GERoNiMO

Generalized EMF research using novel methods. An integrated approach: from research to risk assessment and support to risk management

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4.1 Final publishable summary report

Executive summary

Electromagnetic fields (EMF) are one of the most ubiquitous exposures, with new EMF technologies and novel applications being actively developed and commercialised. GERoNiMO focused on the investigation of possible health effects from exposure to radiofrequency fields (RF), from, for example mobile phones and WiFi, and intermediate frequencies (IF) from sources such as anti-theft gates. It developed an integrated approach, building upon existing European expertise and resources and using novel methods, to fulfil its objectives: i) evaluate possible health effects of exposure to RF and IF in children and adults; ii) better understand mechanisms of biological effects of RF and IF; iii) collect data on population exposure and improve health RF and IF risk assessment; and iv) underpin policy development in Europe on EMF. GERoNiMO completed its objectives and remaining scientific manuscripts will be submitted in 2019.

In the Epidemiology Module, analyses of data from birth cohorts suggest an association between maternal cell phone use during pregnancy and neurodevelopment outcomes (behavioural problems, language and motor skills and cognition scores), pregnancy duration and risk for preterm birth. A higher risk of behavioural problems was observed in subjects with longer call time and higher RF exposure during childhood and adolescence. Results must be interpreted with caution given potential residual confounding. The MOBI-Kids case-control study of brain tumours in young people recruited 899 brain tumour cases and 1910 controls. Environmental and occupational IF exposure levels were very low. An algorithm was developed to estimate spatial RF and IF dose distribution in the brain at different ages. Analyses of risk in relation to mobile phone use history and ELF and RF exposure were conducted. Several manuscripts on exposure assessment and results are in preparation. In the INTEROCC case-control study of brain tumours in adults, estimates of individual occupational RF and IF exposure were derived based on a Source-Exposure Matrix developed in the project. Exposure prevalence was low: 10% for RF; 1% for IF. There was no clear evidence for associations between cumulative occupational RF or IF exposure and brain tumour risk. Reproductive effects of occupational IF exposure were assessed in a Finnish cohort study among cashiers working near electronic article surveillance systems. No difference in risk of miscarriage, reduced birth weight or preterm birth was observed. Exposure levels were very low.

In the experimental part of the project, specific aging and Alzeimer's disease (AD) mice model were used to study the effects of RF and IF on these outcomes. Exposure to IF to investigate neurobiological, reproductive and behavioural effects and genotoxicity in mice model suggested mild cognitive impairment, no adverse effects on fertility indicators after exposure, no genotoxicity in the exposed. Results of the pregnancy studies provided no evidence of adverse effects from prenatal and early postnatal exposure to IF MFs. Exposure of nerve cells to IF and RF alone, at levels higher than those in our environment, appear unlikely to affect the cell biology at the cellular or molecular levels. Co-exposure with chemical showed some, though inconsistent, interactions that require further investigation.

In the Exposure Assessment Module, RF and IF measurements across different domains were made and RF and IF sources identified. Measurements of whole-body personal RF exposure showed downlink sources are most important for both parents and children, followed by uplink and broadcast, though this varied by age and country. Relatively higher exposures were found during transport. A Source-Exposure Matrix and a Job-Exposure-Matrix were developed to assess occupational EMF exposures. Far-field exposure models were validated and an integrated RF exposure model developed for all sources, for use in epidemiology and population exposure assessment.

In the Integration module, a health risk/impact assessment (HIA) was focused on glioma and acoustic neuroma (tumours of the brain and central nervous system) for which the number of good quality studies available to date was judged adequate. Novel methodologies developed and used allowed the synthesis (pooling) of human and animal evidence, accounting for differences between species, study designs and RF modulations. In relation to the identification of non-technological means to reduce the exposure from new technologies, distance from the source is confirmed as the most effective mean to reduce the exposure, although EMF exposure still raise people concerns, with particular reference to exposures of children and pregnant women and to new emerging technologies such as 5G and the way risk are communicated to the general public.

Summary description of project context and objectives

The European population is increasingly exposed to new physical and chemical agents in the environment, some of which may be detrimental to public health. Among these, electromagnetic fields (EMF) are one of the most ubiquitous, and their application in new technologies continues to grow, with novel uses being actively developed and commercialised. Although there is substantial interest, and some concern, in the public and among public health professionals about possible health effects related to EMF, previous studies have been inconclusive.

Considerable research has been carried out in Europe and worldwide on both the biological effects of extremely low frequency fields (ELF, <300 Hz) and RF (30 MHz-300 GHz), and on potential health effects of exposure to these fields. The extent, diversity and fragmentation of research activities, and the lack of a truly multidisciplinary approach, have made it particularly challenging to provide relevant, authoritative, and timely input to public health policies on EMF. Furthermore, although the use of IF – defined here as frequencies between 300 Hz and 30 MHz to include a diverse range of applications (anti-theft technologies, device tagging and identification) – is increasing rapidly, little is known about their possible effects on human health.

GERoNiMO was built upon the hypothesis is that the best way to address current questions pertaining to EMF and health is through an integrated pan-European approach, focusing on a range of frequencies, bringing together researchers from diverse disciplines, research institutions and member states. Within GERoNiMO, we therefore built upon existing European resources (large-scale epidemiological studies, exposure assessment techniques, and mechanistic and animal models) using novel methods (including systems biology approaches and state-of-the-art exposure assessment instruments into epidemiological studies) and existing expert networks, to better understand mechanisms underlying possible health effects of EMF, to better characterise current and future population levels of exposure in Europe, thus furthering the state of knowledge on EMF and health and improving population health risk assessment. Such an integrated approach has significantly improved the coherence and coordination of European research into EMF and health, leading to improved assessments of health risks and impacts (including assessment of the effectiveness of non-technological means of exposure reduction). In this way, up-to-date scientific information on EMF and health is provided to the EU and national regulatory bodies, assisting them in the development of effective evidence-based risk communication and management strategies.

GERoNiMO primarily focused on RF and IF fields. Further investigation was needed for RF since knowledge of possible health effects was insufficient, given the large number of individuals exposed in the general population and the ever-increasing uses of RF energy for commercial, medical, personal and household applications (most notably communications). More information was also required on IF fields, particularly in terms of improving characterisation of sources and exposure assessment and investigating potential associations with a number of health outcomes, as the state of knowledge in all these areas was very limited.

General objectives

GERoNiMO aimed to **generate new knowledge** on possible health effects of RF and IF (focusing on the risk of **cancer, neurodegenerative diseases, behaviour, reproductive outcomes and aging**) and on the **biological mechanisms** underlying these, **characterise current and future population levels of exposure in Europe** to improve **assessment of potential health impacts** of EMF exposures in Europe, **underpin policy development** and **propose non-technological means to reduce exposure.**

This was achieved by using an **innovative integrative research strategy, combining complementary approaches and disciplines.** This combination **makes this consortium unique and improves the strength, coherence, credibility, visibility and coordination of all areas of European research into EMF and health**, ultimately leading to reduced fragmentation of research and improvements in the assessment of public health risks**.** The GERoNiMO consortium includes highly experienced experts from all fields required for achieving the objectives of the project (Appendix Table 1).

GERoNiMO comprised a strong set of highly integrated components, including epidemiology, experimental work, exposure assessment, health impact assessment and risk communication and management. The project made optimum use of existing resources, taking advantage of European studies (large-scale prospective epidemiological cohort and case-control studies of distinct population), techniques and expertise (exposure assessment, mechanistic and animal models, modelling of health impacts) using, where appropriate, novel methods (systems biology, integration of potential biological markers and exposure assessment instruments into epidemiological studies) and existing expert networks to attain these objectives.

Not only were health and biological impacts of RF and IF studied but, where possible, the effects of joint exposure to different EMF frequencies and other potential modifiers – including chemicals in both occupational and non-occupational environments. These were investigated through epidemiological and experimental studies. This is an issue of particular importance as human populations are *de facto* exposed to mixtures of agents in their everyday life, and understanding the nature of complex exposures may hold the key to better understanding possible risk factors and mechanisms of action.

Specific objectives of GERoNiMO

Using an integrated approach – from research to health impact assessment and support of health risk management – GERoNiMO established a coordinated, interdisciplinary team of leading pan-European researchers to address all aspects of the EC call according to the following four major research objectives:

i) Evaluate possible health effects of exposure to RF and IF in children and adults

- To investigate potential effects of RF field exposure on reproductive outcomes and on neurodevelopment of children and young people, building upon existing data from five prospective population-based cohort studies, implementing a standardised outcome assessment of **cognitive and behavioural development**, and including exposure measurements **for near- and far-field RF sources**.
- To evaluate the role of **RF and IF** on **brain tumour risk in young people**, taking advantage of the existing MOBI-Kids study infrastructure, collecting information about IF sources and studying joint effects of co-exposure to different EMF frequency ranges and chemicals.
- To characterise **the risk of brain tumours** associated with **occupational exposure to RF and IF**, building upon the existing INTEROCC study, which also includes data on ELF and chemical exposures and will allow investigation of joint effects of different EMF frequency ranges, and joint effects of EMF and chemicals.
- To fill an important research gap by assessing the **potential reproductive effects** associated with **occupational exposures to IF** by implementing a pilot cohort study of supermarket cashiers, possibly leading to a future large-scale multinational study of IF-exposed populations.

ii) Better understand mechanisms of biological effects of RF and IF fields

- To investigate mechanisms that may **link exposure to RF and IF to behavioural and reproductive effects, as well as cancer, ageing and Alzheimer's disease** (AD) using a series of interlinked animal and cellular models and systems biology. Where appropriate, joint effects with chemical exposures were also evaluated.

iii) Collect better data on population exposure

- To identify near- and far-field sources of **RF and IF** and estimate levels of **exposure in the general population**.
- To use dosimetric modelling to derive **novel organ specific metrics** for use in epidemiological studies, for **near- and far-field sources in occupational and non-occupational settings**.
- To **integrate exposure** across frequencies, sources, and types resulting in cumulative exposure metrics.

iv) Improve health risk assessment and underpin policy development in Europe on EMF

- To develop a novel approach for integrating epidemiological and experimental study results in order to quantify potential **health impacts** of exposure to EMF (including IF, RF but also other frequency bands such as ELF if informative data from other complementary projects are available) in the EU27 population overall, as well as under several scenarios related to possible **future trends** in EMF technologies and to **non-technological means of reducing exposure**.
- To identify priorities for EMF and health risk and explore plausible **non-technological means of reducing exposure** through a detailed review process and stakeholder engagement, review the plausibility of these means and quantify the reduction of exposure that such measures would entail in order to underpin policy development.
- To recommend best practices in **risk communication and management** to **support EU policy makers**.

Specific progress beyond the state of the art of the GERoNiMO project design

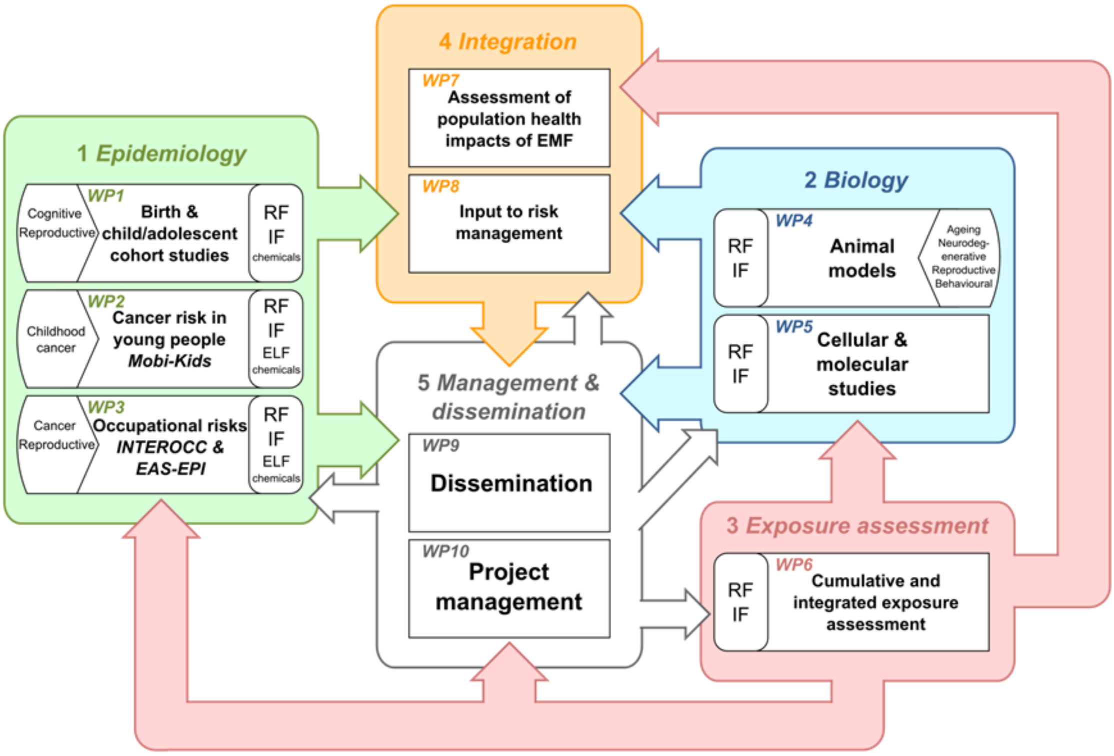
GERoNiMO used an integrated, modular approach (see Pert Chart below) to advance scientific understanding of EMF and health and inform effective policy-making.

