Health impact of 5G

STUDY

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Health impact of 5G

Current state of knowledge of 5G-related carcinogenic and reproductive/developmental hazards as they emerge from epidemiological studies and in vivo experimental studies

The upcoming deployment of 5G mobile networks will allow for significantly faster mobile broadband speeds and increasingly extensive mobile data usage. Technical innovations include a different transmission system (MIMO: use of multiple-input and multiple-output antennas), directional signal transmission or reception (beamforming), and the use of other frequency ranges. At the same time, a change is expected in the exposure to electromagnetic fields (EMF) of humans and the environment. In addition to those used to date, the 5G pioneer bands identified at EU level have frequencies of 700 MHz, 3.6 GHz (3.4 to 3.8 GHz) and 26 GHz (24.25 to 27.5 GHz). The first two frequencies (FR1) are similar to those used for 2G to 4G technologies and have been investigated in both epidemiological and experimental studies for different end points (including carcinogenicity and reproductive/developmental effects), while 26 GHz (FR2) and higher frequencies have not been adequately studied for the same end points.

The International Agency for Research on Cancer (IARC) classified radiofrequency (RF) EMF as 'possibly carcinogenic to humans' (Group 2B) and recently recommended RF exposure for re-evaluation 'with high priority' (IARC, 2019). Since 2011 a great number of studies have been performed, both epidemiological and experimental. The present review addresses the current knowledge regarding both carcinogenic and reproductive/developmental hazards of RF as exploited by 5G. There are various *in vivo* experimental and epidemiological studies on RF at a lower frequency range (450 to 6000 MHz), which also includes the frequencies used in previous generations' broadband cellular networks, but very few (and inadequate) on the higher frequency range (24 to 100 GHz, centimetre/MMW).

The review shows: 1) 5G lower frequencies (700 and 3 600 MHz): a) limited evidence of carcinogenicity in epidemiological studies; b) sufficient evidence of carcinogenicity in experimental bioassays; c) sufficient evidence of reproductive/developmental adverse effects in humans; d) sufficient evidence of reproductive/developmental adverse effects in experimental animals; 2) 5G higher frequencies (24.25-27.5 GHz): the systematic review found no adequate studies either in humans or in experimental animals.

Conclusions: 1) cancer: FR1 (450 to 6 000 MHz): EMF are probably carcinogenic for humans, in particular related to gliomas and acoustic neuromas; FR2 (24 to 100 GHz): no adequate studies were performed on the higher frequencies; 2) reproductive developmental effects: FR1 (450 to 6 000 MHz): these frequencies clearly affect male fertility and possibly female fertility too. They may have possible adverse effects on the development of embryos, foetuses and newborns; FR2 (24 to 100 GHz): no adequate studies were performed on non-thermal effects of the higher frequencies.

AUTHOR

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Executive summary

1. Background

Recent decades have seen an unparalleled development of technologies known as information and communications technologies (ICT), which include wireless communication used for mobile telephones and, for example, Wi-Fi using radiofrequency (RF) electromagnetic fields (EMF).

The first generation of handheld mobile phones was available in the late 1980s. Subsequently, the second (2G), third (3G) and fourth (4G, long-term evolution = LTE) generations dramatically increased their penetration rates in society, so that today in Europe there are more devices than inhabitants. In addition, Wi-Fi and other forms of wireless data transfer have become ubiquitous and are globally available. Nevertheless, there are new inequalities in terms of access to high-speed internet (even within high-income countries) and control by authoritarian regimes shows risks for democracy and European values.

The introduction of the next generation of RF, 5G, has begun on mobile networks. 5G is not a wholly new technology, but an evolution of already existing G1 to G4 technologies. 5G networks will work within several different frequency bands, the lower frequencies of which are being proposed for the first phase of 5G networks. Several of these frequencies have been or are currently being used for earlier mobile communication generations. There are also plans to use much higher radio frequencies at later stages of the 5G technology evolution. The new bands are well above the ultra high frequency (UHF) range, having wavelengths in the centimetre (3–30 GHz) or millimetre ranges (MMW) at 30-300 GHz. These latter bands have traditionally been used for radar and microwave links and very few have been studied for their impact on human health.

2. Methodology

This review of the currently available scientific evidence focuses on both the carcinogenic and the reproductive/developmental effects of RF from mobile phone telecommunications systems using 2G-5G networks, based on both in vivo animal studies and human epidemiological studies. The studies evaluated have been divided into two groups:

1) studies evaluating health effects due to RF at the lower frequency range (FR) (FR1: 450 to 6 000 MHz), which also includes the frequencies used in the existing 2-4 generations of the broadband cellular network. The current evidence from 2G-4G studies is the best evidence currently available. The studies were evaluated using *narrative* methods;

2) studies evaluating health effects due to RF at the higher FR (FR2: 24 to 100 GHz - MMW). The higher frequencies are new, not previously used for mobile communication and specific to the new 5G technology, which has particular physical characteristics and interactions with biological matter (lower penetration, higher energy, etc.): they were considered separately using a scoping review method.

Narrative review (FR1) will be distinguished from scoping review (FR2), but the selection and assessment criteria indicated for scoping reviews were adopted for both searches and for including/excluding studies on the cancer and reproductive/developmental biological end points.

In finally assessing the results of both epidemiological and experimental study, and of cancer and reproductive/developmental outcomes, consideration was given to the parameters indicated in the IARC Monograph Preamble (2019), tailored to the needs of the present report, and valid for both end points (i.e. cancer and reproductive/developmental effects):

Sufficient evidence: a causal association between exposure to RF-EMF and the specific adverse effect has been established. That is, a positive association has been observed in the body of evidence on

exposure to the agent and the specific adverse effect in studies in which chance, bias, and confounding factors were ruled out with reasonable confidence.

Limited evidence: a causal interpretation of the positive association observed in the body of evidence on exposure to RF-EMF and the specific adverse effect is credible, but chance, bias, or confounding factors cannot be ruled out with reasonable confidence.

No evidence: there are no data available or evidence, suggesting lack of adverse effects (to be specified).

The overall evaluation for both cancer and reproductive/developmental effects was obtained by the integration of the human/animal evidence as follows:

Evidence in humans	Evidence in experimental animals	Evaluation based on strength of evidence
Sufficient	Not necessary	Clear association between exposure and the adverse effect
Limited	Sufficient	Probable association between exposure and the adverse effect
Limited	Less than sufficient	Possible association between exposure and the adverse effect
Inadequate	Inadequate or limited	Not classifiable

3. Exposure assessment

The question of exposure assessment with the introduction of 5G is complicated, above all concerning the monitoring of the continuous changes in activity of both base stations (BS) and user equipment (UE) related to MIMO (multiple input, multiple output) technology. Furthermore, the technical approach to exposure assessment in the future scenario, relating to 1G, 2G, 3G, 4G and 5G concurrent emissions, is still being formulated and is hence uncertain.

4. Non-thermal effects

The harmful effects of non-thermal biological interaction of RF-EMF with human and animal tissues have not been included in the determination of the ICNIRP 2020 guidelines (ICNIRP 2020a), despite the huge amount of available scientific publications demonstrating the harmfulness or potential harmfulness of those effects. Athermal bioresponses exist, and indeed some frequencies are being used for therapeutic purposes in a number of branches of medicine. Any drug, as we well know, even the most beneficial, may also entail some adverse effects. So, thermal as well as non-thermal effects of RF-EMF have to be considered in risk assessment.

5. State of the art of the research on RF-EMF

The introduction of wireless communication devices that operate in the RF region of the electromagnetic spectrum (450 to 6 000 MHz, lower frequencies) has triggered a considerable number of studies focusing on health concerns. These studies encompass studies on humans (epidemiological), on animals (rodent experimental studies), and on in-vitro cellular systems.

5G networks will increase the number of wireless devices, necessitating a lot more infrastructure, so as to allow for a higher mobile data volume per geographic area. Moreover, it is necessary to build up increased network density, as the higher frequencies required for 5G (24 to 100 GHz, MMW) have shorter ranges. The studies available on these frequencies are few in number and of mixed quality.

This raises thee questions as to whether these higher frequencies would have health and environmental effects different from those at lower ferquencies. Worldwide, assessments of RF safety have been performed at different levels, with the publication of scientific and policy papers.

With regard to cancer, the IARC 2011 analyis of the literature reviewed up to 2011 (Baan, 2011), published in 2013, and cited throughout as IARC (2013), defined RF-EMF in the frequency range from 30 kHz to 300 GHz as 'possibly carcinogenic' to humans, based on 'limited evidence of carcinogenicity' in human and in experimental animals. The studies available in 2011 examined RF in the range we here call FR1, that is from 450 to 6 000 MHZ. The FR2 frequencies (24 to 100 GHz) lie in the MMW range.

The IARC 2011 analysis evaluated RF-EMF. While there were no studies on 5G, some studies on high frequency occupational radar and microwave exposures were included.

The new MMW frequencies (FR2: 24 to 100 GHz) will be added to the lower frequencies already in use including in part by 5G. It follows that, for 5G in the range 450 to 6 000 MHz (FR1) there are many studies, many collected in the IARC Monograph in relation to cancer, while for 26 GHz and other MMW frequencies in general there is little literature exploring the possible adverse effects on health. The simple reason for this is that hitherto these frequencies have never been used for mass communication and hence there were few suitable populations exposed to these frequencies to study; there are likewise very few adequate studies on non-thermal effects on laboratory animals.

6. Results of the present review

Using PubMed and the EMF Portal database, and applying the scoping review methodology to our research, we found 950 papers on the carcinogenicity of RF-EMF in humans, and 911 papers on experimental rodent studies, totalling 1 861 studies. Regarding reproductive/developmental studies, we found 2 834 papers for epidemiology and 5 052 studies for experimental rodent studies, totalling 7 886 studies. From the present review of the literature and the considerations reported above, we come to the following conclusions:

6.1 Cancer in humans

FR1 (450 to 6 000 MHz): there is limited evidence for carcinogenicity of RF radiation in humans. Updating the results of the overall 2011 evaluation to 2020, positive associations have again been observed between exposure to radiofrequency radiation from wireless phones and both glioma (tumour of the brain) and acoustic neuroma, but the human evidence is still limited.

FR2 (24 to 100 GHz): no adequate studies were performed on the effects of the higher frequencies.

6.2 Cancer in experimental animals

FR1 (450 to 6 000 MHz): there is sufficient evidence in experimental animals of the carcinogenicity of RF radiation. New studies following the 2011 IARC evaluation showed a positive association

between RF-EMF and tumours of the brain and Schwann cells of the peripheral nervous system, the same type of tumours also observed in epidemiological studies.

FR2 (24 to 100 GHz): no adequate studies were performed on the higher frequencies.

6.3 Reproductive/developmental effects in humans

FR1 (450 to 6 000 MHz): there is sufficient evidence of adverse effects on the fertility of men. There is limited evidence of adverse effects on fertility in women. There is limited evidence of developmental effects in offspring of mothers who were heavy users of mobile phones during pregnancy.

FR2 (24 to 100 GHz): no adequate studies were performed on the higher frequencies.

6.4 Reproductive/developmental effects in experimental animals

FR1 (450 to 6000 MHz): there is sufficient evidence of adverse effects on male rat and mouse fertility. There is limited evidence of adverse effects on female mouse fertility. There is limited evidence of adverse effects on the development in offspring of rats and mice exposed during embryo life.

FR2 (24 to 100 GHz): no adequate studies on non-thermal effects were performed on the higher frequencies.

7. Overall evaluation

7.1 Cancer

FR1 (450 to 6 000 MHz): these FR1 frequencies are probably carcinogenic to humans.

FR2 (24 to 100 GHz): no adequate studies were performed on the higher frequencies.

7.2 Reproductive/developmental effects

FR1 (450 to 6000 MHz): these frequencies clearly affect male fertility. They possibly affect female fertility. They possibly have adverse effects on the development of embryos, foetuses and newborns.

FR2 (24 to 100 GHz): no adequate studies were performed on non-thermal effects of the higher frequencies.

8. Policy options

8.1 Opting for novel technology for mobile phones that enables RF-EMF exposures to be reduced

The sources of RF emissions that seem at present to pose the greatest threat are mobile phones. Though transmitting installations (radiobase masts) are perceived by some people as providing the greatest risk, actually the greatest burden of exposure in humans generally derives from their own mobile phones, and epidemiological studies have observed a statistically significant increase in brain tumours and Schwann cell tumours of the peripheral nerves, mainly among heavy cell-phone users.

Accordingly, action is needed to ensure that safer and safer telephone devices are manufactured, emitting low energy and if possible only working when at a certain distance from the body. The cable earpiece solves much of the problem but is inconvenient and hence puts users off; on the other hand, it is not always possible to use speakerphone mode. The option of lowering RF-EMF exposure as much as possible in connection with telephones still applies whatever the frequencies being used, from 1G to 5G. Countries such as the US and Canada, which enforced stricter mobile phone SAR limits than in Europe, were still able to build efficient 1G,2G, 3G, 4G communications

(Madjar, 2016). Since 5G aims to be more energy-efficient than the previous technologies, adopting stricter limits in the EU for mobile phone devices would be at once a sustainable and a precautionary approach.

