consisting of a waveguide and the electronic components needed to generate the signal, will be integrated into two 26 GHz EMF-shielded boxes, in which the volunteers will place their forearms. Only one forearm will be exposed in a real or fictitious way in a double-blind way, which means that neither the volunteer, nor the accompanying researcher will have any external cues as to which forearm is exposed or not, or as to the status of the exposure system (ON or OFF). The protocol will be submitted to the evaluation of our partners, exposure will be characterised and checked by simulations and in situ measurements, and test conditions will be controlled (background EMF, temperature, humidity, etc.) to allow a replication of the results within the scientific community.

4.3 *In vivo* experiments on Caenorhabditis elegans for reproduction and development

Caenorhabditis elegans (*C. elegans*) is a 1 mm-long and transparent nematode, with a fast reproduction cycle and a short life (2-3 weeks) [92]. More than 50 years ago Sidney Brenner started investigating worms of the *Caenorhabditis* genus as a suitable model to study development and the nervous system. It is also a suitable model to study fertility and effects on the skin. In these simple organisms, it is possible to follow cell division under the microscope and Brenner demonstrated that specific mutations could be induced in the genome of *C. elegans* [93]. Since then, *C. elegans* has become an important model organism, and a substantial corpus of knowledge on its cellular anatomy, lineages and genetic information is available. In particular, *C. elegans* is the first genome. This makes this organism a powerful analytical tool for research in many areas of biology and medicine and especially, in aspects related to reproduction and development. In fact, the *C. elegans* genome sequence revealed a set of universal developmental control genes, i.e., conserved gene systems across animal phylogeny and within vertebrates in particular [94]. For instance, regarding the genes involved in the regulation of anatomical regulation patterns (known as homeobox genes), it has been found that, out of 103 *C. elegans* homeobox genes, 70 are co-orthologous to human homeobox genes [95]. In spite of its suitability, only few studies have so far made use of the *C. elegans* model to investigate biological effects of EMF (Figure 21).

The group led by David De Pomerai at University of Nottingham conducted one of the earliest studies using a specific mutant that had been previously developed to study the effect on the worms of different stressors (heat, heavy metals) which allowed to detect the expression of heat shock genes (*hsp*) [96]. Following this early study, the same team reported non-thermal effects of 750 MHz microwaves at very low SAR (0.001 W/kg) [97]. However, this publication was later retracted in light of their new findings showing that the observed heat-shock response was in fact caused by a small heating effect with an associated temperature increase of only 0.2 ºC [98]. The Nottingham group also studied the influence of other GSM frequencies on *hsp* expression, finding no evidence of significant effects under SAR up to 1.8 W/kg ([99][100]). Later studies investigated the influence of exposures (SAR=3 W/kg at 1750 MHz) on a broad gene expression profile, finding changes in larval stages (L4) and adults of *C. elegans*, in the expression of genes associated to developmental aspects, but could not observe any harmful effect on development and longevity [101]. Recent publications reported possible biological effects of 5G exposure at prolonged exposure on 20 generations of nematodes and also high-peak power exposure [102][103]. In the first study, [102], *C. elegans* are exposed in a prolonged manner to (SAR=4W/kg at 9.4 GHz) for 20 generations and also at high-peak power exposure (>2000 W/cm^2 at 9.4 GHz), [103]. The first study showed a significant decrease in the *C. elegans* fecundity from the 15th generation and decreased growth and motility, as well as oxidative stress, from the 10th generation [102]. A significant decrease of the survival rate was observed in nematodes exposed to high-peak power [103]. However, another study [104] found no significant physiological changes in *C. elegans* exposed to GSM frequencies, evidencing controversy in the field and the need of further investigation.

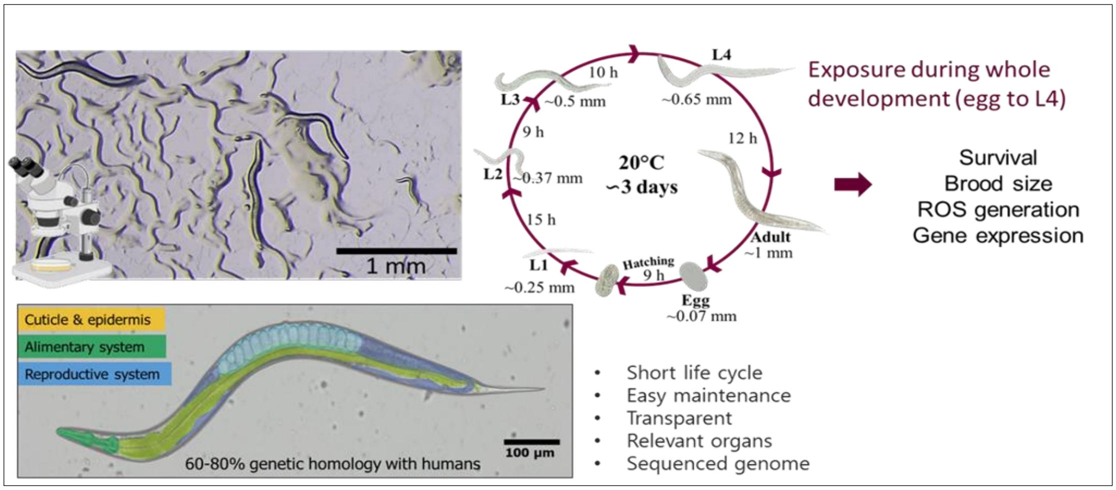


Figure 21: Nematode C-Elegans as model organism for the investigation of biological effects due to EMF exposure

The potential exposure to EMF and other physical or chemical agents has increased concerns regarding fertility and development. *Caenorhabditis elegans* (*C. elegans*) offers a platform to evaluate how the EMF could impact different generations of worms thanks to its fast reproduction cycle and a short life. The different development stages during the life cycle could at some point relate to different age of the organism. Additionally, it allows to assess if the reproduction rate is influenced upon EMF exposure.