The project has furthered interdisciplinary research, bringing together scientists from diverse research disciplines and countries. It has optimised the use of resources, particularly by building upon existing epidemiological studies and experimental models, as well as by bringing into the project, at no additional cost, expertise from Japan, Korea and the USA for exposure assessment and an additional birth cohort from Korea. It has established links with existing large national EMF programmes in Australia and Israel to avoid effort duplication and, through its multidisciplinary and multinational Scientific Advisory Group, it received valuable input and advice to maximise the results of the project.

GERoNiMO also improved our understanding of the biological effects of EMF and possible mechanisms underlying these effects by using novel cellular/molecular techniques and animal models. The collection of new exposure data using, where appropriate, state-of-the-art methods and technologies, was paramount to improving exposure assessment for both IF and RF. Stepping away from traditional unitary methods of risk assessment, the integrated design of GERoNiMO has fostered interdisciplinary collaboration. The synthesis and processing of data both generated within the project and from published sources that will be done in the Integration module, both in the assessment of population health impacts related to EMF and in generating inputs to risk management, maximized the utility of all project outputs to a variety of stakeholders. Due to increasing public concern in the EU regarding potential health effects of EMF, policy makers in Member States are increasingly required to have a coherent position on a subject characterised by a number of very complex issues that cross both scientific and policy boundaries. GERoNiMO provided recommendations to improve evidence-based risk communication to

a variety of stakeholders. Information generated in GERoNiMO also provides much needed input for assessing potential health impacts of RF and IF exposure in the EU, and identify priorities for EMF and health risk and research gaps.

The integrated design of GERoNiMO has ensure the most appropriate contributions to meeting the objectives of the FP7 Environmental Theme, in particular taking steps towards closing gaps in knowledge relating to exposure to EMF and its potential effects on human health. Results, methods and tools developed in the project will serve the European community in better understanding and prioritising EMFs as environmental hazards and risks to health and will feed into risk management and communication actions.



Pert Chart – Organisation of GERoNiMO activities by WP and Module

Description of the main S&T results/foregrounds

As shown in the Pert Chart above, the work in GERoNiMO was broken down into 10 complementary Work Packages (WP), regrouped into 5 modules: Epidemiology, Biology, Exposure Assessment, Integration and Management and Dissemination. The main results of the project are presented below, by WP and Module.

Module 1 - Epidemiology

WP1. EMF and health and development of children and adolescents – exploiting (large-scale) prospective cohorts

Objectives

WP1 aimed to evaluate potential effects of RF exposure on reproductive outcomes and on neuropsychological development of children and young people, exploiting existing data from large-scale European cohort studies, implementing a standardised outcome assessment of cognitive and behavioural development, and including exposure measurements for near and far-field RF.

To achieve this, WP1 used data from five prospective birth and child/adolescent cohort studies across Europe. Four of these are birth cohorts (ABCD in the Netherlands, DNBC in Denmark, INMA in Spain, and MoBa in Norway) that have been following mothers since the start of their pregnancy and are now examining health and development of the children. The fifth is the HERMES adolescent cohort study in Switzerland, set up to evaluate health and development outcomes as a result of RF exposures. These cohorts were selected because they had existing data to study RF-related health and developmental effects. The MOCEH cohort from Korea was also added to the pregnancy analysis, at no cost to the project. By combining and comparing findings in these different cohorts, GERoNiMO assembled large and in-depth datasets to evaluate RF exposure from different sources during different age windows; this has not been achieved before. The specific objectives of WP1 were:

1. To harmonise outcome assessments across the cohorts, including the harmonisation of outcome data already collected in the cohorts at younger ages and the collection of neurodevelopment assessments at older ages (DNBC age 11 years, ABCD age 10-11, INMA age 8-10 and age 18, HERMES age 13-16);
2. To study the association between maternal mobile phone use during pregnancy and child neuropsychological development and birth outcomes;
3. To study the association between near- and far-field RF exposures during childhood and adolescence and neuropsychological development, sleep, and non-specific symptoms in older children and adolescents.

The work for objective 1) resulted in a central database and protocols for standardised and harmonised exposure and outcome assessments in the Geronimo cohorts participating in WP1. The studies planned under objectives 2) and 3) then used this database to evaluate possible health effects (cognitive and behavioural development and reproductive effects) of exposure to RF. These investigations combine data from European birth and adolescent cohorts and from the Korean birth cohort in joint analyses of relevant outcomes, resulting in the largest epidemiological investigations of these associations to date:

1. Maternal mobile phone use during pregnancy and birth outcomes and neurodevelopment

To evaluate the effects of RF exposures during pregnancy, WP1 used four prospective birth cohort studies across Europe (DNBC in Denmark, ABCD in the Netherlands, MoBa in Norway, and INMA in Spain). Outside of the GERoNiMO project, the MOCEH cohort in Korea was added to the pregnancy analysis, as they had prospective maternal cell phone use data and were interested in participating. These cohorts have been following mothers since the start of their pregnancy and are now examining health and development of the children.

Based on inventory of previously collected data in these cohorts, we identified a common exposure variable (maternal cell phone use during pregnancy) and four common outcome variables: birth outcomes, cognitive development, behavioural problems, and language development. These outcomes have been assessed at different ages depending of the cohort. DNBC, ABCD, INMA and MOCEH cohorts completed data use agreements and sent data to ISGlobal for harmonization. MoBa data remained on site in Norway for local analysis only.

Results of each of the four outcome areas have been published, as summarised in Table 1 below:

1. Results from a meta-analysis of five birth cohorts (n=83,884) suggest that maternal cell phone use during pregnancy may be associated with an increased risk for behavioural problems, particularly hyperactivity/inattention problems, in children ages 5-7 (Birks et al., 2017).
2. In the Norwegian MoBa birth cohort (n=45,389), results suggest a decreased risk of low language and motor skills at age 3 in relation to prenatal cell phone use, which may be explained by enhanced maternal-child interaction among cell phone users (Papadopoulou et al., 2017).
3. A meta-analysis in three birth cohorts (n=3,089) found lower mean cognition scores among children ages 3-5 in relation to high frequency maternal prenatal cell phone use (Sudan et al., 2018).
4. Finally, a meta-analysis among four birth cohorts (n=55,507) indicated that maternal cell phone use during pregnancy may be associated with shorter pregnancy duration and increased risk for preterm birth (Tsarna et al., 2019, accepted Am J Epidemiol).

All conclusions emphasize caution in interpreting results and the possibility of residual confounding.

Table 1: Analyses of maternal mobile phone use during pregnancy and behavioural, cognitive and birth outcomes

Outcome assessed	Birth cohorts	N mother-child pairs	Age when outcome assessed	More calling during pregnancy linked to :
1. Behavioral problems	Denmark, Korea, the Netherlands, Norway, Spain	83,884	5y to 7y	↑ risk for behavioral and hyperactivity/inattention problems
2. Language and motor skills	Norway	45,389	3y	↓ risk for low language and motor skills
3. Cognition	Denmark, Korea, Spain	3,089	3y to 5y	↑ risk for lower cognition scores
4. Birth outcomes	Denmark, Korea, the Netherlands, Spain	55,507	birth	↑ risk for preterm birth and shorter pregnancy duration

1) Birks et al 2017, 2) Papadopoulou et al 2017, 3) Sudan et al 2018, 4) Tsarna et al 2019, accepted for publication.

2. Childhood RF exposure and neurodevelopment, sleep and non-specific symptoms

This objective evaluates association between RF exposure in children and adolescents, combining exposures from near and far field RF sources. We focus in these analyses on children over the age of 8 years. Analyses in younger children were not further pursued due to the lack of data on far field sources at these ages combined with the lack of exposure to near field sources at these young ages. Related to this objective, we assessed neurodevelopment and other symptoms and collected information about mobile device use in children and adolescents in four longitudinal cohorts (ABCD, INMA, HERMES, and additional non-Geronimo cohort Generation R). With WP6, we modelled exposure to mobile phone antennas through NISMAP and estimated RF dose to the brain and whole body of the children and adolescents using the Integrated Exposure Metric (IEM) developed in WP6.

Description of Dose to Brain Tissue and Body in European Children

Daily median RF dose to 9 tissues of the brain and the whole body was modelled in 8,358 children and adolescents in prospective cohorts from the Netherlands (ABCD, age 12, and Generation R, age 10), Switzerland (HERMES, age 14), and Spain (INMA Young, ages 8-10 and INMA Menorca, age 18) using an integrated exposure model (IEM) (Birks et al 2019, in preparation). The IEM modelled RF dose based on questionnaire data reporting daily duration of digital enhanced communication technology (DECT) phone use, mobile phone

(MP) use, tablet use, and laptop use, as well as geographic proximity to mobile phone base stations through use of 3D-radiowave propagation NISMap modelling or previously collected environmental RF measurements. We used adjusted mixed effects models with cohort random effects to estimate associations of individual characteristics and sociodemographic factors with RF dose the brain and body.

Results*:* Mobile device use habits differed between adolescents (14-18 years old) and children (8-12 years old), with adolescents more frequent users of mobile phone and children more frequent users of tablets. Adolescents experienced highest median RF dose to the brain (451.92 and 107.13 mJ/kg/day in the oldest cohorts, HERMES and INMA Menorca, respectively) due to more mobile phone calling (Figure 1.1). Children experienced lower RF dose to the brain (medians 98.89, 85.26, and 52.60 mJ/kg/day in ABCD, Generation R, and INMA Young cohorts, respectively). In children and adolescents that reported mobile phone calls, dose was highest in the temporal lobes of the brain (median 316.86 mJ/kg/day for the temporal lobes), followed by the frontal lobe, and these doses came overwhelmingly from calls on 2G networks. Adolescents and females experienced higher RF dose to the brain. Children who did not use mobile phones received most of their RF dose from use of laptops or tablets, and this dose was mostly absorbed by the body (Birks et al 2019, in preparation).

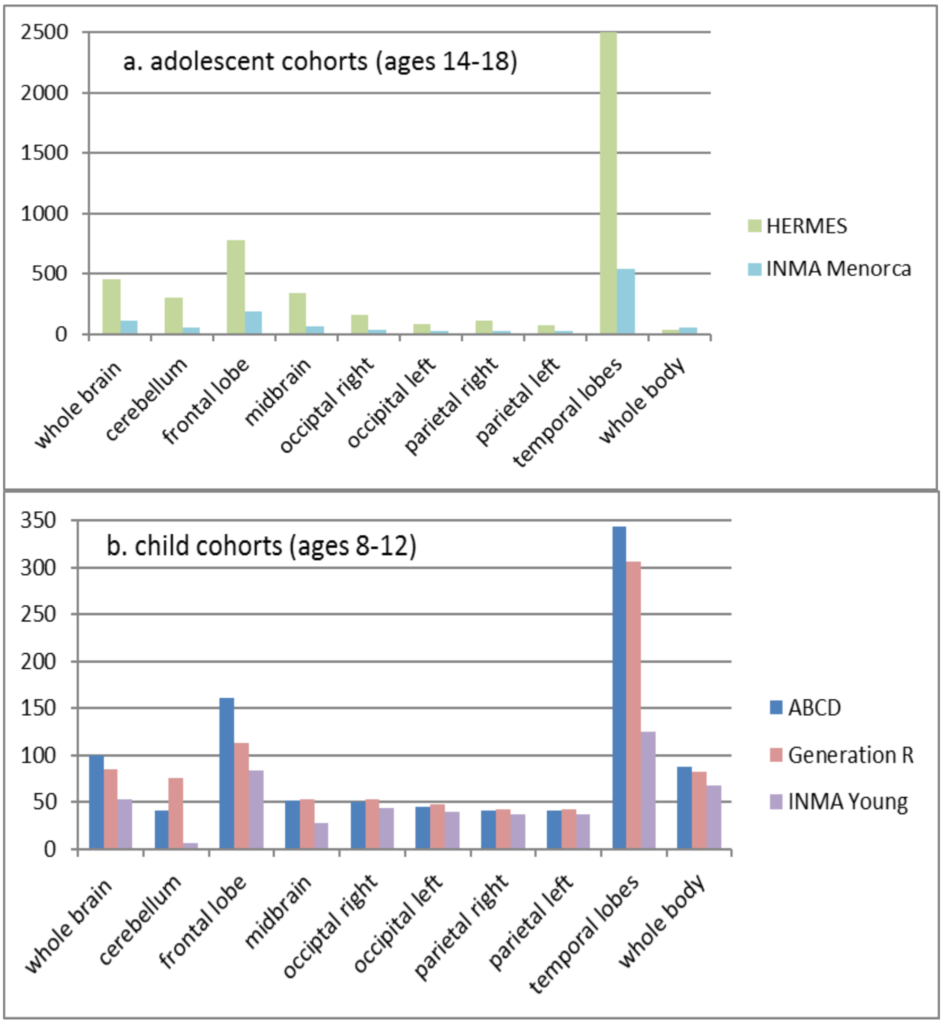


Figure 1.1. Median daily RF dose (mJ/kg/day) to brain tissues by cohort among a) adolescent cohorts (larger scale) and b) child cohorts (smaller scale). (Birks et al 2019, in preparation)

Conclusion: RF dose to brain tissues from mobile device use increases heavily with increased calling on 2G networks, which happens more in adolescents, compared to children. In children, use of laptops or tablets is more common, leading to increased RF dose to the body. In adolescents, RF dose to the brain could be reduced by avoiding calls on 2G networks; while in children, whole body dose could be reduced by limiting daily duration of high laptop or tablet use.