8.2 Revising exposure limits for the public and the environment in order to reduce RF-EMF exposure from cell towers

Recently, EU policies (European Commission, 2019) have promoted the sustainability of a new economic and social development model that uses new technologies to constantly monitor the planet's state of health, including climate change, the energy transition, agro-ecology and the preservation of biodiversity. Using the lowest frequencies of 5G and adopting precautionary exposure limits such as those used in Italy, Switzerland, China, and Russia among others, which are significantly lower than those recommended by ICNIRP, could help achieve these EU sustainability objectives.

8.3 Adopting measures to incentivise the reduction of RF-EMF exposure

Much of the remarkable performance of the new wireless lower frequency 5G technology can also be achieved by using optic-fibre cables and by adopting engineering and technical measures to reduce exposure from 1-4G systems (Keiser, 2003; CommTech Talks, 2015; Zlatanov, 2017). This would minimise exposure, wherever connections are needed in fixed sites. For example, optic fibre cables could be used to connect schools, libraries, workplaces, houses, public buildings, and all new buildings etc., and public gathering places could be 'no RF-EMF' areas (along the lines of no-smoking areas) so as to avoid the passive exposure of people not using a mobile phone or long-range transmission technology, thus protecting many vulnerable elderly or immune-compromised people, children, and those who are electro-sensitive.

8.4 Promoting multidisciplinary scientific research to assess the long-term health effects of 5G and to find an adequate method of monitoring exposure to 5G

The literature contains no adequate studies that would rule out the risk that tumours and adverse effects on reproduction and development may occur upon exposure to 5G MMW, or to exclude the possibility of some synergistic interactions between 5G and other frequencies that are already being used. This makes the introduction of 5G fraught with uncertainty concerning both health issues and forecasting and or monitoring the actual exposure of the population: these gaps in knowledge justify the call for a moratorium on MMW of 5G, pending completion of adequate research.

In light of these uncertainties, one policy option is to promote multidisciplinary team research into various factors concerning exposure assessment and also into the biological effects of 5G MMW at frequencies between 6 and 300 GHz, both on humans and on the flora and fauna of the environment, e.g. non-human vertebrates, plants, fungi, and invertebrates.

MMW will only be brought in with the final 5G protocol, i.e. not until three to five years' time. Given this time frame, one option is to study their effects before exposing the whole world population and environment.

Implementing MMW 5G technology without further preventive studies would mean conducting an 'experiment' on the human population in complete uncertainty as to the consequences. To restrict our scope to Europe, this could occur within a field like that of chemistry, currently governed by REACH (EC, 1907/2006).

REACH aims to improve the protection of human health and the environment through better and earlier identification of the intrinsic properties of chemical substances. EU REACH regulates the registration, evaluation, authorisation, and restriction of chemicals. It also aims to enhance the innovation and competitiveness of the EU chemicals industry. EU REACH is based on the principle of 'no data, no market', placing responsibility on industry to provide safety information on substances.

Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database in the European Chemicals Agency (ECHA). One policy option can be to apply the same approach to all types of technological innovation.

The results of these studies could form the basis for developing evidence-based policies regarding RF-EMF exposure of human and non-human organisms to 5G MMW frequencies. Further studies are needed to better and independently explore the health effects of RF-EMF in general and of MMW in particular.

8.5 Promoting information campaigns on 5G

There is a lack of information on the potential harms of RF-EMF. The information gap creates scope for deniers as well as alarmists, giving rise to social and political tension in many EU countries. Public information campaigns should therefore be a priority.

Information campaigns should be carried out at all levels, beginning with schools. People should be informed of the potential health risks, but also the opportunities for digital development, what infrastructural alternatives exist for 5G transmission, the safety measures (exposure limits) taken by the EU and Member States, and the correct use of mobile phones. Only with sound and accurate information can we win back citizen trust and reach a shared agreement over a technological choice which, if properly managed, can bring great social and economic benefits.

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List of abbreviations

1G , 2G, 3G, 4G, 5G	First-fifth generation of telecommunication
2-ME	2-methoxyethanol
3β HSD	3β-Hydroxysteroid dehydrogenase
17 β HSD	17β-Hydroxysteroid dehydrogenases
3GPP	3rd Generation Partnership Project
ABCD	Amsterdam-born children and their development study
AKR/J	mouse strain
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
AOR	covariate-adjusted odds ratio
APD	annual power density
AR	acrosome reaction
ASP	annual summarised power
AUDIPOG	assessment of neonatal growth (score expressed as a percentile)
B6C3F1/N	mouse strain
BALB/c	mouse strain
BAX	Bcl-2-associated X
BCL-2	B-cell lymphoma 2
BCL-XL	B-cell lymphoma-extra large
BLL	blood lead level
BMI	body mass index
BS	base stations
C3H/HeA	transgenic mouse
C57BL/6	mouse strain
CANULI	From the danish 'cancer og social ulighed' (cancer and socal inequality), cohort study
CAT	catalase
CEFALO	multicentre case-control study
CERENAT	multicentre case-control study
CDF	cumulative distribution function
CDMA	code division multiple access
CGRP	calcitonin gene-related peptide
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
CW	continuous wave
DECT	digital enhanced cordless telecommunications

DFI	DNA fragmentation index
DNA	neoxyribonucleic acid
DNBC	Danish national birth cohort
ECHA	European Chemicals Agency
EARTH	Environment and Reproductive Health Study
EMF	electromagnetic field
ENU	N-ethyl-N-nitrosourea
EPM	elevated-plus maze
EPRS	European Parliamentary Research Service
Erα	estrogen receptor alpha
Erβ	estrogen receptor beta
EU	European Union
Eμ-Piml	transgenic mouse
F	female
FCC	Federal Communications Commission
FOEN	Federal Office for the Environment
FOMA	freedom of mobile multimedia access
FR1	lower frequency band (450 MHz- 6 GHz)
FR2	higher frequency band (24 - 100 GHz)
FST	forced swimming test
GA	gallic acid
GADD45	growth arrest and DNA damage 45
GBD	global burden of diseases, injuries and risk factors
GD	gestational day
GERoNiMO	generalised EMF research using novel methods
GFAP	glia fibrilliary acidic protein
GHz	giga hertz
GIS	geographical information systems
GSH	glutathione
GSH-Px	glutathione peroxidase
GSM	global systems for mobile communications
GR	γ-radiation
H2O2	hydrogen peroxide
HSP70 (or 25, or 32): 70 (or 25, or 32)	kilodalton heat shock proteins
IARC	International Agency for Research on Cancer
IATPF	International Academy of Toxicologic Pathology Fellow
ICNIRP	International Commission on Non-Ionizing Radiation Protection

ICR	mouse strain
ICT	information and communications technology
IEC	International Electrotechnical Commission
IEEE	Institute of Electrical and Electronics Engineers
IEMFA	International EMF Alliance
IL-6 (or 10, or 32)	interleukine-6 (or 10, or32)
ILO	International Labour Organization
INMA	Spanish Environment and Childhood Project
INTERPHONE	a set of international case-control studies
INTEROCC	international case-control study
IoT	internet of things
ISTISAN	Italian National Institute of Health (Istituto Superiore di Sanità) report
IRR	incidence rate ratio
ITA	Austrian Institute fur Technickfolken
IT'IS	Foundation for Research on Information Technologies in Society
JECS	Japan Environment and Children Study
kHz	kilohertz
LH	luteinising hormone
LTE	long-term evolution
M	male
MARHCS	Male Reproductive Health in Chongqing College students cohort study
MDA	malondialdehyde
MDI	mental development index
MEL	melatonin
MHz	megahertz
MIMO	multiple-input and multiple-output antennas
MMP2 (or 14)	matrix metallopeptidase 2 (or 14)
MMW(s)	millimeter wave(s)
MoBa	prospective population-based pregnancy cohort study
MOCEH	Korean Mothers and Children's Environmental Health Study
MOE	moringa extract
MPBS	mobile phone base stations
MW	millimeter waves
MWM	Morris water maze
NéHaVi	cohort study
NIR	non-ionising radiation
NMRI	mouse strain

NO	nitric oxide
NOS	nitric oxide synthase
NTP	national toxicology programme
NTP TR	national toxicology programme technical report
OECD	Organisation for Economic Co-operation and Development
OFT	open field test
OR	odd ratio
OSI	oxidative stress index
PARP	poly (ADP-ribose) polymerase
P21	cyclin-dependent kinase inhibitor 1
P450scc	cholesterol side-chain cleavage enzyme
P53	tumour protein P53
PCNA	proliferating cell nuclear antigen
PD	power density
PDI	psychomotor development index
PECO	population, exposure, comparator and outcome
PEM	personal exposure meter
PGE2	prostaglandin E2
PND	postnatal day
PRISMA-ScR	preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
REACH	registration, evaluation, authorisation and restriction of chemicals
RF	radiofrequency
RFR	radiofrequency radiation
RF-EMF	radiofrequency electromagnetic field
RL	reference level
ROS	reactive oxygen species
RR	relative risk
RWTH	Rheinisch-Westfälische Technische Hochschule Aachen
SAR	specific absorption rate
SCENIHR	European Commission Scientific Committee on Emerging and Newly Identified Health Risks
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SDQ	strengths and difficulties questionnaire
SEM	source-exposure matrix
SF1	splicing factor 1
SOD	superoxide dismutase
SPOCK3	PARC (osteonectin), cwcv and kazal-like domains proteoglycan 3

SSM	Swedish Radiation Safety Authority
SR	scoping review
StAR	steroidogenic acute regulatory protein
STOA	European Parliament's Panel for the Future of Science and Technology
TAC	total antioxidant capacity
TETRA	terrestrial trunked radio
TSC	total sperm count
TST	tail suspension test
UE	user equipment
UHF	ultra-high frequencies
UMTS	universal mobile telecommunications system
UK	United Kingdom
V/m	volt/meter
VEGF	vascular endothelial growth factor
W/kg	watt/kilogram
WHO	World Health Organization

1. Introduction

1.1 Background

Recent decades have experienced an unparalleled development of technologies known as Information and Communications Technology (ICT), which include wireless communication used for mobile telephones and, for example, Wi-Fi using electromagnetic fields (EMF). The first generation of handheld mobile phones were available in the late 1980s. Subsequently, the second (2G), third (3G), and fourth (4G, Long-Term Evolution = LTE) generations dramatically increased their penetration rates in society, so that today there are more devices than inhabitants in Europe. In addition, Wi-Fi and other forms of wireless data transfer have become ubiquitous, and are globally available. At present we are starting to introduce the next generation of RF, 5G, on mobile networks. 5G is not new technology, but an evolution of already existing G1 to G4 technologies.

1.2 The exposure scenario

1.2.1 Present scenario of exposure

The different exposure situations that may occur with the intensive deployment of telecommunications was well described in Monograph 102 of the International Agency for Research on Cancer (IARC, 2013). Monograph 102 is concerned with non ionising radiation in the RF range of the electromagnetic spectrum, i.e. between 30kHz and 300 GHz, thus including the frequencies relevant to the present review.

The corresponding wavelengths (the distance between successive peaks of RF waves) range from 10 Km to 1mm, respectively. EMF generated by RF sources couple with the human body, which results in induced electric and magnetic fields and associated currents inside body tissues (IARC, 2013). Human exposures to radiofrequency electromagnetic fields (RF-EMF) can occur from use of personal devices (e.g. mobile telephones, cordless phones, Bluetooth, and amateur radios), from occupational sources (e.g. high-frequency dielectric and induction heaters, and high-powered pulsed radars), and from environmental sources such as mobile-phone base stations, broadcasting antennas, and medical applications.

For workers, most exposure to RF-EMF comes from near-field sources, whereas the general population receives the highest exposure from transmitters close to the body, such as handheld devices like mobile telephones. Exposure to high-power sources at work might involve higher cumulative RF energy deposited in the body than exposure to mobile phones, but the local energy deposited in the brain is generally lower.

Typical exposures ofthe brain from rooftop or tower-mounted mobile-phone base stations and from TV and radio stations are several orders of magnitude lower than those from global systems for mobile communications (GSM) handsets. The average exposure from use of digital enhanced cordless telecommunications (DECT) phones is around five times lower than that measured for GSM phones, and third-generation (3G) phones emit, on average, about 100 times less RF energy than GSM phones, when signals are strong. Similarly, the average output power of Bluetoothwireless hands-free kits is estimated to be around 100 times lower than that of mobile phones.