The studies to be undertaken within the NextGEM Project will aim at assessing the possible biological effects of 5G EMF. We aim at contributing to the state-of-the-art with studies focusing on EMF exposure effects. Initially we will focus on easily evaluated biology parameters of the nematodes, such as live/dead, locomotion, and developmental rate. This will be combined with RNAseq screening in order to investigate the genetics underlying the observed physiological effects. The results obtained will serve as a basis to establish the course of subsequent experiments.

The standardization of the *C. elegans* experiments will follow the requirements set for the *in vitro* cell models. *C. elegans* strains will be purchased from the world leading provider, and phenotypes will be checked regularly. Negative control samples (petri dishes with nematodes placed in standard incubator) will provide information on the background level of the endpoint under examination.

In order to meet the relevant quality criteria, sham and positive control will be included along with an accurate dosimetry evaluation, a rigorous temperature control, and a blind procedure will be satisfied.

- The sham control sample (*C. elegans* placed in a RF exposure device identical to the one employed for the exposure but with zero RF field) represents the true control of the experiment, considering the microenvironment in the exposure device, and the experimental conditions that could affect the *C. elegans* endpoint under examination.
- Monitoring the specific absorption rate (SAR, W/kg) distribution pattern, or power density of the incident field (W/m^2) by means of numerical and/or experimental dosimetry within the system, is of paramount importance. An accurate temperature control and monitoring is also required to avoid undesired local heating within the sample.
- Positive control provides evidence for a correct assay procedure assuring that the methodology is adequate to detect the effect of a well-known damaging agent.
- Preliminary measurements on how long it takes for the temperature to stabilize inside the reverberation chamber and temperature of the agar medium exposed to EMF will serve to discard confounding heat-related effects.

4.4 Molecular responses, identification of markers of responsiveness of human RBCs to EMF exposure

The *in vitro* and ex vivo testing facility that need to be developed and build for studies of RF-EMF exposed RBC should take into account the shortcomings in the few studies of such cells that were performed previously. This means a very precise and stable system should be built capable of generating reproducible exposure circumstances, yielding precise devices and strict protocols. Especially there is a need to ascertain the very stable temperature of the tissue, the very precise exposure area determination by using small probes, and an EMF generator transmitting a stable signal with repeatable signal features (i.e. intensity, frequencies, modulation, peaks) [9][10]. In this way the fundamental mechanisms of acute (minutes to hours) responses of red blood cells should be measurable. Modelling the internal dose of the cutaneous tissue and blood vessels and red blood cells will be performed in order to determine the actual exposure at the RBC from a realistic incident 5G signal.

Within the NextGEM project it is planned to focus on the **molecular mechanisms** of non-thermal interaction of radiofrequency EMF with red blood cell components (hemoglobin, plasma membrane) and the changes in protein conformation and kinetics of post-translational protein modifications resulting from the irradiation. The latter will be evaluated in hemoglobin solutions, in which the impact of EMF exposure on protonation-deprotonation of thiols and amino groups will be tested. Protein conformation will be assessed through the changes in water and proton dynamics within the protein hydration shell. Propensity of thiol groups to S-glutathionylation and amino groups of terminal lysines to glycosylation will be compared in sham samples of hemoglobin solutions and those exposed to the RF-EMFs. We shall test the impact of carrying frequencies and the modulation on the hemoglobin post-translational modifications. The same experiments will then be repeated using intact red blood cell suspensions and, finally, in whole blood. Impact of the EMF on the Ca^{2+} and Na^{+} transport across the red cell membrane will be explored which, if occurring, could account for any changes in osmotic resistance. Rouleaux formation and aggregability, as well as deformability of RBC will be measured in sham and irradiated whole blood samples and in red cell suspensions to test for the impact of plasma proteins on the hypercoagulation state reported for the people irradiated with microwave EMFs. Time-dependence and reversibility of the effects will be assessed. The obtained data will be then used to define the possible set of EMF-sensitive parameters in red blood cells, that will be tested in a case study in which the possible response of blood and red blood cells to EMF irradiation will be explored in healthy human volunteers.

4.5 The influence of EMF on RBC behaviour and other blood cells

Although possible EMF exposure effects on the living organism and specifically cellular systems, have attracted a significant research interest over the last few decades, there are still many contradictory observations. The most important part of the scientific understanding of the biological effects of the EMF exposure to the living organisms lies in the complexity of the exposure, the variety of the propagation conditions, and the parts of the exposed living organisms. The occupational health and safety perspective on the ICNIRP guidelines on EMF in the frequency band of 100 kHz−300 GHz was analysed in [105]. In this work, the difference between the occupational and residential effects (short) and (long) effects were discussed. Traditionally, the interaction of microwave radiation and human beings, was considered as just an absorbing sponge stratum filled with water. However, in [36] it was shown that the presence of the sweat ducts in the human epidermis led to a high specific absorption rate of the skin in extremely high frequency band. Evidence of the cellular EMF exposure effects on the human red blood cells were also presented in [106] where RBC shape and mechanical properties were investigated with Raman spectroscopy.