3 Associations between RF dose and child and adolescent outcomes

Analyses in children and adolescents include four main outcome domains:

1. behavioural problems at 7-18 years
2. cognitive development at 7-18 years
3. sleeping problems at 7-18 years, and
4. non-specific symptoms at 11-18 years

In the first of these analyses, we included four prospective cohorts to evaluate associations between **RF dose and behavioural outcomes** (Birks 2018; Birks et al., 2019b). Daily dose to the whole brain, right frontal lobe, and right temporal lobe was modelled using the IEM in 7,871 children and adolescents from prospective cohorts: children (ages 8-12) from the Netherlands (ABCD and Generation R) and Spain (INMA Young), and adolescents (ages 14-18) from Switzerland (HERMES) and Spain (INMA Menorca). For the purpose of separate control analysis for other exposures associated with mobile device use (blue light, social media, etc), texting, screen time, and calling were categorized into low, medium, and high categories. Child and adolescent behavioural problems were reported (by parents in child cohorts and by self in adolescent cohorts) using the Strengths and Difficulties Questionnaire or Child Behavior Checklist, and were classified in the borderline/clinical and clinical ranges using validated cut-offs in children and adolescents aged 8–18 years. Cohort specific risk estimates were meta-analysed.

Results: Children experienced less RF dose to the whole brain (median RF dose 82.63 mJ/kg/day) compared to adolescents (median RF dose 327.24 mJ/kg/day). Even so, in children there was a weak association between RF dose and increased risk for conduct problems in the borderline/clinical range (OR 1.15 95%CI 0.98, 1.36 per increase of 1 J/kg/day to the frontal lobe) (Table 1.2). In adolescents a higher RF dose to the brain was associated with an increased risk for hyperactivity/inattention problems (OR 1.13 95%CI 1.04, 1.22 per increase of 1 J/kg/day to whole brain), and conduct problems (OR 1.21 95%CI 1.11, 1.32) in the borderline/clinical ranges. In a control analysis, increased risk for hyperactivity persisted, but lost statistical significance, among adolescents categorized as high texters or high screen time users, compared to low use categories. In children and adolescents, higher callers had an increased risk for conduct problems in the borderline/clinical range (younger: OR 1.72 95%CI 1.18, 2.53, older: OR 2.24 95%CI 1.25, 3.99), compared to low callers. Table 2 summarises these results (Birks et al 2019, in preparation).

Table 1.2: Analysis of childhood RF exposure and neurobehavioural outcomes (Birks et al 2019, in preparation)

Cohorts	Age group	N	Median RF dose to brain tissue per day	More integrated RF dose (J/kg/day) to brain linked to :	More texting and screen time (marginal RF dose) linked to:	More call time (high RF dose) linked to:
The Netherlands, Spain	Children 8y to 12y	6,730	121.8 mJ/kg	↑ risk for conduct problems	↑ risk (NS) hyperactivity/inattention and conduct problems	↑ risk for conduct problems
Switzerland and Menorca, Spain	Adolescents 14y to 18y	1,141	352.0 mJ/kg	↑ risk for behavioral, hyperactivity/inattention, and conduct problems	↑ risk (NS) hyperactivity/inattention and conduct problems	↑ risk for conduct problems

Conclusions: Results suggest that increased RF dose to the brain and longer mobile phone call time may be associated with risk of hyperactivity and conduct problems. Results were more robust in adolescents versus children. Reverse causality and effects of mobile device use, apart from RF dose, cannot be entirely excluded as explanations for these results.

Results regarding RF dose to the brain and associations with cognition, sleep and non-specific symptoms are forthcoming.

WP2. Role of IF and RF in brain cancer risk in young people

Objectives

WP2 built upon the MOBI-Kids study, a multinational case-control study conducted in 14 countries to assess the potential carcinogenic effects of exposure to RF from mobile communication technologies on the central nervous system of children adolescents. In this WP, the objective was to maintain the network already in place to prolong case and control enrolment in the study (thus increasing the statistical power of MOBI-Kids) and to extend exposure assessment to address IF exposures (in addition to RF, ELF and other environmental factors already being assessed in the study) in MOBI-Kids subjects through questionnaires and surveys.

Methods

The MOBI-Kids study is a collaborative case-control study that recruited cases with benign or malignant brain tumours and hospital controls in 14 countries around the world: Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zealand, Spain and The Netherlands. The common study protocol was published in 2014 (Sadetzki et al 2014). Cases were subjects aged 10-24 years with a diagnosis of brain tumour not located in the midline and diagnosed between 2010 and 2016 in the different participating centres. A case was excluded if s/he had insufficient knowledge of the study language(s) and/or a known genetic syndrome related to brain tumours (e.g. neurofibromatosis). Two hospital controls per case were originally recruited. Controls were appendicitis patients, and were matched by sex, age (±1 year for cases younger than 17 years and ±2 years for cases 17 years and older), date of interview and geographic area of residence. All eligible subjects were invited to participate in the study. The study was approved by the ethical committees of the participating hospitals. All cases and controls had to give consent to be included in the study; in the case of minors (≤12 years old), parents gave the consent of their behalf.

Each participant responded to a face-to-face questionnaire administered by a trained interviewer. The questionnaire collected information on mobile and cordless phone voice use, mobile phone data uses, WiFi (Wireless Internet) use and exposure to other sources of electromagnetic fields (EMF) such as induction cookers and chargers. The questionnaire also collected information on residential history, contact with animals at home, occupational history (for those who were old enough to have worked) – including questions on exposure to specific EMF sources (including Electronic Article Surveillance (EAS) systems) –, medical radiation exposure history and medical history. Six countries (Spain, Korea, Italy, New Zealand, Canada, Greece) also asked questions related to potential exposure to disinfection by-products (DBPs). In Spain, samples of toe nails were collected to study the potential role of metals on brain tumour risk in young people.

Parents were also asked to complete a questionnaire regarding exposures that might have occurred during the first years of life of the participant. Specifically, mothers were asked about their educational level, conditions suffered during pregnancy and 3 months pre-conception, medications taken during that period, medical radiation exposure during pregnancy. Further, questions were asked about alcohol intake, smoking and use of mobile phones and electric appliances during the period that covered 3 months prior to conception until 3 months after birth of the study subject. Information was also collected on delivery of the subject, exposure of the child to medical radiation during the first years of life, child's school history, mother's occupational history around the pregnancy, family history of cancer and some questions related to exposure to DBPs (only in the 6 countries listed before). Fathers were asked about their educational level and occupational history – longest job held and jobs during the period 3 months before conception to 3 months after birth of the subject.

Information regarding the tumour characteristics was collected in a clinical questionnaire completed using hospital records, pathological anatomy records, answers from the cases' surgeon, oncologist as well as, when needed, charts and records kept by the parents. The questionnaire included information regarding symptoms previous to the diagnosis, diagnostic procedure and surgical and histological information of the tumour.

A software including 3D representations of the brain was created (the XGridmaster) by Whist Lab on which a 1cm^3 grid was superimposed for neuro-radiologists to map the tumour location, choosing the most appropriate brain (XGrimaster included four phantoms brains representing different ages 8, 11, 14, and adult and produced by IT'IS (Christ et al., 2010). This allowed estimation of the RF and ELF exposures in the tumour and different brain areas (see below).

Several sub-studies were conducted to evaluate the potential for biases and errors in risk estimates – including recall error in responses to the mobile phone use and bias related to mobile phone use and non-participant bias.

Mobile phone use validation studies included:

- a study in which volunteers and consenting controls from 12 countries installed the XMobiSense application on their phones, an application that recorded mobile phone usage (voice, text and data), hands-free usage and laterality of use (see WP6, Task 6.1), and were asked to recall their phone use during the recording period 6 and 18 months after the end of that period (Goedhart et al, 2018)
- a study in which operators records were obtained for consenting subjects and operator data compared with self-reported mobile phone use at 3 months, 1 year, and 2 years before the interview date (van Wel et al, 2019 in preparation).

To account for potential participation bias, subjects who declined to participate in the study were asked to respond to a very short non-respondent questionnaire and information provided was compared to the participants of the study (Turner et al 2019).

Validation of tumour diagnosis was conducted on a sample of cases from each country by a panel of neuro-pathologists.

Algorithms for the estimation of exposure from mobile and DECT phones were developed in the previously funded MOBI-Kids project were checked and finalised in order to estimate exposure in the tumour and in different structures and locations in the brain of the study participants (Calderón et al, 2019) using the XGridmaster (see above). An envelope brain was created in in which all the 1cm^3 of the age-specific phantoms were mapped, allowing estimation of ELF induced current density (ICD) and RF Specific Absorption Rate (SAR) in each cube of the envelope brain, as a function of age at exposure, phone characteristics (type of phone, SAR) and telecommunication frequency. Algorithms (similar to that used in the INTERPHONE study for RF (Cardis et al, 2011) were developed to estimate, the cumulative and time weighted average ELF ICD and RF SAR in each 1 cm3 cube of the reference brain, as a function of reported historical mobile and DECT phone use and historical network characteristics. This algorithm allowed estimation of both ELF ICD and RF SAR at the location of the tumour, in its centre of gravity as well as in different anatomical structures of the brain. The algorithm also took into account laterality of phone use and use of hands-free kits (including bluetooth). The algorithm is described graphically in Figure 2.1.

Occupational histories of the study subjects and of their parents have been coded using the ISCO codification system by two occupational hygienists (H. Kromhout, UU and G. Benke, Monash). Comparisons and resolution of coding discrepancies are underway. Once this is complete, the job codes will be linked to various Job-Exposure Matrices (JEM) for chemicals and ELF in order to estimate occupational exposures for subjects and their parents.

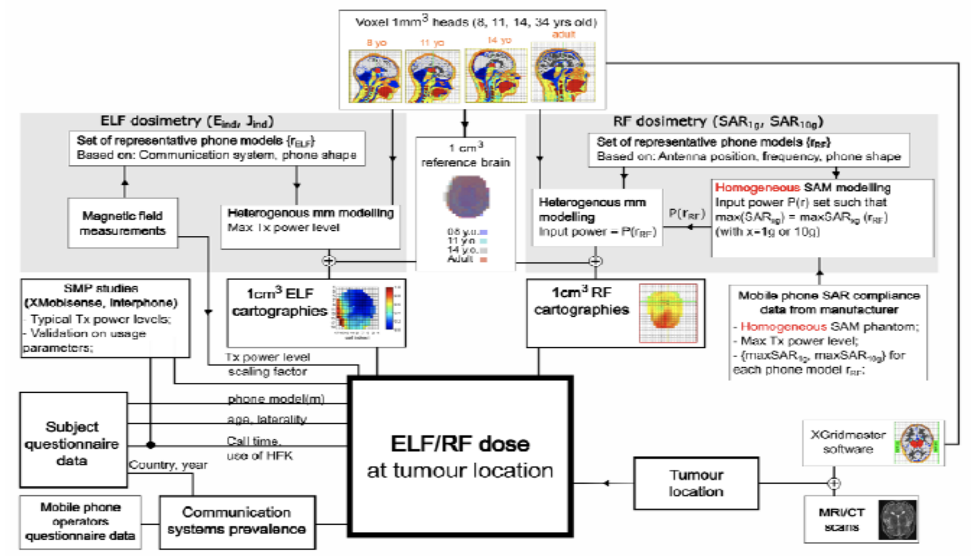


Figure 2.1: ELF and RF algorithms for MOBI-Kids for mobile phone exposure. Algorithm for Digital Enhanced Cordless Telecommunications (DECT) phones and Wi-Fi VoIP voice calls is similar *(Calderón et al, 2019*)

Statistical methods

All study centres sent the information collected, anonymised, to ISGlobal, Spain, the coordinating centre of the study, where all questionnaires and complementary data were combined – and validated – to obtain a central database.

Conditional logistic regression was used, adjusted by socio-economic status (defined as a function the highest of mother and father's education level) and interview period within countries. Age was categorized into 3 groups: 10-14, 15-19 and 20-25 years of age. Likelihood ratio tests were used to test for homogeneity of risk across levels of model variables.

The reference date of cases was set to the date of the first image showing a space occupying lesion. For controls it was set to the date of appendicitis operation.

Phone use variables were defined a priori: time start of use; and ever use of a mobile/DECT phone, lifetime cumulative number of calls and lifetime cumulative call time in hours, including both mobile and cordless (DECT) phone use up to 1 year before the reference date. Reported use of Hands-Free kit and laterality of phone use – adjusted by the results of the XMobi-Sense validation study – was taken into account to calculate the exposure. Analyses were conducted both on categorical mobile phone use variables (defined as quintiles of the distribution of these variables among controls) and continuous variables.

Issues in the analysis of the data

Matching: Originally, and according to the study protocol, 2 matched controls per case were selected. All efforts were made to fulfil this criterion, but it was not possible in all countries, and 8% of the cases had no matched controls and 20% of the controls no matched case. In addition, the original matching in some cases resulted in large time intervals between the diagnosis of the case and that of the control (one year or more), which, in a study of a rapidly evolving technology like that of mobile communication, can induce a bias. In order to minimize the number of cases without any controls and ensure a closer matching in time, post-hoc matching was performed for neuroepithelial cases only, the main morphological group of all the cases. The criteria used for this matching was: same sex and country; age difference between case and control at reference date less than 1 year in subjects younger than 17 and up to 2 years for those older than 17 years, difference of interviews dates <1 year. Repetition of controls was allowed, and the 3 closest matched controls were selected for each case (where there were more than 3 eligible controls). In this case, 99% of cases were matched. For non-neuroepithelial tumours, the original matching was kept. Sensitivity analyses were conducted without repeating controls.