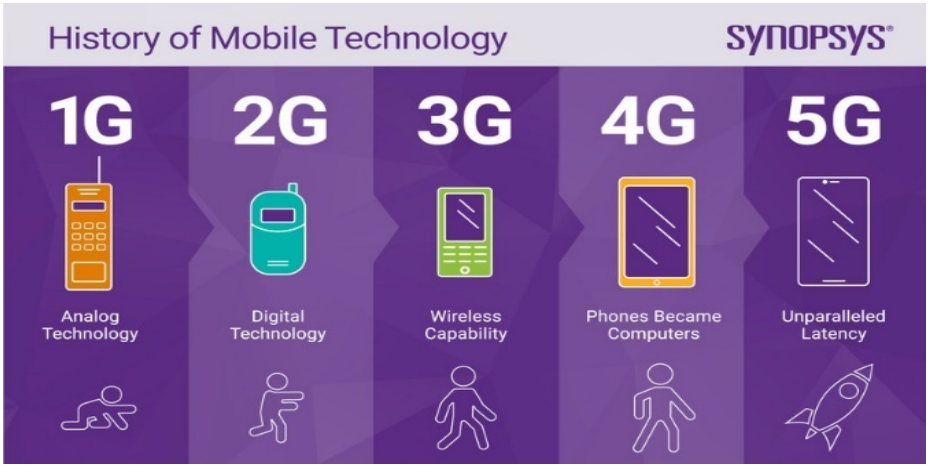
EMFs generated by RF sources couple with the body, resulting in induced electric and magnetic fields and associated currents inside tissues. The most important factors that determine such induced fields are the distance of the source from the body and the output power level (IARC, 2013). The near field and far field are regions of the EMF around an object, such as a transmitting antenna, or the result of radiation scattering off an object. Non-radiative near-field behaviours dominate close to the antenna or scattering object (mobile phone), while electromagnetic radiation far-field behaviours dominate at greater distances (BC Center for Disease Control, 2013).

Additionally, the efficiency of coupling, and resulting field distribution inside the body, strongly depends on the frequency, polarisation, and direction of wave incidence on the body, and anatomical features of

the exposed person, including height, bodymass index, posture, and dielectric properties of the tissues. Induced fields within the body are highly non-uniform,varying over several orders of magnitude, with local hotspots. Holding a mobile phone to the ear to make a voice call can result in high specific RF energy absorption-rate (Specific Absorption Rate = SAR) values in the brain, depending on the design and position of the phone and its antenna in relation to the head, how the phone is held, the anatomy of the head, and the quality of the link between the base station and phone. When used by children, the average RF energy deposition is two times higher in the brain and up to ten times higher in the bone marrow of the skull, compared with mobile phone use by adults. Use of hands-free kits lowers exposure to the brain to below 10% of the exposure from use at the ear, but it might increase exposure to other parts of the body (IARC, 2013).

1.2.2 The 5G scenario of exposure

Figure 1 – History of mobile technology



With the upcoming deployment of 5G mobile networks, significantly faster mobile broadband speeds and increasingly extensive mobile data usage will be ensured. Technical innovations include a different transmission system (MIMO: multiple-input and multiple-output antennas), directional signal transmission or reception (beamforming), and the use of other frequency ranges. This is made possible by the use of additional higher frequency bands (millimetre waves = MMW). 5G is intended to be the intersection of communications, from virtual reality to autonomous vehicles to the industrial internet and smart cities. In addition, 5G is considered the basic technology for the Internet of Things (IoT), where machines communicate with machines. At the same time, a change is expected in the exposure to EMF of humans and the environment (Figures 1 and 2).

Figure 2 – 3G vs 4G vs 5G

		3G	4G	5G
	Deployment	2004-05	2006-10	2020
	Bandwidth	2mbps	200mbps	>1gbps
	Latency	100-500 milliseconds	20-30 milliseconds	<10 milliseconds
	Average Speed	144 kbps	25 mbps	200-400 mbps

The 5G networks will work within several different frequency bands, of which the lower frequencies are being proposed for the first phase of 5G networks. Several of these frequencies (principally below 1 GHz - Ultra-High Frequencies, UHF) have been or are currently being used for earlier mobile communication generations. Furthermore, much higher RF are also planned to be used at later stages of the evolution of the technology.

The operating frequencies at low and mid bands can overlap with the current 4G band at 6 GHz or below. The biological effects of RF radiations at these lower-frequency bands are thus likely to be comparable to 2G, 3G or 4G. However, the scenarios of high band 5G, especially for 24 GHz to 60 GHz in the MMW region for high-capacity, short-range wireless data communications, are relatively recent new arrivals, and pose considerable challenge to health-risk assessment (Lin, 2020). These latter bands have traditionally been used for radar and microwave links (Simkò and Mattsonn, 2019) and very few have been studied for their impact on human health.

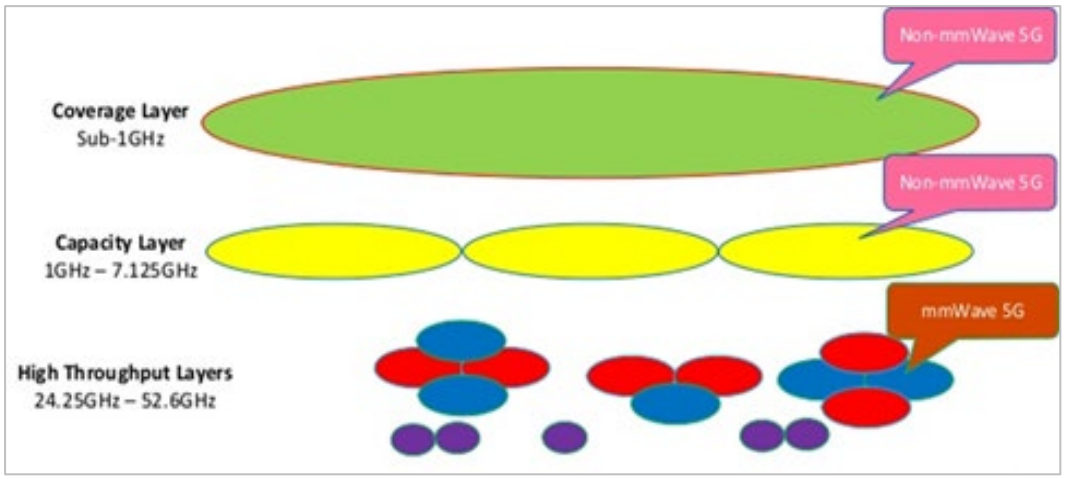
1.2.3 5G: beam forming and MIMO

The recent increase in cell-phone traffic over the microwave frequency band has shifted attention towards the broad MMW spectrum, which has hitherto been under-used. Up until 4G technology, cellular communication used frequencies below 3GHz and the idea that higher frequencies (greater than 3 GHz) incur more attenuation by physical obstacles tended to make the lesser frequencies seem more reliable. However, intelligent beamforming is improving the coverage and cutting interference to a minimum. The technique of dynamic radio masts employing beamforming, combined with multi-user MIMO (MU-MIMO), forms the basis of 5G NR (New Radio); working together they will enable over 1,000 more devices per square metre to be supported than with 4G, sending many more users ultra-fast data with high precision and low latency.

MIMO was originally developed for Single-User (SU-MIMO) applications so as to improve the efficiency of LTE (4G) networks. It was soon realised that such technology could be extended to Multi-User applications with a view to reducing or avoiding the problem of interference within a cell. This led to a series of solutions known as MU-MIMO (David and Viswanath, 2005). On the other hand, implementation of these inevitably raised queries as to the health impact. The European Parliament tackled the issue in a 2019 document concerning the state of advancement of 5G distribution in Europe, the US and Asia:

"Significant concern is emerging over the possible impact on health and safety arising from potentially much higher exposure to radiofrequency electromagnetic radiation arising from 5G. Increased exposure may result not only from the use of much higher frequencies in 5G but also from the potential for the aggregation of different signals, their dynamic nature, and the complex interference effects that may result, especially in dense urban areas. The 5G radio emission fields are quite different to those of previous generations because of their complex beamformed transmissions in both directions – from base station to handset and for the return. Although fields are highly focused by beams, they vary rapidly with time and movement and so are unpredictable, as the signal levels and patterns interact as a closed loop system. This has yet to be mapped reliably for real situations, outside the laboratory" (Blackman and Forge, 2019).

Figure 3 – 5G needs different frequency bands



Source: Qualcomm, 2020

5G will use a broad range of radio spectra (Fig.4). They divide into three distinct levels according to user need:

- the "*coverage layer*", with frequencies lower than 1GHz, provides broad outdoor coverage and deep indoor coverage. It basically consists of a frequency band used by digital television that performs well in penetrating obstacles. This system does not use beamforming, and in terms of management is similar to Radio Base Stations (RBS) using 4G technology, though possibly applying a corrective factor (peak power reduction coefficient) which takes account of the mean power used by the transmitting system;

- the "*coverage and capacity layer*", between 1GHz and 6GHz, is one of the major novelties of 5G. It uses the Massive – MIMO system to ensure an optimum compromise between coverage and capacity, i.e. the speed of data transfer per unit of frequency. It includes the band C spectrum, around 3.5 GHz. This non-millimetre frequency band operates in beamforming mode so as to concentrate most of the radiated power upon the target terminal;

- the "*super data layer*", from 6GHz up to MMW frequencies of 30 GHz and over, offers the breadth of band and data speeds required by the top-performing International Telecommunication Union Radiocommunication Sector (ITU-R) of the International Mobile Telecommunications (IMT)-2020 standard. This frequency band also uses the beamforming technique.

The main frequency bands for 5G standards taken up globally5G technology will not just be geared to communication among people, but also to interconnected automated systems (Internet of Things) using electromagnetic waves on a frequency belonging to the band 26.5-27.5 GHz. The frequency of such electromagnetic waves is so high that they are unable to penetrate buildings or get past obstacles. So 'solving' that difficulty calls for installation of many small cells of sizes ranging from about 10 metres (indoor) to several hundred metres (outdoor) - greatly inferior in range to the macro-cells of previous technologies which may extend for several kilometres. In Europe, the general picture might be summarised as reported in Fig. 4, 5 and 6 (Source: Qualcomm, 2020).

Figure 4 – 5G spectrum status by dashboard and auctions in Europe

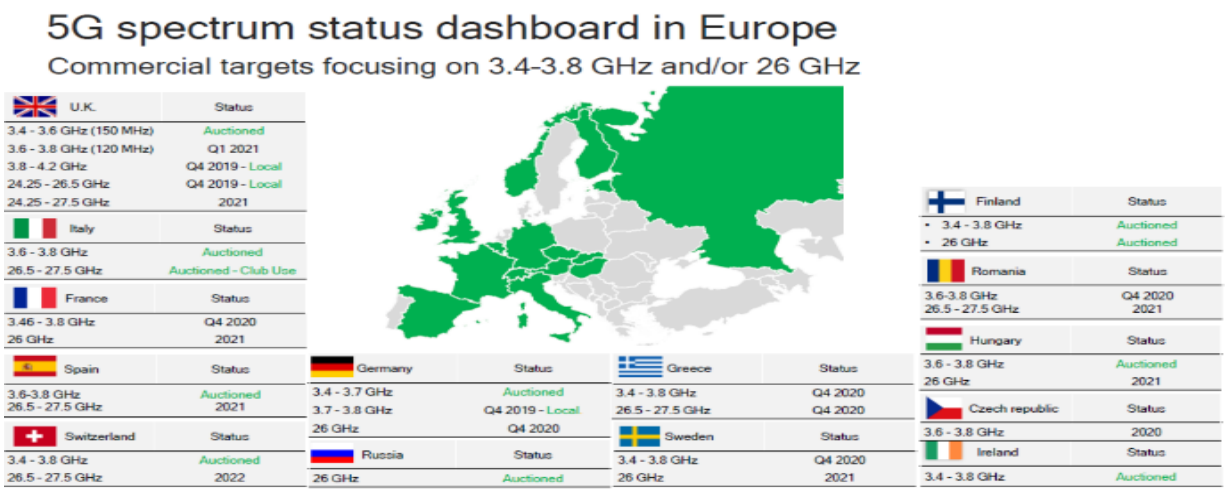


Figure 5 – 5G spectrum status by auctions in Europe (FR1: 700 MHz)

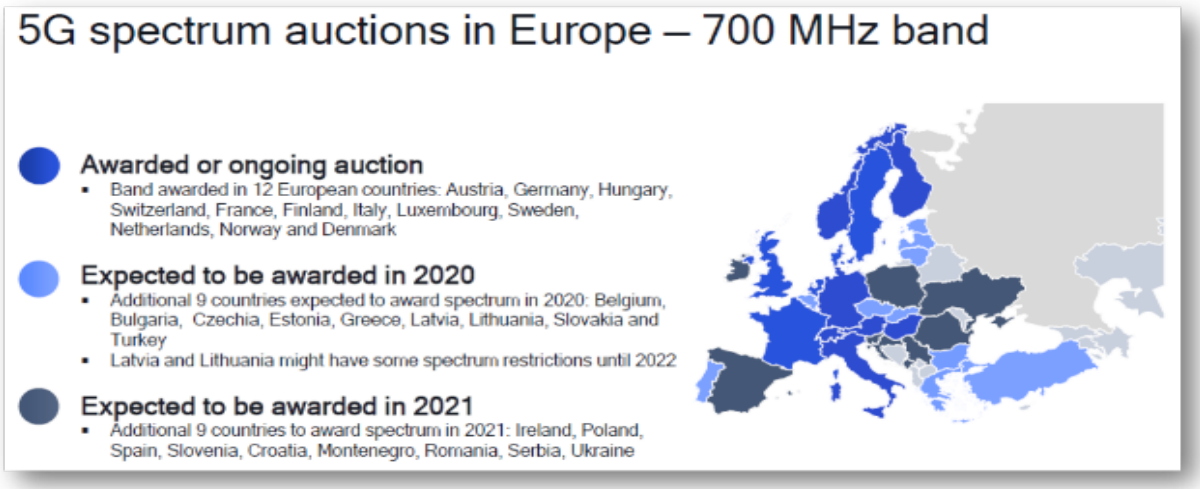


Figure 6 – 5G spectrum status by auctions in Europe (FR1: 3.4 -3.8 GHz)