The nomenclature of dielectric dispersion of biological tissues was first designated by H. P. Schwan [107]. In general, the permittivity decreases with increasing frequency and can be divided into three major regions (i.e. dispersions), known as α, β, γ, and a further subsidiary dispersion, known as δ. Using the nomenclature are: the α-dispersion is related to ionic mobilities, β-dispersion is related to interfacial polarizations of cellular structures, and γ-dispersion is the relaxation of bulk water. The α-relaxation process is observed mainly in the low-frequency region, below 10 kHz. This dispersion is the result of the slow migration of ions or deformation of ion clouds at the expansive surfaces of cell membranes or tubular systems, such as the sarcoplasmic reticulum in muscle fibers or along DNA molecules [108][109]. The β-dispersion usually occurs in the range of 0.1 – 10 MHz [109][110] and is related to the cellular structure of tissues where poorly conducting membranes separate the cytoplasm and extracellular space, each with different dielectric properties. The polarization of these cellular membranes leads to a large frequency-dependent permittivity. This is also known as a Maxwell-Wagner polarization [109][110]. The γ-dispersion is due to the relaxation of free water.

Its maximum is detected in the microwave frequency region, around 25 GHz at 37°C (the typical temperature of living tissue) [111][106], which is currently reserved for 5G communication.

Based on these considerations, the protein tumbling, interface polarization response of cell membranes, small organelles and membrane proteins cannot occur in response to the EMF exposure at the considered 3G/4G/5G frequencies. Instead, RF-EMFs used for 3G/4G operation frequencies influence the fast mobility of amino acid residues, and 5G operation frequencies influence the dynamics of water dipoles and protons/hydronium ions only. Thus, water dipoles and protons are the top candidates to respond directly to the 5G frequency bands. The underlying hypothesis for the interaction of the proteins with the carrying frequency bands of 0.9-2.4-3.6-27 GHz are based on the fact that dielectric relaxation of water in these frequency bands alters the mobility of water dipoles (orientational defects) and the proton hopping, and the increase in the exchange rate between the bulk and the bound water pools, as a result of the accumulation of ionic defects (protons) [106]. This may cause changes in protein surface charge distribution due to the alteration in protonation-deprotonation of amino acid residues and, hence, in protein conformation. The implication of this mechanism in molecular response to the RF-EMF has never been tested experimentally. One more line of evidence suggesting that the changes in protonation of thiol (and amino) groups may be caused by the non-thermal impact of microwave EMF irradiation comes from a recent *in silico* modeling-based study that revealed the changes in pKa of thioredoxin protein in response to exposure to the RF-EMF [112].

The RBC sedimentation rate (Sed) test was used for decades as a measure of inflammatory activity that increases RBC aggregability. We have used Sed response as a marker of RBC response to RF-EMF irradiation. This preliminary experiment was motivated by the fact that RBCs sedimentation can be monitored directly during the RF-EMF exposure. Blood from healthy donors was placed into the standard Z-potential cuvettes (Malvern, Worcestershire, UK) one of which served as a control whereas the other was exposed for 45 minutes to the sequence of modulated pulses, which mimic the 3G cellular communication transmissions (Figure 22).

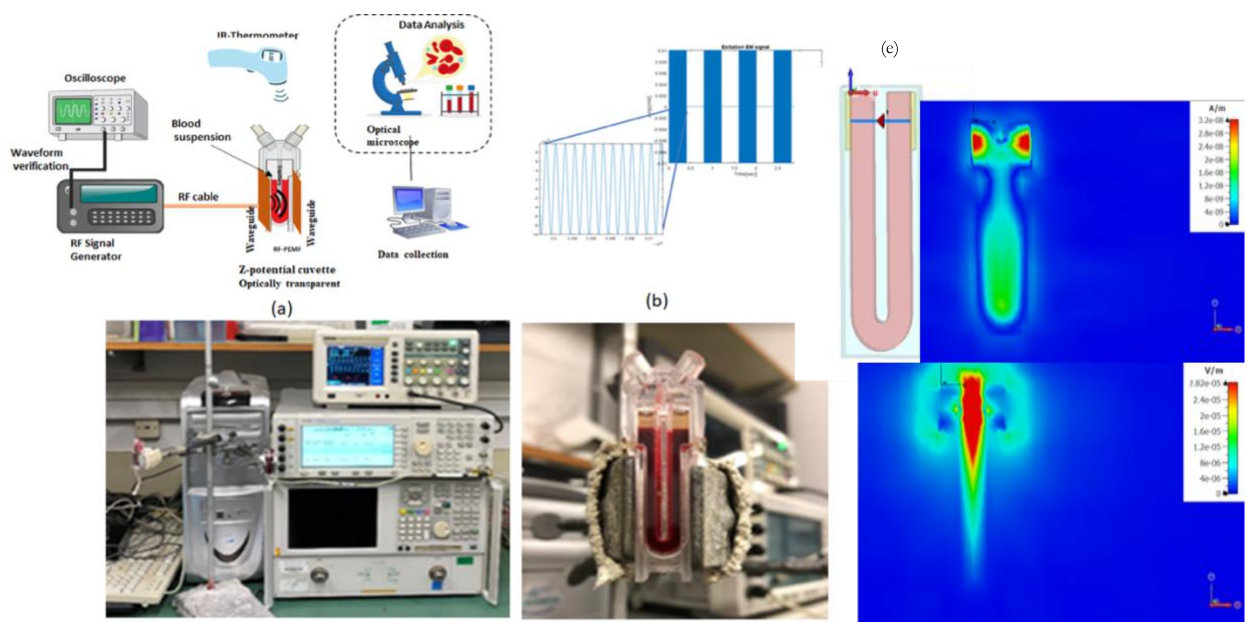


Figure 22: Schematic (a) and the photography (c) of the experiment setup, signal used (b) and sedimentation of the blood sample (d) and the CST model of the experimental cuvette (e).