The main analyses focused on neuroepithelial cases, although some analyses on the second most frequent group – embryonal tumours – were also performed, though numbers were small and statistical power was limited.

Major age dependence of phone use. Since the study spanned a wide range of ages: from 10 to 25 years, mobile phone use history differed vastly by age, with the vast majority of the adolescents and adults being regular mobile phone use and a much lower percentage in the 10-14 years of age group. When amount and duration of phone use were characterised into quintiles therefore, a high proportion of young subjects were in the lowest quintiles and most of the older subjects in the higher quintiles. Thus, though analyses are systematically adjusted for age there was little variability of use in some of the age categories. To address this issue, it was decided to develop age-specific quintiles, which permit the comparison of risk across quintiles of use in each age category. Non-regular users (NRU) and subjects with less than one year of use were grouped together with the first quintile of users when analysing cumulative number of calls or cumulative call time. These categories are used as reference for the conditional logistic regression analyses.

Results

Task 2.1 Data collection and validation of MOBI-Kids database

Questionnaire data was collected until March 2016, with a total of 899 cases and 1910 controls eligible and interviewed. Table 2.1 shows the characteristics of the cases and controls. Overall, there were more males than females and a larger proportion of subjects in the 10-14 years category than in the 15-19 and 20-24 years category. Overall, 75% of all cases were neuroepithelial tumours, 82% of which were glioma. Among the non-neuroepithelial tumours, nearly 60% were embryonal. Only 47 meningioma were seen in this age group. A manuscript on the clinical characteristics of the tumours is in preparation (Zumel et al, 2019a)

Table 2.1 Preliminary characteristics of the study subjects (Castaño-Vinyals et al 2019a, in preparation)

	Cases N=899	Controls N=1 910
Sex		
Female	387 (43%)	830 (43%)
Male	512 (57%)	1 080 (57%)
Age category		
10-14 years	378 (42%)	783 (41%)
15-19 years	290 (32%)	636 (33%)
20-25 years	231 (26%)	491 (26%)
Morphology		
Neuroepithelial tumors	***676 (75%)***	
Glioma	556 (82%)	
Neuronal and Mixed	116 (17%)	
Other Neuroepithelial	4 (1%)	
Non-neuroepithelial tumors	***223 (25%)***	
Embryonal	129 (58%)	
Meninges	47 (21%)	
Choroid plexus tumours	15 (7%)	
Cranial paraspinal nerves	21 (9%)	
Other	11 (5%)	

Validation of the reported mobile phone use history has been conducted through two studies, as above. The study of volunteers and consenting MOBI-Kids controls (Goedhart et al 2018) indicated that that young people can recall phone use moderately well (Spearman's correlation coefficients 0.68 and 0.65 respectively for number and duration of calls). As in previous studies, low mobile phone use underestimated their use, while individuals who reported the highest level of phone use were more likely to overestimate their use. Individuals who reported using the phone mainly on the right side of the head used it more on the right (71%) than the left (29%) side. Self-reported left side users, however, used the phone only slightly more on the left (53%) than the right (46.7%) side. Recorded percentage of hands-free increased with increasing self-reported frequency of handsfree device usage. Frequent (≥50% of call time) reported headset or speaker mode use corresponded with use about 17% of the time, however. These results have been taken into account in the modelling of the effect of laterality of phone use and % of hands-free use in the ELF and RF algorithms as well as in the cumulative number and duration of phone use estimates for risk analyses.
Analyses of results of the operator validation study have been conducted and a manuscript is under preparation. Preliminary results suggest no significant difference between recall of cases and controls, though both systematic and random non-differential recall errors were observed. Again, low users tended to underestimate their use and high users overestimate it (van Wel et al 2019 – in preparation).

In the non-participation bias study (Turner et al 2019), regular users appeared to be over-represented among participants than non-response questionnaire respondents in the 10-14 years of age group, and longer term use (5+ years) was reported more among study participants than non-response questionnaire respondents. Different scenarios of non-participation bias generally suggest that these differences may lead to a small underestimation of risk – selection bias estimates 0.96-0.97 for ever regular use and 0.92-0.94 for time since start of use >= 5 years. Regression analyses allowed evaluating the factors most related to participation, including case-control status, education, amount and duration of mobile phone use and to derive inverse probability weights to be used in the analyses of brain tumour risk in relation to mobile phone use and RF and ELF exposure to adjust for the observed non-participant bias.

Task 2.2 Estimation of IF exposures from environmental and occupational sources

Information on IF exposure sources was collected through the main and the parental questionnaires, but questions regarding IF exposure were added later in the study, within GERoNiMO. Sixty-two percent of the interviews included in the study have the new version of the questionnaire that includes the questions regarding exposure to IF. Analysis on exposure to environmental and occupational IF sources showed that children and adolescents are exposed very little to IF: only 33% of subjects reported ever being occupationally active: among these, exposure to occupational IF sources ranges from 0.5% (working with industrial sewing machines, or dielectric heater sealers) to 5-7% (working close to electronic article surveillance (EAS) systems and electrical welding equipment, respectively).

Environmental exposure of the mother through use of induction cookers or electric sewing machines was low, with a mean of 14 and 13 hours per week (Castaño-Vinyals et al 2019b in preparation)

Task 2.3 Potential effects of RF and IF, alone and in combination with chemicals, and risk of brain tumours

This task comprises the analyses of the effects of RF and IF (using the estimates derived in Task 2.2) on the risk of brain tumours in young people, alone and in combination with ELF and potential chemical risk factors (water pollutants, metals, pesticides etc.).

Given the distribution of morphological types of tumours in the study, the main analysis focuses on neuroepithelial cases and its matched controls (672 cases and 1889 controls).

Analyses of effects of mobile phone history and RF and ELF "dose" at the tumour location and in different analytical structures have been conducted and a manuscript prepared. These will be submitted for publication in the coming months (Castaño-Vinyals et al 2019a and Cardis et al, 2019 – in preparation).

Analyses of occupational exposure to EMF will be conducted shortly, as soon as the job coding of occupational histories is complete and validated and job-codes have been linked to existing Job-Exposure Matrices (including the RF JEM developed in WP6, Task 6.2) to allow individual estimates of occupational exposures to EMF and chemicals. All of the jobs reported by the subjects and their parents have been translated into English and coded by expert hygienists using ISCO codes: this included 2505 jobs for the study subjects, 1800 jobs of mother and 2261 jobs of fathers.

Estimates of brain dose from phone data use (including texting, streaming, voice over IP calls) and WiFI use will be derived using the Integrated Exposure Model (IEM) from WP6 task 6.6. And an analysis of brain tumour risk will be conducted taking into account RF and ELF doses from voice calls, from data uses, other environmental sources and occupational exposures.

Analyses of potential individual risk factors for brain tumours in young people have been conducted or underway. This includes:

- medical radiation exposures (Pasqual et al, 2019, manuscript in preparation)
- water disinfection by-products (Zumel et al, 2019b, manuscript in preparation)
- metals and brain tumours in young people in Spain (Zumel et al, 2019c, manuscript in preparation)
- Maternal and foetal exposures and brain tumour risk in childhood and adolescence (Arnon et al 2019, in preparation)
- The possible role of atopic conditions, morbidities and family history of cancer in the development of malignant brain tumours among children and adolescents (Ben Avraham et al 2019, in preparation)

WP3. Occupational Exposure to EMF and Risks to Health

WP3 consisted of two tasks to conduct novel epidemiological research on the potential health effects of occupational RF and IF exposure. The first task (3.1) sought to build upon the large, established INTEROCC study to examine associations between RF and IF exposure estimated from questionnaire data together with the Source-Exposure Matrices (SEM) derived in WP6 (Task 6.2) and risk of glioma and meningioma overall, as well as potential synergies with occupational chemical exposures. The second task (3.2) sought to conduct a register-based cohort study in Finland to examine potential reproductive health effects of occupational IF among female cashiers and to serve as a pilot study for a potential future multinational study of cashiers.

Task 3.1 Effects of EMF and Chemicals on Cancer in Adults – Exploiting the Work of INTEROCC.

The INTEROCC project is a large-scale population-based multinational brain tumour case-control study, conducted in seven countries (Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom) between 2000 and 2004, based on the parent INTERPHONE study. The objective of INTEROCC is to address outstanding questions concerning occupational agents for brain tumour risk. Although estimates of chemical and ELF exposures were previously determined for INTEROCC participants, and associations with brain tumour risk examined, work in GERoNiMO focused on associations between RF and IF exposures based on a novel SEM-based exposure assessment approach (derived in WP6) and risk of glioma and meningioma overall, as well as potential synergies with occupational chemical exposures.

A total of 1,943 glioma cases, 1,862 meningioma cases, and 5,387 control subjects were included in the analysis. Individual indices of cumulative exposure to RF and IF-EMF (overall, with both 1- and 5-year lags, and in specific exposure time windows 1-4, 5-9, and 10+ years in the past) were assigned to study participants linking detailed interview data on work with or nearby EMF sources with the exposure estimates from the SEM. Conditional logistic regression models were used to investigate associations of cumulative RF E- or H-field, or IF H-field exposure and glioma and meningioma risk stratified by age (5-year groups), sex, study region and country, and adjusted for education.

Overall, approximately 10% of study participants were ever exposed to RF, while only 1% were ever exposed to IF-EMF (1-year lag). The sources with the highest level of exposure were “RF sealers/welders for plastic & rubber” for RF and “Electronic Article Surveillance (EAS) system” for IF. The RF and IF sources most frequently reported were “walkie-talkie” and “induction heater” respectively. The mean (SD) number of sources reported per subject was 1.33 (0.83) for glioma cases, 1.31 (0.65) for meningioma cases, and 1.35 (0.92) for controls.

There was no clear evidence for associations between RF or IF-EMF exposure and either glioma or meningioma risk, but many of the odds ratios (ORs) were below 1.0. The largest ORs were obtained for cumulative exposure to RF magnetic fields (as A/m-years) in the highest exposed category ($\geq 90^{th}$ percentile) for the most recent exposure time window (1–4 years before the diagnosis/reference date) for both glioma (OR=1.62, 95% confidence interval (CI): 0.86, 3.01) and meningioma (OR=1.52, 95% CI: 0.65, 3.55), though results are non-significant and imprecise (Vila et al, 2018).

Estimates of occupational exposure to 29 metals, solvents or other chemical agents were assigned to study subjects based on their job titles using a modified version of the Finnish job-exposure matrix (FINJEM). Ever exposure to any of these chemicals was defined as a probability of exposure ≥25% for at least one year, with a 5-year lag. Although there was no clear evidence for interactions with the majority of chemical agents examined, there were some significant interactions observed on the multiplicative scale between cumulative RF exposure (both E- and H-fields, in the 1- to 4-year exposure time window) and cumulative exposure to either iron or welding fumes for glioma risk (Vila et al, 2019a, in preparation).

Results of this study warrant further investigation in populations with higher RF exposure prevalence.

Task 3.2 Reproductive Effects of Occupational IF Exposure: A Pilot Cohort Study.

An epidemiological study was conducted in order to investigate potential reproductive effects of IF magnetic field exposure among cashiers working near electronic article surveillance (EAS) systems. The study cohort was identified among personnel of a large retail company. The cohort included 4157 women aged 18 to 40 years who had worked as cashiers in supermarkets with EAS devices operating at a frequency of 8.2 MHz or grocery stores without EAS devices during years 2008-2015. The women working in supermarkets were considered as exposed and those working in grocery stores as unexposed. Measurements were also performed to characterize the MF exposure of cashiers at both store types as the previous measurement data was collected from stores with EAS devices operating at kHz frequencies.

The cohort was linked to the nationwide health registries to obtain information on births and miscarriages. Only those women who had a contract of employment at the time of miscarriage or at the tenth week of pregnancy were included. A total of 536 births and 38 miscarriages occurred during the study period. Age was the only background information available for women who had had a miscarriage. Information on previous deliveries, previous miscarriages and smoking status was also available for women who had given birth. Generalized estimating equation for logistic regression and generalized linear mixed model were used for statistical analyses.

The measurements showed that exposure of the cashiers to 8.2 MHz occurs only when they pass by the gates at short distance. This may happen several times during the work shift. Cashiers working in the supermarkets were also exposed to static magnetic fields from the demagnetizing devices. The measured ELF MF levels were higher in smaller stores compared to supermarkets. No differences on the risk of miscarriage, reduced birth weight or preterm birth were observed between cashiers in different store types (Khan et al, 2018).

Further studies on potential reproductive effects of IF MF exposure are needed as the number of devices operating within this frequency range is increasing. Studies should attempt to include study subjects working near EAS systems producing stronger IF MFs at kHz frequencies. ELF should also be considered as a possible confounding factor. Attempts should also be made to collect information on routines of cashiers during the work shift, e.g. how many hours they sit at cashier's seat and how many times they pass by the surveillance gates.

WP4. Animal models

Methods

In this WP, neurobiological, reproductive and behavioural effects of long-term exposure to intermediate frequency (IF) magnetic fields (MFs) and radiofrequency (RF) fields in laboratory mouse strains were investigated. The effect of exposure on genetic damage (genotoxicity) was also studied.

Intermediate frequencies

For the behavioural and genotoxicity studies of IF, male C57BL/6J mice were exposed continuously for 5 weeks to 7.5 kHz MFs at 12 µT or 120 µT, or were sham exposed. The exposures are similar to fields found in the vicinity of induction cookers, and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (1998) reference level for public exposure at 7.5 kHz is 6.25 µT. The animals were 2 months old at the onset of exposure. After exposure, neurobiological effects such as motor activity and coordination, anxiety, aggression, and spatial learning and memory were assessed using a well-established battery of behavioural tests, including a standard water maze test and a fear motivated test. After the behavioural testing, mice were sacrificed and sperm count, sperm motility and sperm morphology were analysed. Genotoxicity was assessed from the blood samples of exposed mice by measuring DNA damage using two standard tests, the alkaline Comet assay and the micronucleus assay.