Nasim and Kim (2017) simulates the possible exposure scenario to RF after 5G deployment using beamforming technology. The authors consider that at MMW frequencies, at which future mobile telecommunications systems will most likely operate, two changes that are likely to occur may increase concern as to the exposure of human users to RF fields. First, larger numbers of transmitters will operate. More base stations (BSs) will be deployed due to proliferation of small cells (Rappaport et al., 2013; Agiwal, 2016; Al-Saadeh, 2017) and mobile devices accordingly. This will increase the likelihood of human exposure to RF fields. Second, narrower beams will be used as a solution for the higher attenuation in higher frequency bands (Shakib, 2016; Zhang et al., 2017; Akdeniz et al., 2014). Very small wavelengths of MMW signals combined with advances in RF circuits enable very large numbers of miniaturised antennas. These multiple antenna systems can be used to form very high gains. The authors declare that their paper is motivated by the fact that previous works have not sufficiently addressed such a potential increase in risk. In their conclusions, the authors state*:*
"This paper has highlighted the significance of human RF exposure issue in downlink of a cellular communications system. This paper measured the exposure level in terms of PD and SAR, and compared them to those calculated in Release 9 as a representative of the current mobile communications technology. Unlike previous works that studied uplinks only, this paper has found that the downlinks of a 5G also yield significantly higher levels of PD and SAR compared to Release 9 [the present scenario of exposure]. Our results emphasized that the increase stems from two technical changes that will likely occur in 5G: (i)more access points (APs) due to deployment of smaller cells and (ii) morehighly concentrated RF energy per downlink RF beam due to use of larger phased arrays. As such, unlike prior work, this paper claims that RF fields generated in downlinks of 5G can also be dangerous inspite of far-field propagation. Therefore, the authors call for design of cellular communications and networking schemes that forcean AP to avoid generation of RF fields if pointed at a human user at an angle yielding a dangerous level of PD and SAR. To this end, the paper identifies as a future work developing the idea of techniques that reduce human exposure to RF fields in 5G downlinks" (Imtiaz and Seungmo, 2017).

It is noteworthy that this paper (Imtiaz and Seungmo, 2017) only referred to the 5G frequency of 28 GHz, one of the pioneer ones, with the simulation of only one user device connected, using the whole frequency band in static and stationary conditions.

Another paper (Baracca et al., 2018) from the Nokia group, taking into account massive MIMO base station (BSs), proposes a statistical approach for assessing the RF exposure conditions around massive MIMO BSs based on the 3D spatial channel model developed by the Third Generation Partnership Project (3GPP) and evaluates how the power is focused in a practical system when realistic assumptions regarding user equipment (UE) distribution and traffic models are taken into account. The methodology consists in performing system simulations that take into account realistic deployment scenarios in terms of installation height, user equipment, device distribution, and traffic, to evaluate the cumulative distribution function (CDF) of the BS actualtransmission power. "*The proposed statistical approach contributes to improve the calculation methods already defined by the International Electrotechnical Commission (IEC, 2017) and support the deployment of massive MIMO BSs for 5G and beyond cellular networks".*As a concluding remark, the Authors highlight that*: "All the statistical approaches including our own, although based on realistic assumptions, anyhow require complementary techniques, based for instance on power control and beamforming adaptation (*Sambo et al., 2015*), to ensure that the EMF constraints are met at the BSs for all the possible actual configurations*".

Regarding exposure assessment, Neufeld and Kuster (2018) issued a warning in a paper in Health Physics, urging that existing exposure standards be revised with shorter averaging times to address potential thermal damage from short and strong pulses: "*Extreme broadband wireless devices operating above 10 GHz may transmit data in bursts of a few milliseconds to seconds. Even though the time- and area-averaged power density values remain within the acceptable safety limits for continuous exposure, these bursts may lead to short temperature spikes in the skin of exposed people. ... [Our] results also show that the peak-to-average ratio of 1,000 tolerated by the ICNIRP guidelines may lead to permanent tissue damage after even short exposures, highlighting the importance of revisiting existing exposure guidelines*" (Neufeld and Kuster, 2018).

Kenneth Foster of the University of Pennsylvania, countered that their claims do not hold up: "*Because real-world communications technologies produce pulses of much lower fluence than the extreme pulses considered by Neufeld and Kuster, the resulting thermal transients from them will be very tiny in any event*" (Foster, 2019).

The Istituto Superiore di Sanità (Italian National Institute of Health) in the ISTISAN 2019 Report (available only in Italian) recognises that (translation by the author) : "(…) *on the basis of the technical characteristics of [5G] base stations, in order to correctly monitor the exposure, the mean value of measurements of electromagnetic fields should not be considered alone, but together with the maximum levels reached for short periods of exposure. This aspect calls for an updating of the national law which, up to now, has not considered short time exposures, but only continuous exposure as mean values within 6 minutes [20 V/m, occasional exposure] or 24 hrs [6V/m,residential/occupational exposure for more than 4hrs/day)*" (ISTSAN 19/11, 2019).

Uncertainty on exposure assessment remains unresolved. The above mentioned papers, shows that the question of exposure assessment with the introduction of 5G is complicated, above all concerning the monitoring of the continuous changes in activity of both base stations (BSs) and users (UEs) related to MIMO technology, while the technical position on exposure in the new scenario related to 2G, 3G, 4G, 5G emissions, is still being formulated and is hence uncertain. Exposure assessment constitutes a central matter of discussion before MMW and MIMO technology is disseminated all over the planet.

1.3 Overview of the policy action internationally and in Europe

1.3.1 International organisations

The International Agency for Research on Cancer (Baan et al., 2011; IARC, 2013) classified RF-EMF as "*possibly carcinogenic to humans*" (Group 2B).

The World Health Organization (WHO) recently relaunched a call for expressions of interest for systematic reviews (2020). The WHO is undertaking a health risk assessment of RF-EMF, to be published as a monograph in the Environmental Health Criteria Series. This publication will complement the monographs on static fields (2006) and extremely low frequency fields (2007), and will update the monograph on RF fields published in 1993 (WHO, 1993).

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) in March 2020 published new guidelines covering several new technologies, including 5G (ICNIRP, 2020a). The new guidelines introduce new and revised restrictions concerning 5G. On the ICNIRP website there is extensive information on the new guidelines and differences between the 1998 and 2020 guidelines. The guidelines refer only to thermal effects caused by 6 minutes and 30 minutes of exposure to RF-EMF, so the guidelines concern only short-term exposure. Safety guidelines for the currently deployed of 5G technology have been established though insufficient scientific research has yet been performed, while peer-reviewed science on non-thermal effects of RF already in use has not been evaluated in all ICNIRP guidelines (ICNIRP, 2020c).

1.3.2 European organisations and governments (by year)

The Council of Europe Resolution 1815 highlights that: "*The independence and credibility of the scientific expertise employed is crucial for a transparent and balanced assessment of possible negative effects on human health and environment. The resolution recommends: taking all reasonable measures to reduce exposure to EMF (especially from mobile phones) and particularly to protect children and young people who seem to be most at risk of developing head tumours; reconsidering the scientific basis for the present standards on exposure to electromagnetic fields set by the International Commission on Non-Ionising Radiation Protection, which have serious limitations; distributing information and awareness-raising campaigns on the risks of potentially harmful long-term biological effects on the environment and on human health, especially targeting children, teenagers and young people of reproductive age; giving preference to wired internet connections (for children in general and particularly in schools), and strictly regulating the use of mobile phones by schoolchildren on school premises; increasing public funding of independent research to evaluate health risks.*" (European Parliament Assembly, 2011)

The French Agency For Food, Environmental And Occupational Health and Safety (ANSES) in 2013, "(...) *issues recommendations for limiting exposure to radio frequencies limited levels of evidence do point to different biological effects in humans or animals. In addition, some publications suggest a possible increased risk of brain tumour, over the long term, for heavy users of mobile phones. Given this information, and against a background of rapid development of technologies and practices, ANSES recommends limiting the population's exposure to radiofrequencies – in particular from mobile phones – especially for children and intensive users, and controlling the overall exposure that results from relay antennas. It will also be further developing its work on electro-sensitive individuals, specifically by examining all the available French and international data on this topic that merits closer attention. Therefore, to limit exposure to radiofrequencies, especially in the most vulnerable population groups, the Agency recommends: - for intensive adult mobile phone users (in talk mode): use of hands-free kits and more generally, for all users, favouring the purchase of phones with the lowest SAR [values;- reducing the exposure of children by encouraging only moderate use of mobile phones; continuing to improve characterisation of population exposure in outdoor and indoor environments through the use of measurement campaigns; that the development of new mobile phone network infrastructures be subject to prior studies concerning the characterisation of exposures, and an in-depth study be conducted of the consequences of possibly multiplying the number of relay antennas in order to reduce levels of environmental exposure; - documenting the conditions pertaining at those existing installations causing the highest exposure of the public and investigating in what measure these exposures can be reduced by technical means; - that all common devices emitting electromagnetic fields intended for use near the body (DECT telephones, tablet computers, baby monitors, etc.) display the maximum level of exposure generated (SAR, for example), as is already the case for mobile phones; finally, in order to resolve the various uncertainties it identified when conducting this work, and in addition to the research projects already undertaken under the National Plan for Research on Environmental and Occupational Health, the Agency is also making a series of research recommendations"* (ANSES, 2013).

The European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) had a mandate to evaluate the risks of EMF and periodically reviews the scientific evidence available to assess whether it still supports the exposure limits proposed in Council Recommendation 1999/519/EC. In its latest opinion of January 2015, SCENIHR suggested that there is a lack of evidence that EMF radiation affects cognitive functions in humans or contributes to an increase of the cases of cancer in adults and children (SCENIHR, 2015). However, the International EMF Alliance (IEMFA) suggested that many members of SCENIHR could have a conflict of interests, as they had professional relationships with or received funding from various telecom companies.

Consequently, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), replacing the former SCENIHR, indicated a preliminary estimate of the importance of 5G as high, in a statement in December 2018. Furthermore, it evaluates the scale, urgency and interactions (with ecosystems and species) of possible hazard as high. It suggested that there could be biological consequences from a 5G environment, due to the fact that there is a lack of "*(...) evidence to inform the development of exposure guidelines to 5G technology*" (SCHEER, 2018).

In a briefing of June 2017, the European Parliamentary Research Service stated: *"Finally, little research has been performed on the health impacts of 5G, as most of the studies to date relate to previous generation of mobile technology. According to one recent study, this could prove a further bottleneck should 5G pose health risks owing to, 'its urban concentration and dense cellular structure, its use of much higher microwave frequencies and its highly directional concentration'. In the USA a 2016 government-funded study raised concern, as in its preliminary results it found significantly greater rates of rare tumours of the brain and heart in rats exposed to wireless radiation. Other 2017 research and publications also suggest that long-term mobile phone use could increase brain cancer risk. However the latest opinion published by the Commission's expert group in 2015 and research by the World Health Organization do not recognise a direct link. In France, meanwhile, a review of wireless radiation has concluded that there is a need to evaluate all wireless devices for their impact on children's health and recommends only moderate and supervised use by children. This complex issue therefore remains controversial while further research is ongoing"* (EPRS, 2017).

A more recent EPRS document stated that: *"The recent academic literature illustrates that continuous wireless radiation seems to have biological effects especially considering the particular characteristics of 5G: the combination of MMW, a higher frequency, the quantity of transmitters and the quantity of connections. Various studies suggest that 5G would affect the health of humans, plants, animals, insects, and microbes – and as 5G is an untested technology, a cautious approach would be prudent" (EPRS, 2020).*

The Federal Office for Radiation Protection of Germany published a report, where is stated that: *"In a few years, 5G will lead to higher frequencies. However, the effects of these have not yet been well researched. The Federal Office for Radiation Protection advises a prudent expansion of 5G and will further explore the effects of the new frequency bands"* (FORPG, 2019).

In 2020, the EMF scientific council of the Radiation Safety Authority in Sweden (SSM), published its 14th report. This is a consensus report, which means that all members of the Scientific Council agree with the report in toto. Despite the fact that no health risks with weak EMF have been established to date, the Authority considers that: "*Further research is important, in particular regarding long-term effects as the entire population is exposed. One key issue here is to further investigate the relationship between radio wave exposure and oxidative stress observed in animal studies and to establish whether and to what extent it may affect human health. There is also a need to further investigate the observed decreased sperm counts, sperm viability and decreased serum testosterone due to radio wave exposure of testes in animal studies before any conclusions concerning the possible implications for human health can be drawn*" (SSM, 2020).

The Austrian Institute of Technology (AIT) states: "*1) Electromagnetic fields have already been considered a potential health risk with previous generations of mobile radio communication. In 2011, the International Agency for Research on Cancer (IARC) classified mobile phone radiation as "possibly carcinogenic". To this day, experts continue to discuss this topic with much controversy. 2) 5G, the latest generation of mobile phone networks, promises to transmit larger amounts of data with lower latency. Industry 4.0, augmented reality games or the Internet of things rely on such higher performance. 3) The assessment of risks and gaps of knowledge enables precautionary regulation and a prudent approach to 5G*" (Kastenhofer, 2020).