In Figure 22, (a) and (c) show the schematic and the photography of the experiment setup that consists of the signal generator Agilent E4438C 220 KHz-4GHz ESG vector signal generator interconnected via coaxial cable to one of the Z-potential cuvettes equipped with a set of golden electrodes with the RBC suspension (d), the second cuvette was used for control with the untreated sample. The FLIR T530 thermographic camera was used to monitor blood temperature. The oscilloscope was used to verify the transmitted waveform; (b) shows the signal used for RBC sample treatment; shows the results of the sedimentation of the blood sample treated with the RF-EMF signal in (b) using the setup in (c). The CST simulation model of the experimental cuvette of RF-EMF is shown in (e), where the carrier frequency in simulations corresponds to 3D Model.

5 Health risk assessment and hazard in real-life scenarios

The different studies related to biological effects with health relevance, exposure assessments, dosimetry determinations and modelling, as well as data mining and development of risk assessment protocols will be subjected to further testing and validations in specific case studies that are based on real-life scenarios. The outcomes of the case studies will be the communicated to stakeholders for final relevance assessments in various areas of activities. (The overall project concept is summarized in the Figure 23).

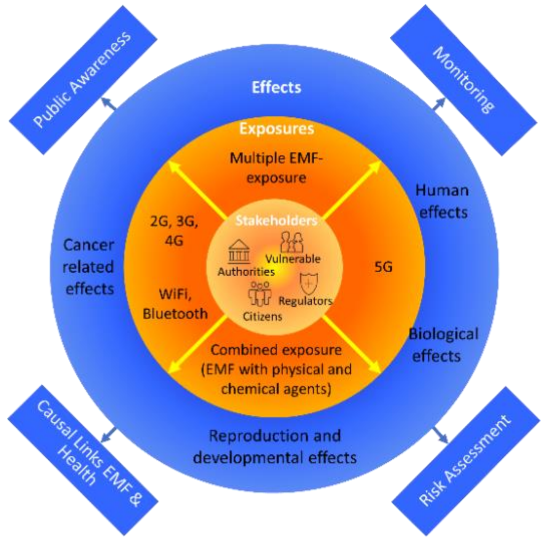


Figure 23: NextGEM overall concept

The recent decades have seen numerous studies that have investigated possible health-related effects of RF-EMF that are used for mobile communication (1G-4G mobile telephony). Both national and international expert committees with mandates from public institutions have assessed published health effect studies related to such RF-EMF exposures. The committees mainly reached the same conclusion, viz. that exposures at or below exposure guidelines provided by the ICNIRP [82] or IEEE-International Commission on Electromagnetic Safety (IEEE-ICES)[114] do not pose any health risks for the exposed population. However, very little interest has been focused on exposures which contain both the EMFs typical of mobile phone use and other EMF sources, or on exposures of RF-EMF and other agents (physical, biological, or chemical). Furthermore, studies that are relevant for risk assessment (RA) of 5G NR, and particularly FR2, are sparse [9].

Another complicating factor regarding the RA of RF-EMF deals with the inconsistency, partial irreproducibility, and questionable quality in many of the studies that have been the foundation for this specific RA. Despite the large number of performed studies, more definitive conclusions regarding certain health effects have not been able to draw. This has prompted competent authorities and the WHO EMF Project to encourage novel overviews of the published literature, in the form of systematic reviews regarding certain health conditions [115]. NextGEM takes this one step further by performing an umbrella review on the possible link between RF-EMF exposure and carcinogenicity. Furthermore, based on already available data and novel data that will be generated within NextGEM, the project will develop and validate new tools for evidence-based RA relevant for novel and emerging exposure situations where 5G NR is a part. The involved stakeholders who will be participating in the validation process are the target audience for these new technologies.

5.1 Umbrella reviews of systematic reviews and meta-analyses of epidemiological studies on exposure to radiofrequency fields and cancer risk

Cancer can be considered the most relevant potential hazard of RF-EMF at exposure levels below current international guidelines [115]. If exposure to radiofrequency magnetic fields would increase the risk of cancer, this would have serious public health consequences and would require population-level preventive strategies, including a revision of the threshold-based limitation principle currently applied to non-ionizing radiation in the radiofrequency range [116]. Neoplastic diseases are also the most investigated potential adverse effect of prolonged exposure to RF-EMF from mobile communication, accounting for about 56% of all related epidemiological studies currently indexed in the specialized literature database EMF-Portal [117].