To study the effects on the offspring of exposed mothers, pregnant mice were exposed 24 h/d to 7.5 kHz MFs at 12 or 120 µT, or sham-exposed from the first day of gestation until the pups were weaned. After weaning, the pups were housed in metal cages in-group with same-sex littermates to avoid social stress and breeding. At the age of 2 months, the battery of behavioural test was conducted.

Radiofrequencies

At PHE, the effects of long-term exposure to RF were investigated in a mouse model of ageing and in a mouse model of Alzheimer's disease.

For the ageing study, senescence accelerated (SAMP8) mice were exposed to 1800 MHz GSM signals for 30 minutes per day, 3-5 times per week from the age of 8 weeks for 2 months. Exposure groups consisted of whole-body averages of 0, 0.3 or 3 W/kg. The signals are similar to those emitted from mobile phones and the whole-body averages used were higher than the ICNIRP general public basic restriction of 0.08 W/kg. Assessment of the mice took place at 8 and 30 weeks of age.

Mice were tested for learning and memory using a standard water maze test where the mice need to learn the position of a platform to escape the water, and after behavioural testing, mice were sacrificed to allow investigation of brain structures. In excised brains we investigated levels and locations of the normal and disease-associated proteins glial fibrillary acidic protein (GFAP), ionized calcium-binding adapter molecule 1 (Iba1), synaptophysin and ß-amyloid 17-24.

For the Alzheimer's Disease (AD) work we used the genetically modified J20 mice exposed to 1800 MHz GSM signals 30 minutes per day, 3-5 times per week from the age of 8 weeks for 2 months. Exposure groups consisted of whole-body averages of 0, 0.3 or 3 W/kg. Assessment of the mice took place at 6 and 12 months of age.

The motor function of mice was assessed using the Accelerated Rotation Rate (ARR) protocol on the rotarod where the ability of mice to remain on a rotating rod is investigated, and mice were tested for learning and memory using the Morris water maze as described above. The O maze was used to examine anxiety related behaviour; in this test mice are assessed for the length of time they remain in open or closed zones of the maze. After behavioural testing, mice were killed and we examined levels and locations of the brain proteins glial fibrillary acidic protein (GFAP), NeuN (Neuronal Nuclei), Synaptophysin, and ß-amyloid 17-24 by antibody staining.

All analyses and statistics were carried out blind to exposure group and animal status.

Results

Intermediate frequencies

No signs of impaired health in mice exposed to IF were observed, and body weights did not differ between exposure groups. Behavioural tests revealed no deleterious effects of exposure (Kumari et al., 2017). However, performance in the water maze test and in the fear motivated task indicated moderate impairment of spatial learning and memory in the 120-µT exposed group. Analysis of brain structures did not reveal significant effects on hippocampal inflammatory markers or neurons. However, expression of the TNFα gene was elevated in the 120-µT group (Kumari et al., 2017). The IF MFs did not affect the reproductive tissue weights, and no exposure-related differences were observed in sperm counts or head abnormalities, but increased sperm motility was observed in the 120-µT group.

In the genotoxicity study, decreased DNA damage was observed in both exposure groups (12 and 120 µT). A significant difference between exposure groups was observed in micronuclei levels in immature red blood cells but levels were not statistically significantly different from the sham-exposed group. The micronuclei frequency in mature cells was significantly increased in the 12-µT group. This finding should be interpreted with caution, because the estimated mature cell data are less reliable than the counted immature cell data, and there was no clear dependency on exposure level. The ratio of mature/immature cells was not affected by the MF exposure, indicating no bone marrow toxicity (Herrala et al., 2018).

No IF MF effects on body weight development of male pups were observed following exposure during pregnancy. The behavioural tests showed no deleterious effects of IF MF exposure on spontaneous explorative activity, measures of anxiety or spatial learning and memory. In contrast, in the Rotarod test, mice in the 12-µT group performed significantly better than the sham-exposed group suggesting improved co-ordination and movement. Another indication that maternal IF MF exposure might have some behavioural effects following exposure in pregnancy was the decreased swimming speed in the water maze test. Hippocampal inflammation and neurons were not influenced by the exposure (Kumari et al., 2018).

Radiofrequencies

Preliminary results show that acute or chronic exposure to RF had no adverse or beneficial effect on learning and memory in the aging mouse model. Exposure to RF also had no effect on synapse structure, or expression of inflammatory markers in the brain. But long term RF exposure can affect cognitive functions in mice.

Manuscripts are in preparation and detailed results will be published in during the year.

Conclusions

In behavioural studies, impaired performance in both the water maze test and the fear motivated task suggest negative effects of 7.5 kHz, 120 µT MFs on learning and memory. Also, expression of the pro-inflammatory cytokine TNFα gene was increased in the 120 µT group. These findings suggest that exposure to a 7.5 kHz, 120 µT MF may lead to mild cognitive impairment possibly through an inflammatory reaction in the brain. The exposure did not affect general health, body weight, spontaneous activity, motor coordination, anxiety or aggression, and no exposure-related changes in brain histopathology or neurons were observed. In male reproductive studies, there were no adverse effects on fertility indicators after exposure, but increased sperm motility was observed in the 120-µT group. This does not indicate adverse effects, but is interesting and needs further investigation.

The genotoxicity results did not provide evidence of genotoxic effects from exposure to 7.5 kHz MFs at 12 and 120 µT. Surprisingly, decreased DNA damage was observed after exposure. It remains to be investigated whether this slightly reduced damage to DNA might relate to the improved sperm motility observed in the reproductive study and to the reported protective effects on DNA damage and relative cell number observed in some *in vitro* studies.

Results of the pregnancy studies provided no evidence of adverse effects from prenatal and early postnatal exposure to IF MFs. Body weight in male offspring was not affected by exposure, and no differences were observed in motor activity, anxiety, spatial learning, or memory. Histopathological analysis did not reveal any effects on inflammatory markers or neurons. The two findings that were observed – improved performance in the Rotarod task in the 12-µT group and decreased swimming speed in the 120-µT group – are likely to be chance findings, as they do not form an internally consistent, dose-dependent pattern indicating specific developmental effects. Since only males were studied, the possibility cannot be excluded that the results may differ in females.

WP5. Cellular /molecular studies

Methods

The aim of WP5 was to perform in-vitro experiments using novel approaches to assess effects of IF and RF exposure and identify action mechanisms. Real-time measurements, metabonomics and induced genomic instability assays provided a basis for a systems biology approach.

Exposure set up

Along with existing equipment, in vitro experiments used a series of dedicated and innovative exposure set ups that were designed and characterized for WP5 such as the XCellRF. Experimental dosimetry and FDTD simulations were performed to provide the most accurate dosimetry.

Real-time measurements

At UB, building genuine bioluminescence resonance energy transfer (BRET) probes, we were able to monitor in real time or not the activation of proteins related to stress or cancer - such as Heat Shock factor 1 (HSF1), thermosensitive receptor TRPV1, Extracellular regulated kinase (ERK), and H-Ras in the human HEK293T cell line. The cells were exposed to RF (1800 MHz), continuous wave (CW, non-modulated) or modulated with GSM, UMTS, LTE, or Wi-Fi. Chemicals able to activate the proteins of interest were used such the tumor promotor Phorbol MeristylAcetate, Arsenic Trioxide and Capsaïcine.

At UB, another innovative approach was to adapt a commercial equipment for bio-impedance measurements to expose cells and assess in real time the so-called cell index, indicative of the global physiological state at the cellular level. The XcellRF set up allowed to expose human cell lines (MCF-7 mammary cancer, SH-SY5Y neuroblastoma cells) and primary rat brain cells (neurons and astrocytes) to isothermal CW and GSM-modulated 1800 MHz at levels ranging from 5 to 24 W/kg.

Induced genomic instability

At UEF, rat primary astrocytes were exposed to IF (7.5 kHz) or RF (872 MHz) fields and genotoxicity and induced genomic instability were assessed after the exposures.

At UB, rat primary neurons and SH-SY5Y neuroblastoma cells were exposed to RF (1800 MHz) fields and genotoxicity and induced genomic instability were assessed after the exposures.

Two known-genotoxic chemicals menadione and methyl methanesulfonate were used as co-exposure to study possible co-genotoxicity. Alkaline Comet assay was used to detect DNA damage and DNA repair, and flow cytometric method was used to measure micronuclei and relative cell number. To assess possible induced genomic instability, the measurements were performed at delayed time-points, between 8 and 45 days after the exposures.

Metabonomics

Samples of cells exposed to IF (7.5 kHz) MF or RF (872 and 1800 MHz) fields are being analysed using the high-throughput metabonomics. Non-targeted metabolite profiling is being performed using LC-qTOF-MS at the Department of Pharmacy of the UEF. The analysis results should be available in March 2019 and the manuscript be submitted in June 2019.

Systems biology approach

The systems biology approach will be based on the dynamical systems theory and focus on system-level (rather than molecular level) responses such as induction of genomic instability and subsequently cancer. The initial plan was to use the metabolomics data for testing predictions derived from the systems biology approach but because of the delay in getting the metabolomics data, a new strategy will be used.

Results

Exposure set up

IF and RF exposure set up were built. Among those, the XcellRF was the most complex set up designed and characterized in terms of dosimetry.

Using the XCellRF, RF is only emitted inside the height of the cell culture layer, so that the heat-power is instantaneously dissipated into the culture medium rending it possible to expose cells to high amplitude 1800 MHz RF fields without heating. Experimentally, we did not measure any temperature increase in cell culture media using an 1800 MHz CW signal up to 24 W/Kg. The set up can also be adapted to 13.56 MHz IF exposure.

Real-time measurements

Increased activity of transcription factor HSF-1 and TRPV1 thermoreceptor were observed in real time under thermal exposure to 1800 MHz RF (SAR > 11 W/kg, no temperature control). However, no effect could be seen when RF exposure was isothermal, whatever the modulation and the SAR level (up to 38 W/kg). The activity of the RAS and ERK oncoproteins was measured post-exposure and was not affected by RF exposure (1.5 and 6 W/kg). RF exposure did not impact the effect of chemicals.

Cell physiology, as determined by bio-impedance monitoring, was not impacted by isothermal exposure to 1800 MHz RF. The bio-impedance signature observed in real time with the chemical treatments was not affected by RF exposure in any cell type, except in MCF-7 cells where GSM-1800, at the highest level of 24 W/kg only, impeded the effect of a tumour promotor.

Induced genomic instability

Exposure to 7.5 kHz MFs at 30 or 300 μT for 24 h did not cause genotoxicity alone or in combination with chemicals in rat primary astrocytes. There was some evidence that IF MFs might reduce the level of genetic damage, and rather strong evidence that relative cell number was increased after exposure to IF MFs. Furthermore, exposure to vertical or horizontal 7.5 kHz MFs at 300 μT did not induce genomic instability alone or in combination with chemicals in rat primary astrocytes. On the contrary, the results indicate that exposure to 7.5 kHz MFs at 300 μT may decrease genomic instability.

Exposure to 872 MHz RF at 0.6 or 6 W/kg for 24 h alone did not cause genotoxicity in rat primary astrocytes and the results of combined exposure with chemicals were inconsistent. Modulation-dependent effects were not seen. Induction of genomic instability by RF fields was evaluated for the first time using 24-h exposure to 872 MHz GSM-modulated RF fields at 0.6 or 6 W/kg alone or in combination with menadione in rat primary astrocytes. No induction or increase of genomic instability was observed.

Exposure to 1800 MHz RF at 0.375, 1.5 or 6 W/kg for 24 h alone did not cause genotoxicity in rat primary neurons and human neuroblastoma cells. The results of combined exposure with chemicals showed an increase in one over two biological parameters, i.e. the micronuclei produced by menadione in neuroblastoma cells. Induction of genomic instability by RF fields was evaluated for the first time using 24-h exposure to 1800 MHz GSM-modulated RF fields at 6 W/kg alone or in combination with menadione in neuroblastoma cells. No induction or increase of genomic instability was observed.

Systems biology approach

The new strategy consists in writing a review and discussion paper considering all EMF frequencies (Manuscript in preparation: Systems biology of electromagnetic fields with particular focus on carcinogenesis and genomic instability). This paper will include predictions that can be tested using suitable future or existing EMF omics data and will hopefully stimulate new experiments (will include recommendations). Target date for submission of the manuscript will be in February 2019. The metabolomics paper (which will be published later when we have the metabolomics data) will include testing at least one of the predictions of the systems theoretical approach (this was taken into account in designing the metabolomics study).

Conclusions

Based on the results it seems likely that IF MFs are not genotoxic alone and do not enhance genotoxicity caused by chemicals. On the contrary, there was some evidence that exposure to 7.5 kHz MFs might reduce the level of genetic damage. As the reason for the increased cell number is not known, it is not possible to draw conclusions concerning possible relevance to human health effects. In further studies, the reasons and possible mechanisms of these observations should be assessed.

The present study revealed that RF fields alone did not cause any biological effect including genotoxicity and genomic instability, target proteins activity, and global cell physiology. Radiofrequency fields combined with chemical exposure indicated some statistically significant differences, but these may be chance findings, as there was no clear consistent SAR- or modulation-dependent pattern. Overall, co-genotoxicity of RF fields and genotoxic chemicals was not consistently supported by the results.