The Health Council of the Netherlands published its opinion on 5G and health in September 2020. A selection of quotes from the report are as follow: *"The rollout of 5G networks has only just begun. Therefore, there are no studies as yet into the health effects of (long-term) exposure to electromagnetic fields with the frequencies that are reserved for 5G"; "According to the committee, it cannot be excluded that the incidence of cancer, reduced male fertility, poor pregnancy outcomes and birth defects could be associated with exposure to RF electromagnetic fields. However, the committee deems the relationship between exposure and these and other diseases or conditions neither proven nor probable"; "There has been almost no research into the effects of exposure to frequencies around 26 GHz"* ; "*The committee recommends not using the 26 GHz frequency band for 5G for as long as the potential health risks have not been investigated"; "The committee recommends using the latest guidelines from the International Commission on Non-Ionising Radiation Protection (ICNIRP) as the basis for exposure policy in the Netherlands. Because it cannot be excluded that exposure under the latest ICNIRP standards also has the potential to affect health, the committee recommends taking a cautious approach and keeping exposures as low as reasonably achievable".* In this report, common adverse effects from RF exposure are reported, but as a conclusion the committee only recommends taking a cautious approach (Health Council of the Netherlands, 2020).

In Switzerland, the Federal Office for the Environment (FOEN) is the government body responsible for monitoring and assessing research on health effects of NIR from stationary sources in the environment. This includes informing and updating the public about the current state of research, which is the basis for the ambient regulatory limits stated in the Swiss "ordinance relating to protection from non-ionising radiation (NIR)". In the case of reliable new scientific knowledge and experiences, the FOEN would advise the Federal Council of Switzerland to adapt these ambient regulatory limits. The FOEN has therefore nominated a consultative group of Swiss experts from various disciplines with scientific competence regarding EMF and NIR, which commenced its work in July 2014. The group is called BERENIS, based on an acronym of the respective German term. The BERENIS experts regularly screen the scientific literature, and assess the publications which they consider relevant for the protection of humans from potentially adverse

effects. As part of the work of BERENIS, non-ionising radiation (NIR) at frequencies below 10 GHz is addressed.

In the special issue of the BERENIS newsletter (BERENIS, 2021), an up-to-date assessment of a possible correlation between oxidative stress and exposure to EMF and their putative effects on health are presented. For this purpose, relevant animal and cell studies published between 2010 and 2020 were identified and summarised. An extended report presenting these recent studies in more detail will be published soon by FOEN 1 (not yet available at the time of this report). The newsletter contains a short version of the report, writing that: "*The majority of the animal and more than half of the cell studies provided evidence of increased oxidative stress caused by RF-EMF (...). This notion is based on observations in a large number of cell types, applying different exposure times and dosages (SAR [Specific Absorption Rate] or field strengths), also in the range of the regulatory limits*.". This review of the literature evidences that one of the mechanisms underlying adverse effects from RF-EMF is oxidative stress, forming free radicals that impair a number of different functions (Yakymenko, 2016).

1.4 Biologically effects other than the ones analysed in this review (both FR1 and FR2)

The present review examines only carcinogenicity and reproductive/developmental adverse effects related to RF exposure observed in epidemiological and laboratory animal studies, published since 1945. However, in order to better understand the impact of RF on human health, we cannot ignore the fact that other biological non thermal effects have been reported. For instance, we need only cite the preponderance of research published from 1990 through 2020, which has found various significant effects from exposure to radio frequency radiation. Overall, 75% (n=711) of 944 analysed radio frequency radiation studies have reported biological effects (Moskowitz, 2018).

The National Toxicology Program (NTP) found that RF-EMF exposure was associated with an increase in DNA damage. Specifically, they found RF-EMF exposure was linked with significant increases in DNA damage in the frontal cortex of the brain in male mice; the blood cells of female mice, and the hippocampus of male rats. There are many factors that influence whether damaged DNA will lead to tumours. NTP plans to conduct additional studies to learn more about how RF-EMF might cause DNA damage (Smith-Roe et al., 2019). Other adverse effects were observed in the NTP studies, including reduced birth weights, DNA strand breaks in brain cells, which is supportive of the cancer findings (Yakymenko, 2015), increased incidences of proliferative lesions (hyperplasia), and exposure-related increases in the incidence of cardiomyopathy of the right ventricle in male and female rats (NTP, 2018).

MMWs rarely included in the above mentioned studies have specific characteristics. MMWs are mostly absorbed within 1 to 2 millimetres of human skin and in the surface layers of the cornea. Thus, the skin or near-surface zones of tissues are the primary targets of such radiation. Since the skin contains capillaries and nerve endings, MMW bio-effects may be transmitted through molecular mechanisms by the skin or through the nervous system. Thermal (or heating) effects occur when the power density of the waves is above 5–10 mW/cm2 (Foster, 1998).

Such high-intensity MMWs act on human skin and the cornea in a dose-dependent manner—beginning with heat sensation followed by pain and physical damage at higher exposures. Temperature elevation affects the growth, morphology and metabolism of cells, induces production of free radicals, and damages DNA. Few studies have examined prolonged exposure to low-intensity MMWs, and no research has focused on exposure to MMWs combined with other RF radiation. Some studies reported that the radiation inhibits cell cycle progression, and some studies reported no biological effects (Le Drean et al., 2013).

(Ramundo-Orlando, 2010) noted that: "*A large number of cellular studies have indicated that MMW may alter structural and functional properties of membranes*". Exposure to MMWs may affect the plasma membrane either by modifying ion channel activity or by modifying the phospholipid bilayer. Water molecules also seem to play a role in these effects. Skin nerve endings are a likely target of MMWs and the possible starting

point of numerous biological effects. MMWs may activate the immune system through stimulation of the peripheral neural system (Ramundo-Orlando, 2010).

In 1998, scientists employed by U.S. Army research institutes published a seminal review of the research on MMWs. They reported: "*Increased sensitivity and even hypersensitivity of individual specimens to MMW may be real. Depending on the exposure characteristics, especially wavelength, a low-intensity MMW radiation was perceived by 8 to 30% of healthy examinees (Lebedeva, 1993, 1995). Some clinical studies reported MMW hypersensitivity, which was or was not limited to a certain wavelength (Golovacheva, 1995). It should also be realized that biological effects of a prolonged or chronic MMW exposure of the whole body or a large body area have never been investigated. Safety limits for these types of exposures are based solely on predictions of energy deposition and MMW heating, but in view of recent studies this approach is not necessarily adequate*" (Pakhomov et al., 1998).

In 1977, Zalyubovskaya published a study which examined the effects of exposing mice to millimetre radiation (37-60 GHz; 1 milliwatt per square centimetre) for 15 minutes daily for 60 days. The animal results were compared to a sample of people working with millimetre generators. The summary of the paper reports: *"Morphological, functional, and biochemical studies conducted in humans and animals revealed that millimeter waves caused changes in body manifested in structural alteration in the skin and internal organs, qualitative and quantitative changes in the blood and bone marrow composition and changes of the conditioned reflex activitiy, tissue respiration, activity of enzymes participating in the processes of tissue respiration and nucleic metabolism. The degree of unfavorable effect of millimeter waves depends on the duration of the radiation and individual characteristics of the organism*" (Zalyubovskaya, 1977).

Microbes are also affected by MMW radiations. In 2014 a review on the effects of MMWs on bacteria was published. The authors summarised their findings as follows: "(…) *bacteria and other cells might communicate with each other by electromagnetic field of sub-extremely high frequency range. These MMW affected Escherichia coli and many other bacteria, mainly depressing their growth and changing properties and activity. These effects were non-thermal and depended on different factors. The consequences of MMW interaction with bacteria are the changes in their sensitivity to different biologically active chemicals, including antibiotics. These effects are of significance for understanding changed metabolic pathways and distinguish the role of bacteria in the environment; they might be leading to antibiotic resistance in bacteria.These effects are of significance for understanding changed metabolic pathways and distinguish the role of bacteria in the environment; they might be leading to antibiotic resistance in bacteria"* (Adebayo et al., 2014).

"Changing the sensitivity of bacteria to antibiotics by MMW irradiation can be important for the understanding of antibiotic resistance in the environment. In this respect, it is interesting that bacteria [that] survived near telecommunication-based stations like Bacillus and Clostridium spp. have been found to be multidrug resistant" (Soghomonyan et al., 2016).

In a recently published paper,it was) found that: "*Taken together, MW-irradiated water [pulsed 3.5GHz high power] microwaves irradiation can alter cellular physiology noticeably, whereas irradiated media and buffered saline solutions induce negligible or irrelevant changes that do not affect cellular health"* (Bhartiya et al., 2021).

Yet we know that athermal bio-responses exist. Indeed, some frequencies are already being used for therapeutic purposes in a number of branches of medicine. These include nerve regeneration, wound healing, graft behaviour, diabetes, and myocardial and cerebral ischaemia (heart attack and stroke), among other conditions. Some studies even suggest possible benefits in controlling malignancy. Low-intensity, intermediate-frequency, alternating electric fields (tumour-treating fields) that target dividing cells in glioblastoma multiforme (brain malignant tumour) while generally not harming normal cells, are used for therapy purposes (Guo et al., 2011; Zimmerman et al., 2013; Alphandéry, 2018).

Since any drug, may also entail some adverse effects, non-thermal adverse effects of RF-EMF should also be considered for risk assessment. In sum, the peer-reviewed research shows that short-term exposure MMW radiation not only affects human cells, it may also result in changes in sensitivity of bacteria harmful to humans, and to various biologically active chemicals, including antibiotics.

Since little research has been conducted on the health consequences from long-term exposure to MMWs, widespread deployment of 5G infrastructure constitutes a massive experiment that may have adverse impacts on public health. Unfortunately, few studies have examined prolonged (long-term) exposure to low-intensity MMWs, and no research that we are aware of has focused on exposure to MMWs combined with other RF radiation.

1.5 Social conflict related to 5G

Another aspect of the 5G discussion is social polarisation. Currently, both activists for the 'Stop 5G' movements and 5G promoters claim there are thousands of studies on the health effects of RF used in wireless communication and their related EMF. Activists claim that studies show a lot of different harmful health effects, 5G promoters claim that studies do not show any adverse health effects. Both sides refer to the EMF Portal, a specialized database in Germany: "*The internet information platform EMF-Portal of the RWTH Aachen University summarizes systematically scientific research data on the effects of electromagnetic fields (EMF). All information is made available in both English and German. The core of the EMF-Portal is an extensive scoping database with an inventory of 32,119 publications and 6,805 summaries of individual scientific studies on the effects of EMF*" (EMF Portal homepage). The number of 32.119 publications (October 20, 2020) includes the studies of all types of biological and technical end points on all EMF originating from RF. However, the collection of 5G MMW frequencies-related studies is scanty (around 100) and, for the most part, regards technical/dosimetric studies. As a consequence, both claims, presence or lack of harms, about 5G MMW safety are based on assumption, not on scientific evidence.

The issue of social conflict is well developed by Leszczynski (2020). It is evident that the scenario in which 5G should be exploited is full of uncertainty on one side, denial on the other, and exaggerated alarmism in yet another.

2. Aims of the study and methodology

This review aims to evaluate the current state of knowledge on non-thermal effects regarding both the carcinogenic and the reproductive/developmental hazards of RF-EMF exploited by 5G as they emerge from in vivo experimental studies and epidemiological studies, considering separately the frequencies 700-3600 MHz and 26,000 MHz.

2.1 Rationale

This review of the currently available scientific evidence focuses on both the carcinogenic and the reproductive/developmental effects of RF from mobile phone telecommunications systems using 2-5G networks, based on both in vivo animal studies and human epidemiological studies.

The studies evaluated have been divided into 2 groups:

1) Studies evaluating health effects due to RF at the lower frequency range (FR) (FR1: 450 to 6000 MHz), which also includes the frequencies used in existing 2-4 generations of the broadband cellular network. The current evidence from 1G-4G studies is the best evidence currently available. The studies were evaluated using narrative methods.

2) Studies evaluating health effects due to RF at the higher frequency range (FR2: 24 to 100 GHz - MMW). The higher frequencies are new, previously not used for mobile communication and specific for the new 5G technology, which have particular physical characteristics and interactions with biological matter (lower penetration, higher energy, etc.): they were considered separately with a scoping review method.

Scoping reviews have great utility for evaluating research evidence and are often used to categorize or group existing scientific evidence in a given field in terms of its nature, quality, other features, and volume. This scoping review was performed assuming the principles of transparency, reproducibility and rigour. This was achieved by adopting the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) as the methodological framework of this work. At least two reviewers worked independently on every stage of this review: uniformity and standardisation in decision making was obtained through discussion and consensus-reaching among the reviewers. A distinction is made between the narrative review (FR1) and the scoping review (FR2), but the selection and assessment criteria indicated for scoping reviews were adopted for both searches and for including/excluding studies on the cancer and reproductive/developmental biological end-points.