To ensure a sound decision making the optimal use of available data and evidence on the topic of radiofrequency fields and cancer risk in epidemiological studies is needed, especially, when evidence is multifaceted and complex. Historically, expert-based narrative reviews were used as an instrument for evidence synthesis. Subsequently, the methods for evaluating and integrating the evidence on environmental and health topics transitioned from expert-based narrative reviews to systematic reviews and meta-analyses [118]. Although systematic reviews of etiological studies are generally regarded as the best practice method for evaluating evidence used in decision making [119], recently the field has been further expanded by the availability of umbrella reviews [120]. Umbrella reviews systematically compile evidence from multiple systematic reviews and meta-analyses into one accessible and usable document or as defined by Belbasis et al. "a systematic collection and assessment of multiple reviews and meta-analyses done on a specific topic" [120]. There is an increasing number of systematic reviews and meta-analyses available. Over 20,000 systematic reviews and approximately 20,000 meta-analyses are indexed in PubMed in 2018, with a clear trend towards further increases in numbers. With the increase in systematic reviews and meta-analyses published, a logical and appropriate next step is the conduct of overviews of existing systematic reviews and meta-analyses [121]. This is especially important as it is common that systematic reviews and meta-analyses on the same topic, even published in the same year, come to different conclusions. By systematically summarizing and comparing results of all available and relevant systematic reviews and meta-analyses on the exposure to radiofrequency fields and cancer risk in epidemiological studies, a complete overview of the highest quality of evidence can be provided and therefore the results are based on a more solid foundation compared to an elective approach of common overview articles. In addition, quantitative approaches, e.g., AMSTAR, can be used in umbrella reviews to grade the evidence [122].

The goal of NextGEM is to systematically summarize the evidence regarding near- and far-field exposure to RF-EMF and cancer risk in the general and working population provided by human observational studies, using the novel approach of the umbrella review. Therefore, a study protocol defining the methods and tools to perform the umbrella reviews of systematic reviews and meta-analyses of epidemiological studies of human cancer hazards from exposure to radiofrequency fields will be set up and published using state of the art methods [121][122][123][124][125][126][127][128]. Based on the study protocol two umbrella reviews will be carried out, namely one review of epidemiological studies on near-field sources of radiofrequency fields and cancer and one on epidemiological studies on far-field sources of radiofrequency fields and cancer. Near-field exposure will be defined as exposure from mobile phones, cordless phones, or other handheld transceivers. Far-field exposure will be defined as whole body exposure from broadcast transmitters, base stations, or other far-field sources [129].

The main steps of the umbrella review will be:

1. the identification and selection of eligible studies,
2. data synthesis and assessment of bias, and
3. evidence grading.

By systematically compiling all relevant evidence on this topic published in the last decade, the umbrella reviews have the potential to provide the highest quality of evidence, according to the criteria described by Papatheodorou [123], and thus form a reliable basis to inform decision-making. Finally, results will be integrated with results of reviews on experimental studies of carcinogenic effects of EMF in animal and cell models.

5.2 Risk assessment on causal links between possible health effects and EMF exposure

As a rule, study findings from different areas are used to carry out assessments of the health-related effects of a chemical substance or a physical agent: studies in humans (epidemiology, experimental studies in humans), animals ("*in vivo*") and cells ("*in vitro*"), and computational modelling ("*in silico*"). The data from these various fields ("lines of evidence") allow researchers to produce an integrative evaluation, although all types of studies have certain limitations. The different areas of studies can be characterized as follows:

- **Epidemiological studies** investigate the incidence and distribution of diseases in populations in order to determine the underlying risk factors, on which basis preventive measures can then be taken. Epidemiological studies are the only means of conducting empirical research into long-term risks for humans. The advantage of epidemiological studies lies in their high ecological validity. This means, for example, that environmental risks can be analysed for exposures occurring under realistic conditions and in interaction with other factors. It also means, however, that exposures above set limits cannot be investigated. For ethical and practical reasons, epidemiological studies concerning environmental risks are observational, and consequently **susceptible to bias** (confounding, reverse causality, errors in estimating exposure etc.).
- **Experimental studies in humans** examine effects of exposure under controlled test conditions. They can be conducted as randomized controlled trials (RCTs), which is considered the gold standard for research design in a clinical context because it enables the influence of other factors to be controlled to a large degree. Since experimental human studies are exclusively able to examine acute effects of exposure, they complement

epidemiological studies and can contribute to the explanation of how mechanisms work. As a rule, exposures in excess of limits are not investigated, for ethical reasons.

– **Experimental studies in animals (*in vivo* studies)** provide information about effects on a whole living organism and present the entire range of body structures and functions, such as the nervous system, endocrine systems and immune responses. *In vivo* studies are extremely important for the assessment of health risks, especially when they confirm epidemiological findings. There are, however, problems with the extrapolation of interspecific and intraspecific variations. In other words, transferring results from one species to another, particularly to humans, is subject to uncertainties.

– **Cellular studies (*in vitro* studies)** investigate toxicological, mechanistic and other relevant effects at the cellular and molecular level. The purpose of these studies is to help understand the development of diseases or cellular changes based on a variety of biological endpoints. *In vitro* tests allow biological processes to be investigated under controlled conditions. They can be used to identify hazardous substances, but their usefulness for the assessment of any health effects is limited (SCENIHR 2009)[130].