The results of the experiments indicated that neither IF MFs nor RF fields induced genomic instability or increased it in combination with chemical treatments.

WP6 - Improved evaluation of cumulative and integrated RF and IF exposure

Occupational exposures to RF and IF fields

Introduction—To estimate occupational exposures to RF-, a database of source-based measurements was constructed from published and unpublished literature resources.

Methods— An EMF occupational exposure measurement database (OEMD) was constructed with measurements collected from the literature, expert judgments for a group of RF sources without available measurements at the time, and measurements for these and other sources obtained by some of the project partners. Based on the data in the OEMD, a novel methodology was created to summarize these data using order statistics and log-normal distribution relationships. Exposure data were combined by EMF source, frequency band and dosimetry type, creating the first EMF Source-Exposure Matrix (SEM). As a follow-up, the first RF job exposure matrix (RF-JEM) was constructed, based on the information in INTEROCC on occupational histories and the exposure estimates assigned to the study subjects, and complementary measurements data obtained through a literature review.

Results—The OEMD, SEM and JEM have been completed and will be made publicly available on the ISGlobal website. The SEM has been used to assign exposure to INTEROCC study subjects and will be used in other sections of the project (e.g. MobiKids). The JEM is currently being applied to a study in France.

Conclusion—The methodology developed is an important step in occupational RF exposure both for epidemiological studies and for health protection in the work place. The SEM allows estimation of RF exposure – and related uncertainty – as a function of RF emitting source (this was applied, together with information about the characteristics and timing of the work with these sources to estimate individual exposure to IF and RF for the analysis of the INTEROCC study (WP3)). This task also permitted the construction of the first RF/IF Job Exposure Matrix (JEM) for use in studies in which only occupational history is available.

Environmental (far-field) exposures to RF

Introduction - Radio frequency electromagnetic fields (RF-EMF) from mobile phone base stations can be reliably modelled for outdoor and indoor locations, using 3D radio wave propagation models that consider antenna characteristics and building geometry.

Methods - We assessed the accuracy of indoor RF-EMF model predictions in three European countries (NL, CH, Sp). We performed 15-minute spot measurements in 294 private homes. At each measurement location. We modelled RF-EMF at the measurement locations with the 3D radio wave propagation model NISMap. We compared model predictions with measured values to evaluate model performance.

Results - We found Spearman correlations between 0.23 and 0.72 (median 0.51) between modelled and measured total downlink RF-EMF from base stations. Absolute levels were in general underestimated with median ratio of modelled versus measured varying between 0.063 and 2.5 with a median of 0.63)

Conclusion - Although there is exposure misclassification, we conclude that it is feasible to reliably rank indoor RF-EMF from mobile phone base stations for epidemiological studies. Generating population estimates is not recommended due to the varying difference between measured and modelled fields.

RF exposure survey

Introduction - Exposure to radiofrequency electromagnetic fields (RF-EMF) from mobile communication technologies is changing rapidly. To characterize sources and associated variability, we studied the differences and correlations in exposure patterns between children aged 8 to 18 and their parents, over the course of the day, by age, by activity pattern, and for different metrics of exposure.

Methods - Using portable RF-EMF measurement devices, we collected simultaneous real-time personal measurements of RF-EMF over 24 to 72 h in 294 parent-child pairs from Denmark, the Netherlands, Slovenia, Switzerland, and Spain. The devices measured power flux density (mW/m^2) in 16 different frequency bands every 4s, and activity diaries kept by the participants were used to collect time-activity information in real-time.

Results -The mean time-weighted average personal exposures was 0.16 mW/m^2 for children and 0.15 mW/m^2 for parents, on average predominantly originating from downlink sources (47% for children and 45% for parents), followed by uplink (18% and 27% respectively) and broadcast (25% and 19%). On average, exposure for downlink and uplink were highest during the day, and for Wi-Fi and DECT during the evening. Exposure during activities where most of the time is spent (home, school and work) was relatively low whereas exposure during travel and outside activities was higher.

Conclusions - Exposure patterns between children and their parents is mostly evident in uplink exposure, due to more and longer uplink and cordless phone calls among parents, and their tendency to spend slightly more time in activities with higher environmental RF-EMF exposure, such as travel.

IF exposure survey

Introduction - Research on the typically emitted fields in the intermediate-frequency (IF) range (300Hz to 1MHz) is limited, although the range of household appliances with electrical components working in the IF range has grown significantly (e.g., induction cookers and compact fluorescent lighting).

Methods - In GERoNiMO, an extensive measurement survey was performed on levels of electric and magnetic fields in the IF range typically present in residences as well as emitted by a wide range of household appliances under real-life circumstances.

Results - Using spot measurements, residential IF field levels were found to be generally low, while the use of certain appliances at close distance (20cm) may result in a relatively high exposure. Overall, appliance emissions contained either harmonic signals, with fundamental frequencies between 6kHz and 300kHz, which were sometimes accompanied by regions in the IF spectrum of rather noisy, elevated field strengths, or much more capricious spectra, dominated by 50Hz harmonics emanating far in the IF domain. The maximum peak field strengths recorded at 20cm were 41.5V/m and 2.7A/m, both from induction cookers.

Conclusions - None of the appliance emissions in the IF range exceeded the exposure summation rules recommended by the International Commission on Non-Ionizing Radiation Protection guidelines and the International Electrotechnical Commission (IEC 62233) standard at 20cm and beyond (maximum exposure quotients EQE 1.0 and EQH 0.13).

Integrative and cumulative exposure assessment

Introduction - Human body exposure induced by wireless telecommunication systems depends on the emitted power, the communication protocols and the frequency bands, the type of use, as well as on the relative position of the emitting device to the subject exposed. Previous studies have either focused their attention on compliance testing when a mobile device is in contact with the human body or very close to it, mainly in single frequency (or technology) conditions, or alternatively focused on sources further away from the body, disregarding or only regarding a limited number of localized sources. However, existing RF mobile systems and new RF technologies are today involved in other usage scenarios, placed at locations not yet tested, and can use different transmitters simultaneously. Exposure assessment studies provide limited information on measured incident fields or on the estimation of the population exposure and are currently unable to determine integrative doses from these exposure values.

Methods - In GERoNiMO an analytical approach for fast estimation of specific absorption rate (SAR) from different devices, positions and technologies was developed. We classified the RF sources in three main groups, far-field, near-to-far-field, and near-field, depending on the distance source-subject. For each exposure group a source-specific transfer algorithm was developed, jointly with the ANSES funded CREST project (Liorni et al 2019, in preparation) which allowed additional measurements and simulations, in order to quantify SAR in different exposure contexts accounting for variations in posture, use, age, sex, morphology and frequency.

Conclusions - Since the increasing use of RF systems continues to raise concerns on their possible health impact in the general population, this transfer algorithm-based approach provides a powerful tool when combined with information on use and output power of devices, to estimate integrated individual RF exposure for epidemiological studies and population health impact assessments.

Development of RF- exposure proxies in population investigations

Introduction - Preferably population exposure scenarios detailing daily doses integrated over all relevant RF-EMF sources are available, with information on which sources contribute most to overall dose. These can be used as input for risk assessment and risk mitigation. To do this detailed knowledge of exposure duration from multiple sources and the transmission power of these sources is needed to come to an integrated RF-EMF dose assessment. In GERoNiMO we developed a model capable of integrating exposure from many RF-EMF sources while taking duration, transmission power, type of use and personal characteristics into account, resulting in dose estimations for 64 target sites (i.e.: organs and tissues).

Methods - The Integrated Exposure Model (IEM) was based on the transfer algorithms developed in GERoNiMO and estimates RF-EMF dose (in millijoule per kilogram per day) using source specific attributes, personal characteristics, and usage patterns. Information on device usage, duration and functions used, was obtained from an international survey performed, within the ANSES CREST funded project, in four European countries (France, Netherlands, Spain, Switzerland) for 1755 participants. Together with output power estimations for each source, the RF-EMF dose was estimated for 64 target sites (i.e.: organs, body areas).

Results - We found median whole brain and whole body doses of be 183.7 mJ/kg/day and 204.4 mJ/kg/day respectively. The main contributor for whole brain dose were mobile phone calls near the head and far field sources, whereas far field sources were the main contributor for whole body dose followed by various other devices. For other target sites 2G phone calls, mobile data, and far field exposure were important contributors.

Conclusions – The IEM developed in Geronimo enables estimating population exposure scenarios and provided insight into the main contributors to total RF-EMF dose; the IEM was used to estimate RF doses for the WP1 analyses of exposures in childhood. Insights from the IEM can be used in future epidemiological studies, risk assessments, and exposure reduction strategies.

WP7. Assessment of population health impacts of EMF

WP7 aimed to provide quantitative estimates of the health impacts attributable to exposure to high-frequency EMF in the population of the European Union based on the most up-to-date evidence from human and animal/biological studies, incorporating new data on exposure and exposure-response developed within the project. It also aimed to improve understanding of the health implications of trends in use of EMF-related technologies and of non-technological means to reduce exposures. A subsidiary aim was to aid integration and coherence of the work across the projects WPs.

Methods

The WP was divided into 5 different tasks: T7.1. A scoping exercise; T7.2. Development of exposure scenarios; T7.3. Outcome assessment; T7.4. Quantifying exposure-response; T7.5. Assessment of health impacts.

7.1 Scoping exercise

The scoping exercise involved mapping the studies under the GERoNiMO project umbrella to make recommendations on how the degree of integration might be maximized among biological, epidemiological, and exposure assessment studies; and proposing a preliminary set of scientific questions which the GERoNiMO WP7 impact assessment might provide an answer to. A set of questionnaires were distributed to all work package leaders (and sub- task leaders where appropriate) to gather information on the characteristics and types of the populations, exposures, health endpoints etc. considered within their studies. The completed questionnaires were returned, and the information gleaned from these was summarized. A set of comparisons were made relating to exposures investigated, health outcomes considered, and the timing of exposure delivery/measurement and outcome ascertainment

7.2 Exposure scenarios

A set of exposure scenarios were defined in line with the findings of the scoping exercise report, in terms of sources and types of exposure. Exposure scenarios related to current applications of EMF-emitting devices using a wide range of EMF frequencies and sources were defined moving from baseline scenarios, potentially associated with higher exposures, to new scenarios using non-technological means of exposure reduction. Given the dependence of this task on the outcomes from WP6, particularly on the development of the Integrated Exposure Model (IEM), the scenarios defined in this task were not assigned quantitative estimates of exposure/dose until later within the project.

7.3 Outcome assessment

This task involved selecting the exposure(s) and outcome(s) to be included in the health risk/impact assessment from those previously identified in the scoping exercise as most relevant among the various WPs within the project. For this purpose, the most up-to-date available evidence in the literature was also used to select both the exposure/frequency and the health outcome(s) for which the weight of evidence is strongest.

In order to identify studies outside the GERoNiMO project which could inform the selected exposure-outcome(s) combinations, a systematic literature review was performed using specific keywords and scientific databases and search engines. Literature searches were performed by two authors and results were compared until reaching an agreement.

A set of quality criteria were defined to assess the quality and relevance of the human (epidemiological) and animal (experimental) studies identified. A novel quantitative methodology was developed to assign semi-quantitative scores to each of the studies assessed which allowed classifying these studies as low, moderate or high quality.

7.4 Quantifying exposure-response

In order to obtain comparable exposure or dose-response data from both human (epidemiological) and animal (experimental) studies to be pooled in an integrated synthesis approach, several challenges needed to be overcome.

First, to combine human and animal evidence, RF dose estimates are required. However, while animal studies usually provide dose information (e.g. SAR, in W/kg), most epidemiological studies on mobile phone and brain cancer have traditionally relied on the use of exposure proxies, such as calling time or number of calls, and few studies provide estimates of RF dose (Cardis et al., 2008). As part of this task, estimates of cumulative exposure time (in minutes), extracted from epidemiological studies on mobile phone use and the brain cancers of interest (i.e. glioma and acoustic neuroma) were transformed into RF dose (in J/kg), using mean SAR estimates based on the type of mobile phone technology used (e.g. 1G, 2G or 3G). SAR values (in W/kg) extracted from animal studies were converted into SA estimates (in J/kg), by using available information on duration of exposure (typically 2 years in carcinogenicity studies).

The second challenge related to obtaining comparable dose-response data involved converting cancer incidence information reported in animal studies into risk estimates (e.g. Odds Ratios). Mathematical methods to obtain these data have been proposed for the purpose of performing meta-analysis of animal studies (Vesterinen et al., 2014).

For each individual animal or human study, dose (in J/kg) and risk (as Odds Ratios or Risk Ratios) estimates extracted or calculated were used to obtain overall dose-response coefficients, including a regression slope (β) and its corresponding standard error (SE). Meta-analysis methods (such as random effects inverse-variance weighted meta-analysis) are commonly used to combine dose-response data (i.e. regression coefficients) from either human or animal studies. However, these methods are not sufficiently flexible when both types of data (human and animal) are to be combined. Therefore, we used a Bayesian multilevel model, based on sceptical (or naïve) and relational (or semi-informed) priors (Jones et al., 2009; Peters et al., 2005).

7.5 Assessment of health impacts

The integrated risk estimates obtained in the previous task were used to estimate health impacts of mobile phone exposure/dose (based on data for mobile phone use) in relation to glioma and acoustic neuroma. Estimates of attributable fraction and attributable cases were obtained for several exposure scenarios involving the use of non-technological means of exposure reduction, based on changes of technology (e.g. changing from 1G/2G to 3G) and use patterns (e.g. mobile phone use near the head versus texting or using hands-free sets). Preliminary estimates of impact were obtained using average disease incidence estimates for both glioma and acoustic neuroma for the entire EU28 population.