2.1.1 Cancer

Epidemiological studies are potentially susceptible to several different sources of error. Study quality was assessed as part of the review process and all informative studies were considered. The informativeness of a study is its ability to show a true association, if there is one, between the agent and cancer, and the lack of an association, if no association exists. Key determinants of informativeness include: having a study population of sufficient size to obtain precise estimates of effect; sufficient time elapsing from exposure to measurement of outcome for the effect, if present, to be observable; presence of an adequate exposure contrast (intensity, frequency, and/or duration); biologically relevant definitions of exposure; and relevant and well-defined time windows for exposure and outcome (IARC Preamble, 2019).

As explained in the IARC Preamble, most human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species. For some agents, carcinogenicity in experimental animals was demonstrated before epidemiological studies identified their carcinogenicity in humans. Although such observation cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals should present a carcinogenic hazard to humans (IARC Preamble, 2019).

All available long-term studies of cancer in experimental animals on RF-EMF were considered in the review, after a thorough evaluation of the study features. Those studies that we judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; exposure assessment, etc) were omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2018a) and their criteria were considered as a reference for assessing the adequacy of studies.

As concerns cancer-related studies on RF, both epidemiological and experimental, comprehensive reviews of the literature had already been performed in the last decades; in particular, we refer to the IARC Monograph 102, which dealt with the RF range 30 kHz-300 Ghz. In May 2011, 30 scientists from 14 countries met at IARC in Lyon, France, to assess the carcinogenicity of RF-EMF. These assessments were published as Volume 102 of the IARC Monographs. A summary of the conclusions of the Working Group and the rationale for the evaluation together with the studies supporting the conclusions was published in May 2011 (Baan et al., 2011), the full Monograph was published in April 2013 (IARC, 2013).

Preparation of the IARC Monograph on RF was scheduled so as to include the results of the large international case-control study INTERPHONE on mobile phone use (performed in 2003-2004; published in 2010). We thus decided to adopt the IARC publication Monograph 102 (IARC, 2013) as a 'key reference' upon which to update the 2011 data to the year 2020 and hence produce the present report. After collecting and examining the original works related to the IARC 2011 analyis, published in 2013, and cited throughout as (IARC, 2013) considering their assessment criteria so as to conform to them in later assessments, we collected all relevant works dating from 2011 on, following the same criteria.

Once we had selected and examined the literature available according to the criteria described below, consistent with a scoping review, we updated the IARC (2013) tables to 2020. The studies selected, in abstract form, are included in the text, and tables in the "Assessment of individual studies" chapter, divided by end-point studied and by study characteristics. Each study is numbered in the same sequence in both abstract and corresponding table. In the summary tables, the studies are classified without specific comments, but only as adequate/inadequate for sample size, study design, exposure assessment and, when adequate, positive/negative/equivocal results:

- *Adequate*: no major qualitative or quantitative limitations.
- *Inadequate*: major qualitative or quantitative limitations affect the study, not valid for showing either the presence or absence of specific adverse effects.

When adequate:

- *Positive*: statistically significant increase of the specific pathology in association with RF-EMF exposure.
- *Equivocal:* adverse effect is demostrated showing a marginal increase (not statistically significant increase) of the specific pathology that may be associated with RF-EMF.
- *Negative*: no RF-EMF-related increases in specific pathologies.

2.1.2 Reproduction/development

Since no adequate, major review of studies on the reproduction/development effects exists to this date, such a review of all studies published between 1945 and 2020 was performed. Once we had selected and examined the literature according to the criteria described below, we summarized data up to 2020 in specific tables.

Regarding animal studies, in order to select informative studies only, another selection of studies was based on the guidelines NTP Modified One Generation Study and OECD 443, assessed in 2014 (Foster et al., 2014), planned in order to study experimental animals (rodents) for evidence of developmental pathology, endocrine disrupters, female reproduction, male reproduction, the reproductive system. The

guideline study design envisages at least 10 animals/sex/group in order to produce statistically robust results.

The abstracts of the selected studies are included in the text and tables in the 'Assessment of individual studies' chapter, divided according to end-point studied and the study characteristics. Each study is numbered and presented in the same sequence of the corresponding table. In the summarising tables, the studies are classified without specific comments, but only as adequate/ inadequate for sample size, study design, exposure assessment and, when adequate, positive/negative/equivocal results:

- *Adequate*: no major qualitative or quantitative limitations.
- *Inadequate*: major qualitative or quantitative limitations affect the study, not valid for showing either the presence or absence of specific adverse effects.

When adequate:

- *Positive*: statistically significant increase of the specific pathology in association with RF-EMF exposure.
- *Equivocal:* adverse effect is demostrated showing a marginal increase (not statistically significant increase) of the specific pathology that may be associated with RF-EMF.
- *Negative*: no RF-EMF-related increases in specific pathologies.

2.2 Search strategy

First a selection of the most appropriate keywords was performed:

Exposure: EMF; RF; 5G; radiofrequency radiation; radiofrequency; electromagnetic field; electromagnetic radiation.

Population (animal): in vivo; experimental; animal; rodent(s); rat(s); mouse; mice.

Population (human): epidemiological; observational; cross-sectional; case-control; worker(s); military; population.

Outcome (carcinogenic effects): cancer; tumour.

Outcome (reproductive effects): reproductive; development; fertility; sperm; ovary; pregnancy; ano-genital; estrus.

Based on the keywords, the following search strings were prepared to collect any studies of interest from PubMed, a major database that comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.

Studies on Humans, Carcinogenic effects

((epidemiologic* OR observation* OR "cross sectional" OR "case control" OR worker OR military OR population OR child OR employ*) AND (EMF OR RF OR 5G OR "radiofrequency radiation" OR radiofrequency OR "electromagnetic field" OR "electromagnetic radiation") AND (cancer OR tumour)) NOT (therapy OR ablation).

In vivo studies (rodents), Carcinogenic effects

(("in vivo" OR experimental OR animal OR rodent* OR rat OR mouse OR mice OR hamster* OR rabbit*) AND (EMF OR RF OR 5G OR "radiofrequency radiation" OR radiofrequency OR "electromagnetic field" OR "electromagnetic radiation") AND (cancer OR tumour)) NOT (therapy OR ablation)

Studies on Humans, Reproductive- developmental effects

((epidemiologic* OR observation* OR "cross sectional" OR "case control" OR worker OR military OR population OR child OR employ*) AND (EMF OR RF OR 5G OR "radiofrequency radiation" OR radiofrequency OR "electromagnetic field" OR "electromagnetic radiation") AND (reproductive OR development OR fertility OR sperm OR ovary OR pregnancy OR "ano genital" OR estrus)) NOT (therapy OR ablation)

In vivo (rodents) and Reproductive- developmental effects

(("in vivo" OR experimental OR animal OR rodent* OR rat OR mouse OR mice OR hamster* OR rabbit*) AND (EMF OR RF OR 5G OR "radiofrequency radiation" OR radiofrequency OR "electromagnetic field" OR "electromagnetic radiation") AND (reproductive OR development OR fertility OR sperm OR ovary OR pregnancy OR "ano genital" OR estrus)) NOT (therapy OR ablation).

We systematically searched the electronic academic database PubMed and the EMF Portal for potentially eligible records. The PubMed search occurred on 24 February 2020 for epidemiological and experimental carcinogenicity studies, and on the 20 July 2020 for epidemiological and experimental studies on reproductive outcomes - all searches being updated on the EMF Portal in January 2021. The first 100 results obtained from Google and Google Scholar were evaluated to check for any relevant, non-duplicate results. We also checked the bibliographies of the studies selected for the same purpose. Finally, we asked experts in the field to revise our lists and suggest any additional relevant studies.

2.3 Selection of the relevant literature

The "Population, Exposure, Comparator and Outcome" criteria (PECO Statement, Morgan et al. 2018) was adopted to clearly define the scope of this work and consequently the criteria for the selection of literature according to:

Population: RF-exposed population from in vivo studies, in particular experimental bioassays on rodents, as they represent the most predictive models for human health, and workers and the general population included in epidemiological studies;

Exposure: exposure to RF used in 5G networks, in particular the frequencies that were established as standard for use by the European Union: 450 MHz to6 GHz, and 24 to 100 GHz.

Comparator: untreated population (controls) from experimental bioassays on rodents, and, where this was available, groups of healthy or not exposed controls from epidemiological studies;

Type of outcome: health effects of particular concern that have been associated with the exposure to RF, namely reproductive effects, and carcinogenicity effects (Vornoli et al., 2019).

We considered all types of study design for the review; non-original studies, letters, and comments were not considered. Peer-reviewed articles in English, published from 1945 to January 2021 were considered. English is the most widely used language for scientific publications, and papers in other languages usually have an abstract available in English.

2.4 Screening process

The screening process was performed using the online systematic review app Rayyan QCRI. Selection of the literature was performed by two reviewers independently examining all references in two steps: in the first, the decision on exclusion/inclusion was based on title and abstract; in the second, the full texts of the potentially relevant articles were examined thoroughly to verify conformity with the aforementioned PECO criteria. At the second stage of selection, all inclusion/exclusion decisions and all doubts were discussed, solved and agreed upon by the two reviewers. Results of the selection process are illustrated in the following sections using PRISMA flow diagrams (Moher et al., 2009).

2.5 Extraction of information from the relevant literature

It was decided to use two different data-charting forms to extract information from the selected literature, since epidemiological and experimental studies have very different characteristics and peculiarities that need to be accounted for. The tools were chosen to achieve a complete and standardized collection of all information relevant to evaluating the conduct of the study, the exposure assessment and the health effects. The data chart for epidemiological studies was based on the one used for the series of reviews performed to elaborate, perfect and test the *WHO/ILO joint methodology for estimating the work-related burden of disease and injury* (Mandrioli et al, 2018; Sgargi et al., 2020). The data chart for experimental studies was based on the format used in IARC Monographs to evaluate carcinogenicity.

Both forms are validated tools, proven providers of exhaustive data on relevant literature. Calibration and uniformity was obtained through several rounds of independent blind trial extraction, discussion, and reaching of consensus among reviewers.

For epidemiological studies, a wide set of information was extracted, namely:
Ref ID; Type of study; Mode of data collection; Country; Year; N; Sex; Age; Occupation; Source of exposure; Duration of exposure; Frequency of exposure; Intensity of exposure; Any other co-exposure/adjustments; Method for exposure assessment; Observed health effects; Measure of observed health effects; Results; Conclusions; Authors; Affiliations; Conflict of interest; Funding.

For experimental studies, the extracted items from the literature were the following:
Reference ID; Type of study; Strain, Species (Sex); Exposure duration; Frequency; Intensity; Any other co-exposure; Exposure time - No of animals; Increased tumour incidence

The information was extracted by reviewers independently, and then double-checked by all reviewers and a senior expert.

2.6 Evidence synthesis

In finally assessing the results of the review for both epidemiological and experimental study, and for cancer and reproductive/developmental outcomes, we took into account the parameters indicated in (IARC Preamble, 2019), tailored to the needs of the present report, and valid for both end points (i.e. cancer and reproductive/developmental effects):

Sufficient evidence: A causal association between exposure to RF-EMF and the specific adverse effect has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and the specific adverse effect in studies in which chance, bias, and confounding factors were ruled out with reasonable confidence.

Limited evidence: A causal interpretation of the positive association observed in the body of evidence on exposure to RF-EMF and the specific adverse effect is credible, but chance, bias, or confounding factors cannot be ruled out with reasonable confidence.

No evidence: There are no data available or evidence suggesting lack of adverse effects (to be specified).

2.7 Overall evaluation of the present review

The results of the review for both cancer and reproductive/developmental outcomes, were finally assessed according to the criteria indicated in (IARC Preamble, 2019), tailored to the needs of the present report. Figure 8 presents the streams of evidence used for reaching the overall classification by IARC. The

reasoning that the IARC used to reach its evaluation is summarised, so the basis for the evaluation offered is transparent. The IARC Monograph Preamble integrates the major findings from studies of cancer in humans, cancer in experimental animals, and mechanistic evidence (IARC Preamble, 2019).

The IARC criteria regard cancer, but equally apply to assessment of effects on reproductive /developmental parameters. Mechanistic evidence was not considered in the present review, so we integrated the results for cancer and reproductive/developmental effects in humans solely with the results for cancer and reproductive/developmental effects in experimental animals, using the criteria indicated in Figure 9.

Figure 7 – IARC criteria for overall classifications (the evidence in bold italic represents the basis of the overall evaluation) (Source: IARC Preamble, 2019)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	**Classification based on strength of evidence**
Sufficient	Not necessary	Not necessary	Carcinogenic to humans (Group 1)
Limited or Inadequate	Sufficient	Strong (b) (1) (exposed humans)	
Limited	Sufficient	Strong (b) (2-3), Limited or Inadequate	Probably carcinogenic to humans (Group 2A)
Inadequate	Sufficient	Strong (b) (2) (human cells or tissues)	
Limited	Less than Sufficient	Strong (b) (1-3)	
Limited or Inadequate	Not necessary	Strong (a) (mechanistic class)	
Limited	Less than Sufficient	Limited or Inadequate	Possibly carcinogenic to humans (Group 2B)
Inadequate	Sufficient	Strong (b) (3), Limited or Inadequate	
Inadequate	Less than Sufficient	Strong (b) (1-3)	
Limited	Sufficient	Strong (c) (does not operate in humans)[b]	
Inadequate	Sufficient	Strong (c) (does not operate in humans)[b]	Not classifiable as to its carcinogenicity to humans (Group 3)
All other situations not listed above			

[a] Human cancer(s) with highest evaluation.
[b] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.