– ***In silico* studies** primarily consist of computer simulations of biological experiments. They are increasingly gaining in importance. Computer-aided simulation of biochemical processes in living organisms, for example, enables experiments to be simulated on a computer and the generated results to be handled in the same way as other experimental observations. The benefit of this approach is its efficiency, and the fact that it can be a substitute for animal experiments. However, the necessary modelling assumptions are always associated with a degree of uncertainty.

Findings obtained using epidemiological methods play a greater role in the assessment of health risks than experimental studies in humans or *in vivo*, *in vitro* and/or *in silico* findings. This only applies, however, if the quality of evidence from epidemiological studies is considered high and potential sources of error are relatively insignificant. Findings from one type of study (or one line of evidence) on its own, i.e., with no findings from other areas to back them up, are considered to be of lesser value in the assessment Table 5.

Table 5: The different lines of evidence and their specific contributions to health risk assessments.

Study / Line of evidence	Definition	Pros / Cons
Epidemiology	**The occurrence and distribution** of diseases and other health-related conditions in populations in context of an exposure; to learn about the causes of disease, which may lead to preventive measures.	Human studies are usually observational and therefore vulnerable to **bias and confounding**.
In vivo	Provide **information about effects on a whole living organism** displaying the full repertoire of body structures and functions, such as nervous system, endocrine system, and immune responses.	**Extrapolation problems** (inter- and intra-species variation). *In vivo* studies are powerful for health risks assessment.
In vitro* and *in silico	**Investigates toxicological, mechanistic, and other relevant effects;** provides evidence for and possible understanding of the development of diseases; (wide variety of biological endpoints).	*In vitro* assays and *in silico* modelling can be used **for hazard** identification and **mechanistic understanding**. Risk assessment usefulness is limited. Substantiates the mechanistic knowledge.

RA for human health is based on i) hazard identification and characterization, ii) exposure assessment and iii) risk characterization which combines the results of the hazard and exposure assessments (Figure 24). Although many institutions perform RA, there is no standard procedure for evidence-based RA [131]. The European Commission suggests a "Weight of Evidence" (WoE) approach [132] where evidence from epidemiological, experimental human, *in vivo*, *in vitro*, *in silico* studies are integrated for an overall RA. Challenges for EMF RA include that RA generally takes exposure guidelines into account, where primarily acute effects are the only ones considered. RA for exposure situations characterised by long-term and combined exposures, and/or co-exposures with other agents do not exist.

Necessary data for RA will be obtained from NextGEM intra-project activities on exposure assessment and hazard identification/characterization complemented by available literature data. Methods:

Step 1. Identification of requirements for human risk assessment models to accommodate different exposure and health situation scenarios. Further, output information criteria will be identified and output formats and modules in a range of existing/novel control banding/risk management, predictive exposure, and RA models will be identified.

Step 2. Identification of existing hazard, exposure and RA models accommodating the required needs: Suitable existing human RA models will be identified and categorized depending on their best match regarding the model elements and output format required, including applicability to *NextGEM* case studies. The input parameters for the identified models will be specified and summarized. Results from NextGEM experiments including -omics may feed back into the development of biological mechanism-based hazard models.

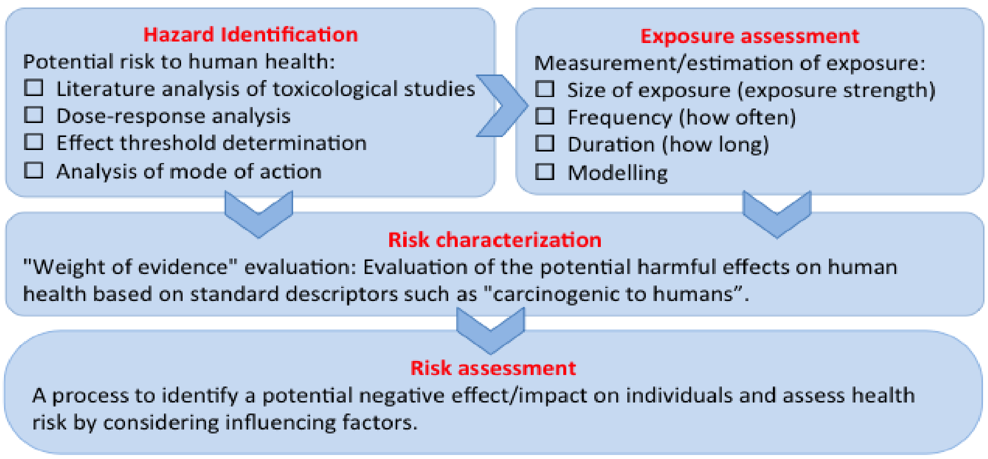


Figure 24: Risk Assessment Procedure

Step 3. Model refinement and establishment of integrated RA methods based on results from NextGEM and on the users' and stakeholders' needs: based on the results from the previous step, this step will further refine the existing human RA models supporting stakeholder needs and opinions. The models will be validated in the NextGEM case studies.

Step 4. Development of a NextGEM RA tool based on experiences from model validation in case studies: Validated RA models will be developed into computational models and guidance documents suitable for the different stakeholders involved in the requirement identification.

For the first time, integrated RA protocols including exposure situations characterised by long-term exposures, combined exposures to different EMFs, and co-exposures with other agents will be provided. NextGEM will ensure this by a pronounced stakeholder involvement, integration of novel exposure and dosimetry methodologies for RF exposure assessment, and identification of health relevant markers in experimental bio-effects studies.