Results

7.1 Scoping exercise

Based on the information collected through the questionnaires, we found that the majority of the characteristics of individual studies within GERoNiMO were well integrated with one another. Of the wide- ranging sets of exposures and health outcomes investigated in the studies that comprise GERoNiMO, a considerable number were found to be common to both epidemiology and biology modules, and approaches in the two modules have been generally complementary. However, a few areas, including specific frequency ranges and timing of exposure and health outcomes, were highlighted in order to consider making changes to further increase the degree of interdisciplinary integration within the project. The module on exposure assessment complemented and indeed supported the epidemiological studies conducted within GERoNiMO, but it had less direct connection with the work done in the biology module.

From the mapping and comparison of characteristics of each WP, we were able to identify those exposures and health outcomes which were common to all the modules, and specified a set of preliminary scientific questions to which the project results of GERoNiMO might provide answers, thereby defining a rough scope for the health impact assessment work to be carried out in Module 4.

7.2 Exposure scenarios

The exposure scenarios were developed in line with the findings of the integrating and scoping exercise report, in terms of sources and types of exposure. A set of descriptions of the most relevant scenarios to incorporate into the WP7 health impact assessment relating to changes in exposure to EMF brought about by decisions made either by individuals or by society in general were developed and discussed with the Consortium. Means of exposure reduction were based on either change of mobile phone technology/generation (1G/2G to 3G/4G) or non-technological changes of use of devices that emit EMF (e.g. speaking versus texting). Although changing mobile phone technology may sound otherwise, we considered this a non-technological measure since it does not require redesign of the hardware/software but rather a change of behaviour of the final user and, primarily, a better awareness of the potential risks associated with the different available technologies.

The list of scenarios proposed comprise changes in exposure that result both from social and behavioural change, and from technical changes to devices, associated set-ups and methods of use. Purely technological (hardware or software) changes to devices were not considered, as these are out of scope since they are being explored in separate EU-funded projects). By introducing the input data into the transfer functions developed within the Integrated Exposure Model (Task 6.6), exposure/dose estimates for various scenarios of mobile phone use were obtained in the last part of the project.

7.3 Outcome assessment

Considering the results of the scoping exercise and the most up-to-date evidence for RF exposure, glioma and acoustic neuroma or Schwannoma were selected as the health outcomes of interest for the health risk/impact assessment. Schwannoma may occur in other tissues apart from the brain, evidence for this type of tumour in other tissues was also considered, especially from animal studies. Mobile phone use or exposure to RF in the frequency range used for telecommunication were selected as the exposures of interest.

In the literature review, a total of 56 epidemiological studies and 16 animal studies, focusing on the exposure and outcomes of interest, were identified and assessed. An overall trend towards higher quality among newer studies was observed in both animal and human publications. Among human studies, most were classified as moderate or high quality for both glioma (n=31) and acoustic neuroma (n=25). Only two studies on glioma and two on acoustic neuroma were classified as low quality. All animal publications, including rat studies (n=12) and mice studies (n=4), were classified as moderate or high quality.

7.4 Quantifying exposure-response

Dose-response data from studies classified as having high quality (n=5 animal and n=13 human) were extracted and treated to obtain comparable data for a quantitative health risk/impact assessment. Methods to overcome challenges affecting most human studies (lack of dose data) and animal studies (lack of risk data) were developed and used. Dose-response data (extracted or estimated) were modelled using least squares weighted linear regression to obtain individual regression coefficients (β & SE) for each selected study. Overall, epidemiological studies provided more precise dose-response coefficient estimates, while estimates from animal studies had wider confidence intervals. The risk estimates obtained in this task were combined and used in task T7.5 to estimate health impacts assuming various scenarios of exposure.

7.5 Assessment of health impacts

The Bayesian methodology developed was based on the use of sceptical (naïve) priors, assuming no correlation between results for different species and modulations, as well as relational (semi-informed) priors, based on available information on relations between species or exposures/modulations. Results using sceptical and relational priors were compared with those using classical (random-effects) meta-analysis. Results using sceptical priors were similar to those using classical methods. Results using relational priors provided the highest pooled risk estimates. The latter were used to assess population impacts in relation to the exposure and outcomes of interest. The worst impact estimates were obtained for exposures to 1G/2G modulations for both glioma and acoustic neuroma, followed by 3G, texting and hands-free, considering the exposure scenarios studied (Manuscripts describing the approach and results are in preparation – Vila et al, 2019b)

Conclusion

This WP aimed at identifying the exposures and health outcomes for which a health risk/impact assessment (HIA) could be performed within the GERoNiMO project. Given the weight of evidence associated with high-frequency exposure, we decided to focus our HIA on glioma and acoustic neuroma (tumours of the brain and central nervous system) for which the number of good quality studies available to date was judged adequate. In fact, available evidence for the association between these two tumours and RF exposure was the major driver for the classification of RF as possibly carcinogenic by IARC in 2011 (Baan et al., 2011). Two recent animal studies (Wyde et al., 2016; Falcioni et al., 2018) also provide insights into this potential relationship.

Data transformations to obtain comparable dose-response data (i.e. risk estimates from animal studies and RF dose estimates from human studies) increased the uncertainty of our results. Mechanistic data may help to choose more appropriate dose-response models (e.g. log-linear, logit-log) to obtain study-specific slopes. Overall, the novel methodologies developed and used allowed the synthesis (pooling) of human and animal evidence, accounting for differences between species, study designs and RF modulations.

WP8. Input to risk management and communication and advice on non-technological exposure reduction

The objectives of WP8 were:

1) to explore non-technological (NT) means for reducing exposure taking into account current and foreseeable technological trends;
2) to provide input on risk communication to EC policy-makers;
3) to synthesize the findings of GERoNiMO and translate these into inputs to risk management.

Methods:

A survey of the existing non-technological (NT) means, defined as simple means a user can take without needing to modify either the devices themselves or the infrastructures they rely on, while allowing the devices to work, was conducted basing on information/suggestions from sources such as public and health authorities, relevant scientific bodies and scientific literature. These data have not been clustered as a function of the frequency spectrum, mainly because practically all the available data/suggestions are made specific to individual devices or types of device. Specifically, the EMF sources that were considered include the most prevalent, current technologies that emit EMF in the Extremely Low frequency (ELF), intermediate frequency (IF) and radiofrequency (RF) ranges.

In order to advance these investigations by adding further data and information a questionnaire (in the following "the GERoNIMO questionnaire") was prepared and administered to stakeholders (182 participants) in the summer of 2016. The questionnaire was disseminated through the web, to facilitate participation of the invited bodies and persons in the initiative and explore the recommendations issued in the participant countries, pertaining to exposure reduction for RF (e.g. mobile phones, wireless internet) and IF sources (e.g. anti-theft gates, induction cookers).

As to the second and the third objectives, entailing the identification of the most appropriate means to be used in risk communication and the most important aspects to be considered for health risk management, WP8 reviewed data and suggestions from sources such as public and health authorities, relevant scientific bodies, scientific literature and previous international project in the field of RF EMF and health published in the period 2012-2018. Moreover, in order to deepen and to elaborate appropriate risk communication strategies for health risk management, a workshop on health risk communication was organized within the WP8 activities of WP8 and held in Barcelona (Spain), on February 7, 2018 at ISGlobal - Campus Mar.

Results:

Identification of effective non-technological means for reducing exposure

In our review at the beginning of the project, the most commonly cited suggestion for reducing EMF exposure by non-technological means were related to:

- Positioning, disconnecting and way of using the EMF devices. This includes:
    - Locating EMF devices as far as possible from the body
    - Reducing use time (emission time)
    - Moving the equipment away from bedside
    - Turning-off devices when not in use
- Positioning of the devices in living areas: this includes locating the EMF emitting devices away from bedrooms and main living areas.
- Verifying the type and quality of the EMF radiating device, including accessories, grounding issues and status of the wiring system. This includes:
    - Avoiding cheap-looking power adapters for PC
    - Maintaining correct functioning of the wiring

Though the review of data published in more recent years identified a large number of exposure scenarios, it can be concluded that the distance from the emitting devices is still the main factor influencing the level of EMF to which a person is exposed. Other suggested methods, such as turning off the device when not in use and not using the EMF emitting devices at all, effectively remove the EMF source altogether and therefore are de facto ways of reducing exposure levels to zero.

These results are in line with the conclusions derived from the GERoNIMO Questionnaire. The majority of respondents confirmed that most existing recommendations for exposure reduction are related to the duration of the mobile voice calls and use of hands-free kits. This reflects the attention given to exposure from mobile communications systems.

The relatively large participation of the general public in the questionnaire survey indicates that the issue of possible health consequence of EMF exposure is still of concern in the general population. Responses pertaining to existing non-technological methods for exposure reduction were in line with responses from EMF experts and the literature, i.e., increasing the distance between the person and the devices and turning off the devices when not in use.

Input on risk communication and health risk management

Based on the literature review and the workshop on health risk communication held in February 2018, it is clear that communication on EMF exposure levels and their potential heath effects is complex and delicate for a variety of reasons, both technical (uncertainties and complexities related to sources of EMF, variety of sources/exposures, frequencies/modulation, etc.) and non-technical (e.g. EMF are invisible, ubiquitous, exposure to EMF is commonly perceived to be beyond the control of the individual, erroneous assumptions on exposure levels are very common among individuals, personal characteristics and cultural factors influence EMF risk perception).

These aspects need to be carefully considered for risk communication to be effective and have to be taken into account in the health risk management process.

An appropriate means to provide effective communication about potential health risks of EMF identified in GERoNIMO is the existence of a dedicated website in which referenced, high-quality and unbiased information on EMF and health issues are collected, synthesised and presented in a way appropriate to different stakeholders (from authorities, to scientists, the general population and children and adolescents). The use of social media to disseminate these messages is also important. The website could provide information on a broad range of topics to allow the general public and others to make informed decisions, while social media could address more topical issues or target those with more specific concerns. The key issues that should be addressed in risk communication include providing information about the importance that distance from an exposure source has on exposure levels, the difference in exposure between voice calls and data use (related to duration of transmission), differences between exposures from phones and base stations, and whether time of day of exposure is important. It is also essential that the uncertainties in our estimation of health effects are presented in a clear and understandable way, that the sources and relative magnitude of EMF exposures are clearly presented, and that information on EMF policies at the local, national, EU and international levels are presented transparently.

In this context, appropriate communication strategies to deal with such a complex and delicate task include:

1) overcoming mere hazard communication,
2) providing background for risk information
3) giving a balanced view on what is known and what is uncertain,
4) emphasize that scientific evidence is more informative than anecdotal evidence,
5) clarifying the relevance of risk information,
6) understanding and listening to people's perceptions and concerns.

Besides investing in health risk communication, health risk management actions should be directed to:

1) Improve the quality and choice of quality criteria of health risk assessment

2) Managing and reducing uncertainty by addressing and filling knowledge gaps that produce public concern. They involve:

a. Increasing the number and the statistical power of population and health effects studies
b. Addressing the populations potentially most vulnerable: children and pregnant women
c. Evaluating the exposure from new EMF emitting technologies such as 5G
d. Efforts for having harmonized standards

Conclusion

WP8 activities related to the identification of non-technological means to reduce the exposure from new technologies substantially confirm that distance from the source is the most effective non-technological mean to reduce the exposure. Though exposure levels from the large variety of sources examined are substantially below the international guidelines, EMF exposure still raise people concerns.

These concerns must be considered and must be addressed by policy and health authorities mainly directed to support repeatable good-quality investigations with particular reference to exposures of children and pregnant women and to new emerging technologies such as 5G, and to elaborate appropriate communication strategies, by taking into account the complexity of the issue, by encouraging the use of website and social media to collect data in a coordinated way and by communicating scientific evidence transparently.

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Potential impact (including the socio-economic impact and the wider societal implications of the project so far) and main dissemination activities and exploitation of results

The use of mobile communicating devices has increased rapidly in the past few decades and is now an important and pervasive component of human society across the globe. Exposure to RF communicating devices is nearly ubiquitous in the population of the European Union, and the development of new RF applications and technologies (with 5G and the Internet of Things IoT) and IF applications is likely to increase population levels of exposure, while our understanding of the potential health effects of such exposure on human health remain limited. Should RF and or IF exposure be harmful, even modest effects could have a huge impact on public health due to its widespread nature. As new mobile phone technologies and applications are rapidly developed, a better characterization of the health effects of this exposure is currently needed.

GERoNiMO has produced a considerable amount of results on the potential health effects of IF and RF and on the exposure of the general population, with a large number still to be published. The public health and sociological impacts of the results are presented below by WP.

WP1. EMF and health of children and adolescents – exploiting (large-scale) prospective cohort studies

Of particular concern are the potential effects of exposure during early life, when neurological and organ systems are rapidly developing, and are therefore particularly vulnerable to damage from hazardous environmental exposures. In WP1, we have provided results on several analyses maternal mobile phone use during pregnancy and birth and neurodevelopmental outcomes, and on associations between RF exposure in children and behavioural problems. The main results are summarised here. **It should be noted that all unpublished results are preliminary.**

Maternal mobile phone use during pregnancy and birth outcomes (Tsarna et al., 2018)**:** Our analyses indicate that maternal cell phone use during pregnancy is not associated with any change in fetus' intrauterine growth, but may be associated with the duration of pregnancy (decreased duration with increased mobile phone use); the overall effect in birth weight –if any- is not significant.