Figure 8 – Criteria for overall evaluation in the present review (FR1 and FR2)

Evidence in humans	Evidence in experimentalanimals	Evaluation based on strengh of evidence
Sufficient	Not necessary	Clear association between exposure and the adverse effect
Limited	Sufficient	Probable association between exposure and the adverse effect
Limited	Less than sufficient	Possible association between exposure and the adverse effect
Inadequate	Inadequate or limited	Not classificable

3. Limitations of the present review

3.1 Assessment of individual studies

Experimental studies adopt a standardised methodology, following specific guidelines, making it much easier to assess the individual outcomes and evaluate the quality of the study and of the results. Blinded assessment of outcomes, adequacy of the sample size, and appropriateness of statistical analysis were also evaluated and reported for each study, when available. We selected and analysed animal studies considering their compliance with the pertinent guidelines.

As regards epidemiological studies, errors of recall are a systematic danger with epidemiology affecting retrospective studies when participants are interviewed or compile questionnaires about exposure that occurred in the past. Usually the problem is that people's memories may be inaccurate or incomplete; this becomes a serious problem in case-control studies, where cases, whose health was affected, are likely to be more conscious and clear about past exposure, whereas controls are often less aware and remember less precisely. This may increase or diminish the cause-effect relation observed.

3.2 Exposure assessment

Exposure assessment is a critical issue in epidemiological studies of RF from mobile communication, as it can be very demanding and, when not up to the highest standards, can render the findings uninformative. We excluded studies which do not contribute any useful information due to shortcomings in their conduct and analysis.

Recall bias, as mentioned in the previous section, may be a major issue in all case-control studies with self-reported exposures. Furthermore, substantial misclassification is often a concern in studies where exposure assessment is based on job titles alone or mobile phone subscriptions alone; in such cases, this was merely an estimate of the exposure. For a meaningful interpretation, we tried to evaluate all original reports objectively, comprehensively and consistently, following a standardised method, but without presuming that our review could compete with any systematic review by a specific working group.

For experimental studies, the comparability of the procedures for dealing with the exposed and control groups, including sham exposure, quality of the exposure system and dosimetry, possibility of thermal effects due to tissue heating, were considered for achieving a correct analysis.

As described in the report, the frequencies are (amongst other things) related to depth of penetration into tissues, but other dimensions of exposure may also affect health outcomes. Given certain new features of 5G (MIMO, beamforming) and the related and acknowledged uncertainties regarding exposure and exposure assessment, it is questionable wether the studies on 1G-4G can be directly generalized to 5G (even when using the same frequencies, here FR1). These uncertainties in exposure characterisation will impact on exposure assessment for new studies (particularly for epidemiological studies on 5G, here FR2), and, in terms of risk assessment, some metrics of exposure to RF-EMF and associated adverse health outcomes (suggested or established) could be different. These considerations should not detract from the fact that the current evidence from 1G-4G studies is the best evidence available.

Experimental investigations also include studies that used a mobile phone in GSM mode with an active call at small distances from the animal's body. Active call mode is usually maintained throughout the experiment; the control group (sham exposed group) is treated with the mobile phone switched off. The exposure depends on the quality of the connection with the base station and exposure is measured throughout the study; we considered this kind of study adequate in terms of exposure assessment as they simulate the human counterpart situation.

3.3 Limits for a systematic review on 5G frequencies

STOA asked the author to collect the information available on the impact of 5G frequencies on health. The original aim was to follow the criteria of a systematic review, but we soon realized there are no adequate studies on millimetric waves for the relevant end points. We thus agreed to perform a narrative review of the lowest frequencies (FR1) already assessed by authoritative working groups at least for carcinogenic effects down to 2011, and a scoping review on millimetric waves (FR2) which, as expected, produced no adequate results. However, the review methodology (the scoping review) was kept same for both FR1 and FR2 outcomes.

3.4 Overall evaluation

A scoping review (SR) requires strong subject matter expertise in several disciplines. The assessment of individual studies represented a great challenge for the scientists involved in the review. A systematic assessment would require a full and in-depth review of the underlying studies. This is beyond the scope of this document, which is prepared for, and addressed to, the Members and staff of the European Parliament as background material to assist them in their parliamentary work.

The evaluation criteria adopted by the IARC as described in its Preamble (IARC Preamble, 2019) were tailored to and used for both cancer and reproductive /developmental effects. We used these consolidated criteria in order to work in complete transparency and allow reviewers to check our work.

This report was written by Dr Fiorella Belpoggi, an expert on RF-EMF, experimental carcinogenesis and experimental studies on reproductive and developmental health outcomes. The author was supported by experts with expertise in systematic/scoping review methodology (DM), biostatistics (DS), cancer research (AV), exposure assessment (FaB) and human reproduction and development (CF, AG). Together, the team fields strong expertise in most domains required for this review, perhaps with some room for improvement in cancer epidemiology.

4. Assessment of individual studies

4.1 Carcinogenicity by frequency range

4.1.1 Cancer in epidemiological studies: Studies evaluating health effects due to RF at a lower frequency range (FR1: 450 to 6000 MHz), which also includes the frequencies used in previous generations' broadband cellular networks (1G-4G)

The articles identified through database searching and other sources were 950. After removal of duplicates (20) and excluding non-pertinent articles (685) based on title and abstracts, 245 articles remained. Based on full-text screening, 90 papers were further excluded, so that the articles with appropriate frequencies to be included in this qualitative synthesis were 155.

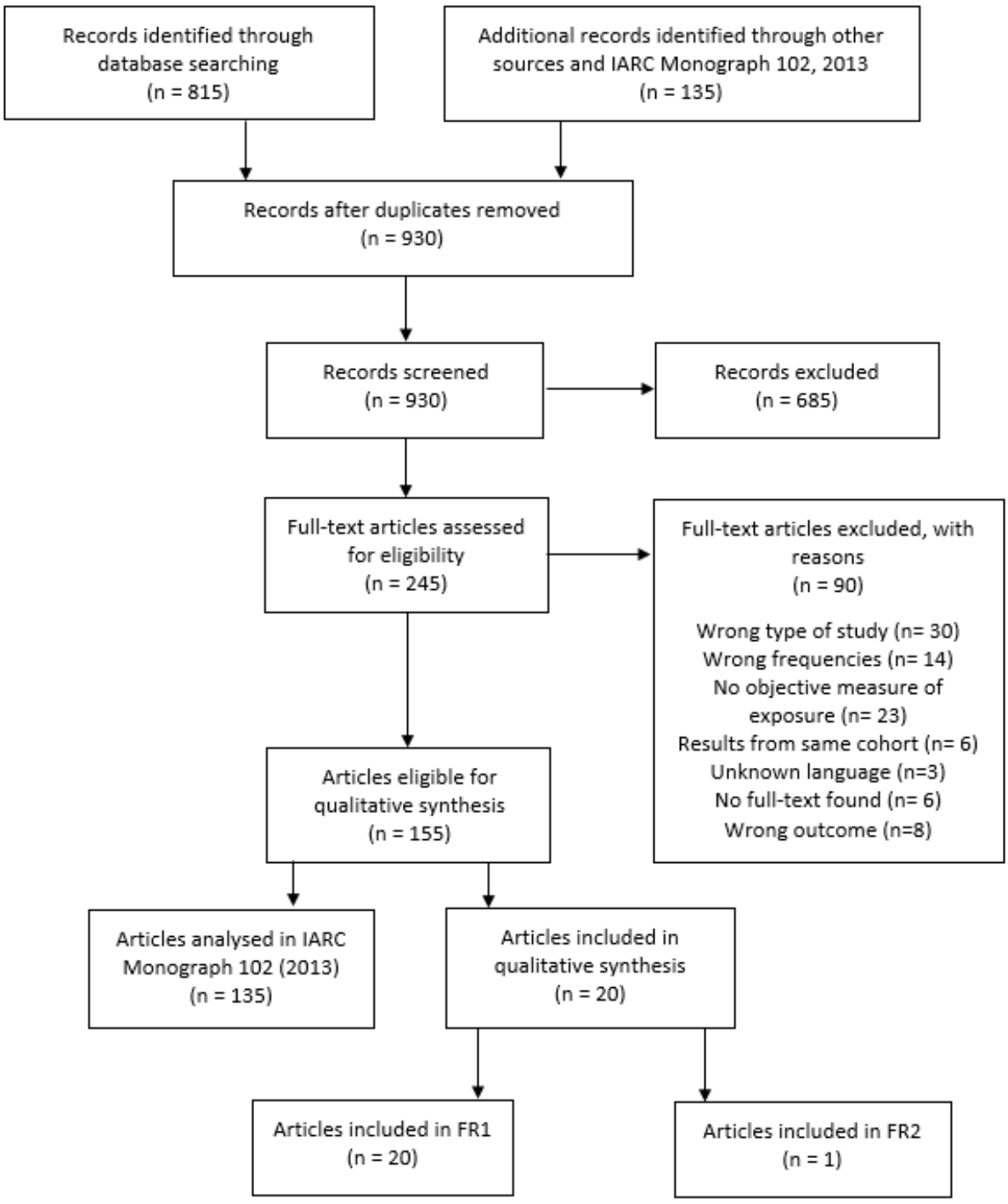
As further explained in the methodology section, we considered IARC (2013) as our key reference for all studies published until 2011: all original papers (135) that were included in the IARC monograph were analysed and referenced in this report as well; of course, for this report we considered only the final IARC classification. The remaining 20 articles published after 2011 were included in this scoping review.

At this stage, a separation based on frequency range was also performed: of the 20 papers included, all 20 reported exposures belonging to the band considered in FR1, and one also reported exposures regarding FR2, in particular MMW from occupational exposure to radar.

For each article, the abstract is presented, together with a table summarising the most important information; furthermore, a senior expert evaluated their adequacy for assessing carcinogenic effects (adequate/inadequate), and expressed an overall synthesis of the results (positive/negative/equivocal) following criteria described in the Methodology section.

The flow chart regarding the selection of papers on cancer epidemiological studies for FR1 is presented in Fig. 9.

Figure 9 – Flow diagram. Epidemiological studies on cancer (FR1)



KEY REFERENCE: IARC 2013

The IARC Monograph 102 (IARC, 2013) is the key reference for the present evaluation. In May 2011, after 1 year of preparing and reviewing drafts, 30 scientists from 14 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of radiofrequency electromagnetic fields (RF-EMF). This assessment was published as Volume 102 of the IARC Monographs (IARC, 2013). Epidemiological evidence for an association between RF-EMF and cancer comes from cohort, case-control, and time-trend studies. The populations in these studies were exposed to RF-EMF in occupational settings, from sources in the general environment, and from use of wireless (mobile and cordless) telephones, which is the most extensively studied exposure source.

One cohort study (Schüz et al., 2006) and five case-control studies (Muscat et al., 2000; Inskip et al., 2001; Auvinen et al., 2002; INTERPHONE Study Group, 2010; Hardell et al., 2011) were judged by the Working Group to offer potentially useful information regarding associations between use of wireless phones and glioma.

Although both the INTERPHONE study and the Swedish pooled analysis are susceptible to bias—due to recall error and selection for participation— the Working Group concluded that the findings could not be dismissed as reflecting bias alone, and that a causal interpretation between mobile phone RF-EMF exposure and glioma is possible. A similar conclusion was drawn for acoustic neuroma, although the case numbers were substantially smaller than for glioma. Additionally, a study from Japan (Sato et al., 2011) found some evidence of an increased risk of acoustic neuroma associated with ipsilateral mobile phone use.

For meningioma, parotid-gland tumours, leukaemia, lymphoma, and other tumour types, the Working Group found the available evidence insufficient to reach a conclusion on the potential association with mobile phone use. Epidemiological studies of individuals with potential occupational exposure to RF-EMF have investigated brain tumours, leukaemia, lymphoma, and other types of malignancy including uveal melanoma, and cancers of the testis, breast, lung, and skin. The Working Group noted that the studies had methodological limitations and the results were inconsistent. In reviewing studies that addressed the possible association between environmental exposure to RF-EMF and cancer, the Working Group found the available evidence insufficient for any conclusion.The Working Group concluded that there is "*limited evidence in humans*" for the carcinogenicity of RFEMF, based on positive associations between glioma and acoustic neuroma and exposure to RF-EMF from wireless phones.

At that time, a few members of the Working Group considered the current evidence in humans "inadequate". In their opinion there was inconsistency between the two case-control studies and a lack of an exposure-response relationship in the INTERPHONE study results; no increase in rates of glioma or acoustic neuroma was seen in the Danish cohort study (Shuz et al., 2006) and up to that time, reported time trends in incidence rates of glioma had not shown a parallel with time trends in mobile phone use (Baan et al., 2011).

REVIEW OF EPIDEMIOLOGICAL STUDIES 2011-2020

Starting from 2011, the present review evaluates by type of study and by year of publication (2011-2020) the epidemiological studies also summarized in Tables 1-4. The author adds to short abstracts her own brief comments on the results of the different studies.