Furthermore, based upon stakeholder (industry, insurers, regulators, and consumers) input, requirements for RA output information criteria will be identified. Data underpinning the various stages of risk assessment from different lines of evidence will be obtained from envisaged activities, assessed for their appropriateness for hazard identification and characterization, exposure assessment, risk characterization, and uncertainty analysis.

NextGEM will achieve stated goals related to the human RA by interactions with stakeholders and by evaluating relevant existing data, producing relevant data within the project, and by testing generated RA models in the framework of the NextGEM case studies. To this aim, relevant data from exposure assessment *in vitro* and *in vivo* experiments, the level of evidence resulting from the umbrella reviews 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.

5.3 Health risks reflected in case studies

A key feature to apply and integrate the different technological developments and research findings within NextGEM is the three different case studies that are foreseen. They will provide novel knowledge about complex exposure environments in specific and selected settings. Furthermore, the studies will generate data on biological and health effects related to these settings from experimental and observational studies. The validation of the NextGEM risk assessment tool will also take place as part of the case studies. To compile, evaluate, and integrate the findings from the different case studies will create a map of complex and realistic exposure environments and their possible health impact. Since initially the map will lack crucial details, an important objective is to identify the knowledge gaps that remains to complement the map structure. The use of the knowledge gaps and other pertinent information obtained during the work will be crucial for designing the necessary next-generation (replication) studies that likely will be needed in future projects.

5.3.1 NextGEM Case Study 1 - Potential effects of indoor levels of RF radiation on reproduction and development of vulnerable people

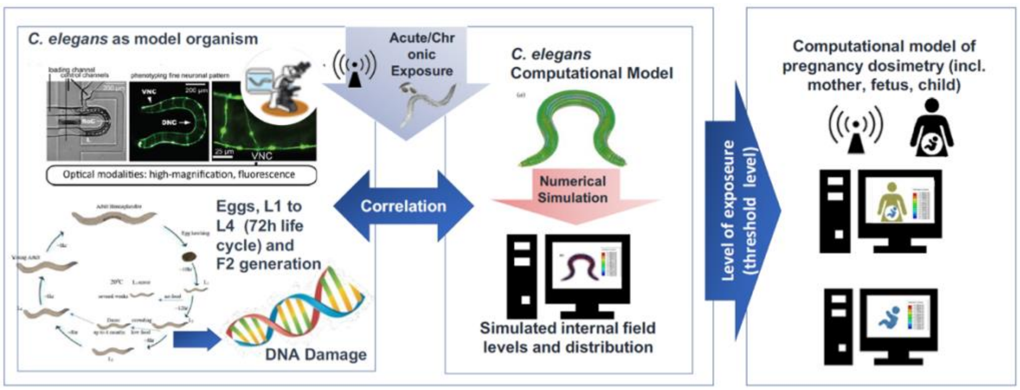


Figure 25: Case Study 1: Potential effects of indoor levels of RF exposure of vulnerable people on reproduction and development

The main scope of NextGEM in case study 1 is to investigate potential EMF effects on vulnerable people by analysing the existing literature and by using *C. elegans* and exposure modelling approaches, to establish possible thresholds for safe/unsafe situations of single and multiple exposures and the potential risk on fertility and children's development. In this case study, as a result of the modelling of human body and how EMF distributes within, the results of the *C. elegans* exposure will feed the model. Due to the large difference in complexity of the *C. elegans* and humans no direct conclusion and extrapolation is possible, however the *C. elegans* experiments will be able indicate under which conditions adverse effects are occurring.

5.3.2 NextGEM Case Study 2 - Optimized outdoor urban planning and 5G design architecture and investigations for public awareness of cancer-related hazards

In this case study, the urban planning and exposure management for 5G NR location design architecture will be assessed, and the possibility of cell site distribution in an urban environment to optimize the exposure and to analyse field distribution over the territory due to MaMIMO antennas, will be examined.

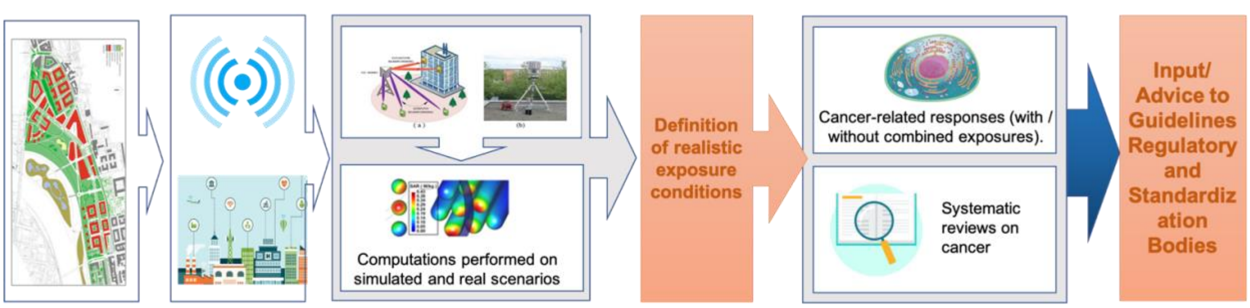


Figure 26: Case Study 2: Optimized outdoor urban planning and 5G design architecture and investigations for public awareness of cancer-related hazards

As a result of the measurements in real exposure scenario, selected realistic exposure conditions will be tested to investigate biological response in "*in vitro*" investigations. Selected cancer-related endpoints will be analysed in a suitable cell model in presence and absence of other agents to mimic the real-life scenario in which exposure to other agents than RF also takes place. An umbrella review of epidemiological studies of cancer risks in relation to near-field and far-field RF-EMF exposure and risk assessment approaches on cancer will be performed (Figure 26).