Maternal mobile phone use during pregnancy and behavioural problems (Birks et al., 2017)**:** Maternal cell phone use during pregnancy may be associated with an increased risk for behavioural problems, particularly hyperactivity/inattention problems, in the offspring. The interpretation of these results is unclear as uncontrolled confounding may influence both maternal cell phone use and child behavioural problems.

Maternal mobile phone use during pregnancy and cognitive development (Sudan et al., 2018)**:** Prenatal cell phone use may be associated with lower childhood cognition scores. This finding is consistent with previous studies that have reported similar associations with behavioural outcomes. However, the potential causal nature and mechanism of this association remain unknown.

Maternal mobile phone use during pregnancy and language development and motor skills (Papadopoulou et al., 2017).**:** We reported a decreased risk of low language and motor skills at three years in relation to prenatal cell phone use, which might be explained by enhanced maternal-child interaction among cell phone users. No evidence of adverse language development effects of prenatal cell phone use was reported.

Child RF dose to the brain and behavioural problem (Birks et al, 2018a, unpublished): Results suggest that increased RF dose to the brain and longer mobile phone call time may be associated with risk of hyperactivity and conduct problems. Results were more robust in adolescents versus children. Reverse causality and effects of mobile device use, apart from RF dose, cannot be entirely excluded as explanations for these results.

These investigations have combined data from European birth cohorts and from a Korean birth cohort in joint analyses of relevant outcomes, resulting in the largest epidemiological investigations of these associations to date. Ultimately, we expect the results from these investigations in combination with knowledge gained from other aspects of the GERoNiMO project will underpin policy development in Europe on RF and other EMF exposures.

WP2 - Role of IF and RF in brain cancer risk in young people

After leukaemia, brain tumours are the second most common cancer type in young people under 25 years of age. Little is known about the aetiology of these tumours. Known risk factors include exposure to ionizing radiation, family history of brain tumours, and some rare medical conditions. Exposure to chemicals and to electromagnetic fields may also be associated with the risk of brain tumours, although this is still uncertain. Recent years have seen a dramatic increase in the use of communication technologies, particularly among young people, and there is growing concern about their potential health effects.

An important limitation of the studies of brain tumours in young people to date has been the relatively small number of children and adolescents included. Although the frequency of brain tumours has tended to increase in young people over recent decades, it is fortunately still a rare disease. Therefore, international studies are needed to better understand the effects of environmental factors on the risk of this disease.

MOB-Kids is the largest and most up-to-date study, including subjects from 14 different countries in a wide age range (from 10 to 25 years) with varying degrees of exposure to communication technologies and, consequently, exposure to electromagnetic fields. The study was developed using a common core study protocol, ensuring homogeneity of data collection and quality control.

As the spatial distribution of RF specific absorbed energy (SAR) and of ELF induced current density (ICD) is quite inhomogeneous in the brain, amount of phone use is not necessarily synonymous with EMF exposure, particularly at higher frequencies. Detailed algorithms were therefore developed to estimate cumulative and time weighted averages RF SAR and ELF ICD at the location of the tumour and in various anatomical structures in the brain in order to better evaluate the possible relation between RF and ELF from mobile phones and risk of brain tumours. The algorithms take into account the location of the tumour, mobile phone use history (including types of phones and operators), data from operator questionnaires about historical technologies and frequency bands used and factors which could modify emitted power such as adaptive power control. Simulations were conducted to estimate the SAR and ICD distribution for different phone categories, different frequencies and different ages in 3-dimensional representations of the brain of children, adolescents and adults.

MOBI-Kids also collected complementary information on data use of mobile phones, on exposure to various sources of EMF in the general and work environment of the cases and controls and of their parents, as well as details of the occupational history of the subject and their parents. This will allow an analysis of brain tumour risk not only as a function of mobile phone use and resulting ELF and RF exposure, but also as a function of EMF exposure from all sources. Possible interactions between EMF and chemicals on the risk of brain tumours in young people will also be evaluated based on estimation of chemical exposures from Job-Exposure- Matrices.

MOBI-Kids, therefore, is the largest and most informative and comprehensive study of the effects of EMF on brain tumours in young people. Analyses have been conducted and publications are underway.

WP3. Occupational Exposure to EMF and Risks to Health

Task 3.1 Effects of EMF and Chemicals on Cancer in Adults – Exploiting the Work of INTEROCC.

Impact

The study produced new information on occupational RF and IF exposures (using a novel SEM-based exposure assessment approach) and risk of glioma and meningioma, as well as potential synergies with occupational chemical exposures in the large-scale INTEROCC study. This study represents the largest study of its kind, and the most comprehensive effort at estimating occupational exposure to high-frequency EMF in a large-scale population-based epidemiological study.

Key messages

Overall, despite major improvements in exposure assessment here, there was no clear evidence for positive associations of cumulative RF or IF-EMF exposure and either glioma or meningioma risk. There were also no clear interactions observed with cumulative RF and the majority of chemical agents examined. Some positive, though imprecise, ORs observed for recent RF magnetic field exposure warrant further investigation with larger numbers of exposed participants, as do potential interactions with both iron and welding fumes.

Task 3.2 Reproductive Effects of Occupational IF Exposure: A Pilot Cohort Study.

Impact

The study produced new information on IF MF exposure of cashiers working near EAS devices working at the frequency of 8.2 MHz. Recommendations are given to facilitate a larger epidemiological study on potential reproductive effects of IF MF exposure.

Key messages

No differences on the risk of miscarriage, reduced birth weight or preterm birth were observed when cashiers working near EAS devices operating at the frequency of 8.2 MHz were compared to cashiers working in stores without EAS systems. Measured MF levels near these devices were low, however. Any further studies should attempt to include study subjects working near EAS systems that produce stronger IF magnetic fields at kHz frequencies.

WP4. Animal models

Impact/ key messages of WP4

Impaired memory and learning in young mice exposed for 5 weeks to 7.5 kHz MFs at 120 µT were observed. These findings were supported by mild inflammation observed in the hippocampus, a brain region responsible for learning and memory. There were also indications of some favourable or protective effects, e.g., increased sperm motility that were also suggested by the *in vitro* findings of decreased DNA damage; these need to be interpreted together.

Animal models are useful for the study of exposure-related effects on the whole physiological system, and yield information that cannot be gained from studies using cells *in vitro. In vivo* animal models can provide numerous biological endpoints that are not achievable in human studies, and in this work package, the maximum available biological information was obtained from each animal and each sample.

The observations from this work package will add to the existing evidence and knowledge relating to the effects of RF/IF fields on behaviour, brain structure and function, and reproductive health. Data obtained with animal models are of greater value for health risk assessment than that provided by any alternative in vitro models, and they allow clearer extrapolation to the potential risks in humans.

It is reassuring that there is a lack of consistent or highly significant effects after exposure to intermediate frequency fields in our studies. It is clear that the models used in this work package demonstrate biological responses and that the techniques used in this work package are sufficiently sensitive to be able to detect such biological responses. It remains the case that there is no known mechanism of interaction of the fields examined in biological materials beyond induced electric field effects and heating, and this is only at higher levels of exposure. The IF and RF experiments performed here were at exposure levels in excess of ICNIRP guidelines, which are based on induced electric field and thermal models.

In general, in this work package, biological effects (with unknown mechanisms) were indicated but the observed effects were small and not consistent over the tests used. Thus, considerable caution is required in the interpretation with respect to human health effects (whether adverse or beneficial) and further research would be required before firm conclusions can be drawn.

WP5 – Cellular /molecular studies

Impact/ key message of WP5

This work investigated IF and RF biological effects in vitro at exposure levels typically higher than those encountered in the environment in Europe and found no effect of exposure to these fields alone.

Indeed, no effects of 7.5 kHz IF and 872 / 1800 MHz RF fields were found on a number of biological endpoints (genotoxicity, genomic instability protein activity, bio-impedance) when used alone and, for RF, at isothermal levels.

In the RF range, exposure at thermal levels was shown to induce the activity of some heat-sensitive proteins such as TRPV1 and HSF1 but isothermal RF exposure up to 38 W/kg did not. RF isothermal exposure for 24 h, up to 6 W/kg did not cause genotoxicity in rat primary astrocytes and neurons and in a human neuroblastoma cell line.

In the IF range, exposure at or up to 300 µT did not cause genotoxicity nor induce genomic instability in rat primary astrocytes.

Moreover, exposure to IF or RF had globally no impact on chemically-induced effects, although some indications of favorable or protective effects were observed with IF exposure (also in vivo) and inconsistent results were observed with RF on immediate genotoxicity.

Interpretation of the co-exposure data with respect to possible health impact for European citizens (adverse or therapeutic) is not possible without further research on IF / RF and chemicals co-exposures on normal and tumour cells.

WP6 - Improved evaluation of cumulative and integrated RF and IF exposure

The exposure assessment work in Geronimo has generated several unique tools that can be used by researchers and policy makers to estimate population exposures to RF and IF-EMF. These tools comprise the Occupational exposure SEM and JEM for IF and RF-exposure enabling estimation of occupational exposures; the further validation of the NISMAP model to model far-field (e.g base station) exposure to RF-EMF; the integrated exposure model that enables estimation of individual exposure levels to RF-EMF by integrating different sources ranging from on-body to far-field. The tools developed by Geronimo are unique and uptake of the integrated model has already occurred in other projects and future epidemiological investigations. However, due to the rapidly changing technologies and uses of communication devices it will be critical to continuously update the IEM. Due to the modular design of the IEM this is technical possible. However, the model depends on the quality of the input data. In the development of the IEM a significant knowledge gap was identified which relates to the dearth of information on actual output powers of devices during different uses in different environments.

WP7. Assessment of population health impacts of EMF

Impact

The results of this WP may help increase public awareness in relation to how the selection of a specific technology (e.g. 3G/4G mobile phones) and how this technology is used (e.g. speaking near the head, texting, hands-free) may have an important effect on the level of exposure/dose and potential risk associated. This increased awareness may also have an impact on the mobile phone industry, encouraging the development and promotion of lower-emission technologies.

WP Key messages

- If the risk estimates used in our calculations were representative of a true causal association, a relatively small proportion of glioma and/or acoustic neuroma cases in the EU28 may have been caused by mobile phone use, particularly due to exposure to older technologies (i.e. 2G).
- The use of older mobile phone technologies (2G) are associated with higher RF exposure/dose levels and, therefore, if a relation exists between RF and brain tumours, higher potential risk of glioma and/or acoustic neuroma.
- The use of newer technologies (e.g. 3G) and other non-technological means of exposure reduction (e.g. texting or using hands-free sets instead of calling) are associated with lower RF exposure/dose levels.
- Users of mobile phones should be aware that different types of uses (voice vs data – texting vs streaming) of mobile phones and different technologies (2G, 3G, … WiFi) may be associated with different exposure levels. The use of non-technological means of exposure reduction (including the selection of technology/generation) and switching from voice to data uses reduces exposure and, hence, potential risk.
- Mobile phone companies should provide clearer information to users about the levels of RF output power in real life scenarios (not just in laboratories) and how different phones may use different technologies which may lead to different exposure/dose levels.

WP8. Input to risk management and communication and advice on non-technological exposure reduction

The main message from this WP is that the exposure levels generated by most of the sources examined, are largely below the international exposure guidelines. The investigation related to non-technological means to reduce RF- IF- EMF exposure, practically resulted in the sole and foreseeable conclusion that distance from the source is the most effective non-technological mean to reduce the exposure, that should be in any case interpreted bearing in mind that we are discussing such a very low level of exposure

Despite the low levels, the ubiquity of EMF sources and increasing uses and applications raise about possible health risks in the population.

It is therefore essential to establish clear, carefully constructed and transparent evidence-based risk communication, tailored to the needs of different stakeholders in order to increase awareness and understanding of exposure levels, potential risks, uncertainties and means to reduce exposure among all.

Moreover, policy and health authorities should support and invest in repeatable good-quality investigations with particular reference to vulnerable groups (children and pregnant women), new emerging technologies such as 5G and in elaborating and improving communication strategies.

Dissemination activities

In addition to the large number of scientific publications and communications (both at scientific conferences and in the media), a position paper is currently under preparation, drawing together all findings (including those still to be published) in order to draw the lessons from GERoNiMO results and prepare public health and societal recommendations concerning exposures and risk, and research gaps.

A stakeholder consultation will be organised to review and provide comments on the position paper by the end of 2019, after which it will be finalised and published, and findings and recommendations made available on the GERoNiMO website and through social media with messages tailored to different groups of stakeholders.

Briefing of EC and national and regional authorities are also foreseen.

The address of the project public website, if applicable as well as relevant contact details.

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Appendix

Appendix Table 1. Expertise of GERoNiMO participants relevant to the project

Expertise	
Epidemiology	Cancer studies
	Birth/childhood cohort studies
	Data management
	Behavioural and cognitive effects
	Reproduction
Biology	Cellular studies
	Animal models
	Biomarkers and molecular assays
	Genomic instability, genotoxicity
	Reproduction
	Cancer related studies
	Neurodegenerative diseases
	Behavioural and cognitive effects
	Systems biology
Exposures and doses	Experimental exposure systems
	Exposure modelling
	Individual exposure measurements
	Job-Exposure-Matrices (JEMs) and Source-Exposure Matrices (SEMs)
	Dosimetry
Health impact assessment	
Risk management	
Non-technological means to reduce exposure	
Risk communication	
Stakeholder involvement	
Ethics	
Project management	