5.3.3 NextGEM Case Study 3 - Health effects of exposure to mmWave EMF in indoor and outdoor environment

To protect the population from scientifically proven adverse health effects the ICNIRP guidelines provide exposure limits. However, for mmWaves neither a substantial amount of epidemiological or experimental data is available and it remains unclear whether long term health effects may occur and whether low intensity exposure may lead to adverse health effects.

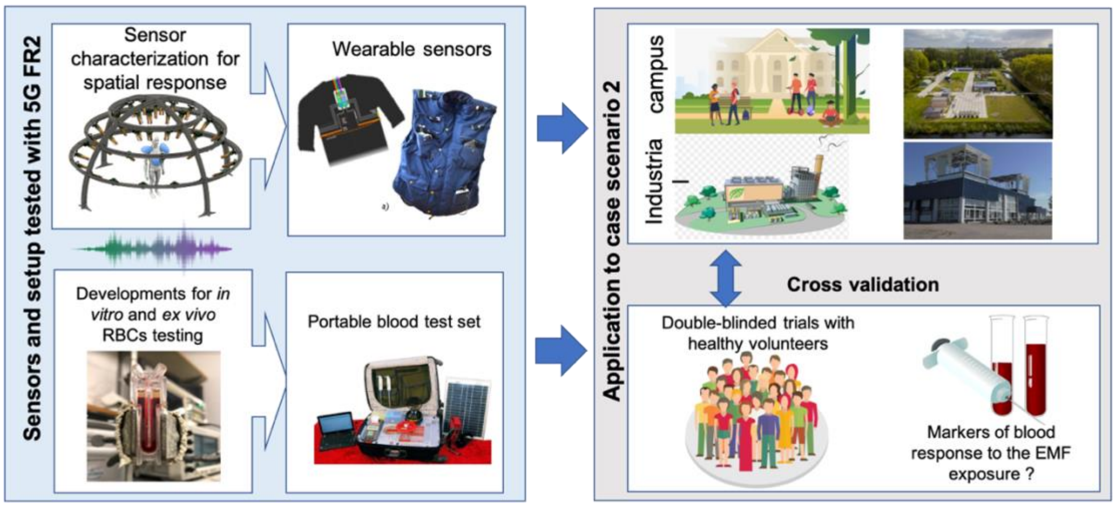


Figure 27: Case study 3: tasks contributing to set up

The goal of the case study 3 is to assess the level of 5G-signals in the FR2 mmWave bands in indoor and outdoor environments and to investigate possible effects of these exposures on red blood cells (RBC). As Figure 27 shows, on the left side it depicts the measurement sensor development in the lab (upper left) in Delft, and the development of blood exposure systems and blood effect measurement systems (lower left). Effects on red blood cells will be explored in two different labs in Jerusalem and Zurich to identify the fundamental mechanisms of acute (minutes to hours) responses of red blood cells and to identify the signal features. On the right it depicts the measurement strategy of exposure, first the systems will be tested at a controlled test location with a 5G mast capable of generating FR2 signals with various beams and intensities, later the actual measurements on people during daily life be performed (upper right). If the modelling of exposure of blood cells due to the actual encountered exposure will be the main indicator regarding the decision of the continuity of the research under this topic to investigate whether a possible effect may occur. If an effect is found, an ex vivo study will be performed.

5.3.4 Expected Outcome from Case Studies

The expected outcome of all case studies can provide different outcomes to the scientific society, citizens, public authorities and regulators. More specifically, case study 1 can upgrade simulation tools and models (exposure assessors) so the scientific community can apply further research on RF-EMF exposure. In addition, health standards will be updated regarding the potential effects of different frequencies (health agencies, risk assessors) and finally, the outcome of the research will generate the basis for practical guidelines. The expected outcome of case study 2 will include the antenna optimization mapping criteria (telecom operators) and updating or verifying RF-EMF limits (regulators). It will also increase knowledge and public awareness regarding the biological responses and 5G frequency exposures. The expected outcome of case study 3 will include the assessment of actual exposure to 5G frequency bands in everyday activities at the campus (regulators). Finally, the identification of the potential correlation between 5G RF-EMF exposure parameters and RBC effects (health agencies, risk assessors) will be made to increase the knowledge and awareness of citizens regarding potential health issues and 5G.

6 Conclusion

Progress in NextGEM's research area is dependent on increasing the knowledge regarding actual exposure patterns, developing improved dosimetry models, extending knowledge about biological and health related effects of exposure, and of developing ways to perform relevant evidence-based risk assessment in a complex exposure environment. NextGEM addresses all these critical issues with the highest technical knowledge and in a dialogue with other research activities and with the different stakeholders. Based on the above, this deliverable presented the EMF value drivers towards the stakeholder needs and safety requirements on the different real scenarios and case studies. In addition, the topics presented with regards to EMF drivers as presented in the Section 3 will be the basis for WP3. In addition, the presentation of experimentation approaches in Section 4 will drive WP4. Finally, Section 5 is related to the WP5 as it analysed the basic requirements for risk assessment based on existing knowledge and under the gained one from the different research and activities of NextGEM and the deployed case studies.

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