CASE-CONTROL STUDIES (Tables 1, a-m)

1. Aydin et al., 2011.

Denmark, Sweden, Norway, and Switzerland. 2004-2008.CEFALO multicenter case-control study.

Mobile phone use association with brain tumour risk among children and adolescents is studied. CEFALO is a multicenter case-control study conducted in Denmark, Sweden, Norway, and Switzerland that includes all children and adolescents aged 7-19 years who were diagnosed with a brain tumour between 2004 and 2008. Interviews, in person, with 352 case patients (participation rate: 83%) and 646 control subjects (participation rate: 71%) and their parents. Control subjects were randomly selected from population registries and matched by age, sex, and geographical region. We asked about mobile phone use and included mobile phone operator records when available. Odds ratios (ORs) for brain tumour risk and 95% confidence intervals (CIs) were calculated using conditional logistic regression models. Regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumours compared with nonusers (OR = 1.36; 95% CI = 0.92 to 2.02). Children who started to use mobile phones at least 5 years ago were not at increased risk compared with those who had never regularly used mobile phones (OR = 1.26, 95% CI = 0.70 to 2.28). In a subset of study participants for whom operator recorded data were available, brain tumour risk was related to the time elapsed since the mobile phone subscription was started but not to amount of use. No increased risk of brain tumours was observed for brain areas receiving the highest amount of exposure. The absence of an exposure-response relationship either in terms of the amount of mobile phone use or by localisation of the brain tumour argues against a causal association.

Comment*: *Extent of exposure not assessed. The study was not statistically powered to detect small risk increases. Several RR increased in highest exposure category, albeit not statistically significant.

2. Atzmon et al., 2012.

Israel, diagnosis between 1989 and 2007. Population-based case control study.

The study was initiated to examine the claims of the residents of the Druze Isifya Village in Northern Israel that their high cancer rates were associated with past exposures to radiation from radio and cellular transmitters.To investigate the association between past exposure to RF/MW transmitters and cancer risks, familial cancer history and occupational exposures and indicators of life-style were taken into account; a population-based case-control study involved 307 residents, of whom 47 were diagnosed between 1989 and 2007 with different types of cancer and 260 controls. Cancer diagnoses were obtained from medical records. Exposure status of individual houses was determined from a map, based on the distances between each house and RF/MW antennas, and calculated using geographic information systems (GIS). Data on additional risk factors for cancer, like smoking and occupation, were obtained from individual questionnaires. The analysis was adjusted for measures of life style and occupational exposure, and Binary multiple logistic regressions was used, for all cancer sites and for individual cancer types for those cancers with at least 5 documented cases. Past occupational exposures to chemicals (e.g., pesticides) and electronics, were found to be strongly associated with increased cancer risks (all sites: OR=2.79; CI=1.14-6.82; P<0.05), but no discernible trend in overall cancer risk was associated with proximity to sources of past RF/MW radiation exposure (n=47 OR=1.00; CI=0.99-1.02; P>0.4). Colorectal cancer showed a negligible elevated adjusted risk associated with radiation intensity (n=11 OR=1.03; CI=1.01-1.05; P<0.01). There was evidence for an increased risk of cancers which were associated with chemicals in manufacturing and agriculture and electronics, where there may have been exposure to EMF, but the study did not confirm the suspicion of increased cancer risks associated with radiation for most cancer types in this village. Misclassification of past exposures could explain the negative finding.

Comment*: *No appropriate measurement of RF radiation was provided. Results inconclusive.

3. Li et al., 2012.

Taiwan, 1998-2007. Population-based case–control study (childhood neoplasms).

This population-based case-control study in Taiwan considered incident cases aged 15 years or less and admitted from 2003 to 2007 for all neoplasms (ICD-9-CM: 140-239) (n=2606), including 939 leukemia and 394 brain neoplasm cases. Controls were randomly selected, with a case/control ratio of 1:30 and matched by year of birth, from all non-neoplasm children insured in the same year when the index case was

admitted. Annual summarized power (ASP, watt-year) was calculated for each of the 71,185 mobile phone base stations (MPBS) in service between 1998 and 2007. Then, the annual power density (APD, watt-year/km(2)) of each township (n=367) was computed as a ratio of the total ASP of all MPBS in a township to the area of that particular township. Exposure of each study subject to radio frequency (RF) was indicated by the averaged APD within 5 years prior to the neoplasm diagnosis (cases) or July 1st of the year when the index case was admitted (controls) in the township where the subject lived. An unconditional logistic regression model with a generalized estimation equation was employed to calculate the covariate-adjusted odds ratio [AOR] of childhood neoplasm in relation to RF exposure. A higher than median averaged APD (approximately 168 WYs/km(2)) was significantly associated with an increased AOR for all neoplasms (1.13; 1.01 to 1.28), but not for leukaemia (1.23; 0.99 to 1.52) or brain neoplasm (1.14, 0.83 to 1.55). This study noted a significantly increased risk of all neoplasms in children with higher-than-median RF exposure to MPBS. The slightly elevated risk was seen for leukaemia and brain neoplasm, but was not statistically significant. These results may occur due to several methodological limitations.

Comment*: *The authors admit several methodological limitation. Inconclusive study.

4. Soderqvist et al., 2012.

Sweden, 2000-2003. Case–control study.

The objective of this case-control study was to assess whether the use of wireless phones is associated with an increased risk of tumour at this site. Sixty-nine patients with salivary gland tumours (63 with a parotid gland tumour) and 262 randomly recruited controls were included. Unconditional logistic regression - adjusted for age at diagnosis, sex, year of diagnosis and socioeconomic index - was used to produce odds ratios and 95% confidence intervals. The use of wireless phones was not associated with an overall increased risk of salivary gland tumours, odds ratio 0.8, 95% confidence interval 0.4-1.5. Neither was there an increased risk for the different phone types when calculated separately nor was there an increased risk for different latencies or when cumulative use was divided into three groups (1-1000, 1001-2000 and >2000 h). The overall results were similar for the risk of parotid gland tumours. In conclusion, our data add to the evidence against there being an increased risk for parotid gland tumours associated with light-to-moderate use of wireless phones and for less than 10 years of use but offers little information on risk related to more prolonged and/or heavy use.

Comment*: *Self-reported exposure from postal questionnaire. Any association for parotid gland tumours and light-to-moderate use of mobile phone.

5. Carlberg et al., 2013.

Sweden, 2007-2009. Case-control study.

The association between use of wireless phones and meningioma is studied. A case–control study on brain tumour cases of both genders aged 18–75 years and diagnosed during 2007–2009 is performed. One population-based control matched on gender and age was used to each case. Here we report on meningioma cases including all available controls. Exposures were assessed by a questionnaire. Unconditional logistic regression analysis was performed. In total 709 meningioma cases and 1,368 control subjects answered the questionnaire. Mobile phone use in total produced odds ratio (OR) = 1.0, 95% confidence interval (CI) = 0.7-1.4 and cordless phone use gave OR = 1.1, 95% CI = 0.8-1.5. The risk increased statistically significant per 100 h of cumulative use and highest OR was found in the fourth quartile (>2,376 hours) of cumulative use for all studied phone types. There was no statistically significant increased risk for ipsilateral mobile or cordless phone use, for meningioma in the temporal lobe or per year of latency. Tumour volume was not related to latency or cumulative use in hours of wireless phones. No conclusive evidence of an association between use of mobile and cordless phones and meningioma was found. An indication of increased risk was seen in the group with highest cumulative use but was not supported by statistically significant increasing risk with latency. Results for even longer latency periods of wireless phone use than in this study are desirable.

Comment*: *Self-reported exposure. No conclusive association for meningioma and use of mobile phone was found.

6. Hardell et al., 2013a.

Sweden, 2007-2009. Case-control study.

Previous studies have shown a consistent association between long-term use of mobile and cordless phones and glioma and acoustic neuroma, but not for meningioma. The aim of this study was to further explore the relationship between especially long-term (>10 years) use of wireless phones and the development of malignant brain tumours. A new case-control study of brain tumour cases of both genders aged 18-75 years and diagnosed during 2007-2009 was conducted. One population-based control matched on gender and age (within 5 years) was used in each case. Malignant cases including all available controls are reported. Exposures on e.g. use of mobile phones and cordless phones were assessed by a self-administered questionnaire. An unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index using the whole control sample. Of the cases with a malignant brain tumour, 87% (n=593) participated, and 85% (n=1,368) of controls in the whole study answered the questionnaire. The odds ratio (OR) for mobile phone use of the analogue type was 1.8, 95% confidence interval (CI)=1.04-3.3, increasing with >25 years of latency (time since first exposure) to an OR=3.3, 95% CI=1.6-6.9. Digital 2G mobile phone use rendered an OR=1.6, 95% CI=0.996-2.7, increasing with latency >15-20 years to an OR=2.1, 95% CI=1.2-3.6. The results for cordless phone use were OR=1.7, 95% CI=1.1-2.9, and, for latency of 15-20 years, the OR=2.1, 95% CI=1.2-3.8. Few participants had used a cordless phone for >20-25 years. Digital type of wireless phones (2G and 3G mobile phones, cordless phones) gave increased risk with latency >1-5 years, then a lower risk in the following latency groups, but again increasing risk with latency >15-20 years. Ipsilateral use resulted in a higher risk than contralateral mobile and cordless phone use. Higher ORs were calculated for tumours in the temporal and overlapping lobes. Using the meningioma cases in the same study as the reference entity gave somewhat higher ORs indicating that the results were unlikely to be explained by recall or observational bias. These findings provide support for the hypothesis that RF-EMFs play a role in both the initiation and promotion stages of carcinogenesis.

Comment*: *Self-reported exposure. This study confirms previous results of an association between heavy mobile and cordless phone use and malignant brain tumours.

7. Hardell et al., 2013b, Hardell and Carlberg, 2015.

Sweden, 1997-2003 and 2007-2009. Case-control study.

A case-control study of acoustic neuroma was previously conducted by the authors. Subjects of both genders aged 20-80 years, diagnosed during 1997-2003 in parts of Sweden, were included, and the results were published. A further study for the time period 2007-2009 including both men and women aged 18-75 years selected from throughout the country was performed. Similar methods were used for both study periods. In each, one population-based control, matched on gender and age (within five years), was identified from the Swedish Population Registry. Exposures were assessed by a self-administered questionnaire supplemented by a phone interview. Since the number of acoustic neuroma cases in the new study was low, pooled results from both study periods based on 316 participating cases and 3,530 controls were presented. An unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index (SEI). Use of mobile phones of the analogue type gave odds ratio (OR) = 2.9, 95% confidence interval (CI) = 2.0-4.3, increasing with >20 years latency (time since first exposure) to OR = 7.7, 95% CI = 2.8-21. Digital 2G mobile phone use gave OR = 1.5, 95% CI = 1.1-2.1, increasing with latency >15 years to an OR = 1.8, 95% CI = 0.8-4.2. The results for cordless phone use were OR = 1.5, 95% CI = 1.1-2.1, and, for latency of >20 years, OR = 6.5, 95% CI = 1.7-26. Digital type wireless phones (2G and 3G mobile phones and cordless phones) gave OR = 1.5, 95% CI = 1.1-2.0 increasing to OR = 8.1, 95% CI = 2.0-32 with latency >20 years. For total wireless phone use, the highest risk was calculated for the longest latency time >20 years: OR = 4.4, 95% CI = 2.2-9.0. Several of the calculations in the long

latency category were based on low numbers of exposed cases. Ipsilateral use resulted in a higher risk than contralateral for both mobile and cordless phones. OR increased per 100 h cumulative use and per year of latency for mobile phones and cordless phones, though the increase was not statistically significant for cordless phones. The percentage tumour volume increased per year of latency and per 100 h of cumulative use, statistically significant for analogue phones. This study confirmed previous results demonstrating an association between mobile and cordless phone use and acoustic neuroma.

A pooled analysis was performed of two case-control studies on malignant brain tumours with patients diagnosed during 1997–2003 and2007–2009. They were aged 20–80 years and 18–75 years, respectively, at the time of diagnosis. Only cases with histopathological verificationof the tumour were included. Population-based controls, matched on age and gender, were used. Exposures were assessed by questionnaire.The whole reference group was used in the unconditional regression analysis adjusted for gender, age, year of diagnosis, and socio-economicindex. In total, 1498 (89%) cases and 3530 (87%) controls participated. Mobile phone use increased the risk of glioma, OR = 1.3, 95%CI = 1.1–1.6 overall, increasing to OR = 3.0, 95% CI = 1.7–5.2 in the >25 year latency group. Use of cordless phones increased the risk toOR = 1.4, 95% CI = 1.1–1.7, with highest risk in the >15–20 years latency group yielding OR = 1.7, 95% CI = 1.1–2.5. The OR increasedstatistically significant both per 100 h of cumulative use, and per year of latency for mobile and cordless phone use. Highest ORs overall werefound for ipsilateral mobile or cordless phone use, OR = 1.8, 95% CI = 1.4–2.2 and OR = 1.7, 95% CI = 1.3–2.1, respectively. The highest riskwas found for glioma in the temporal lobe. First use of mobile or cordless phone before the age of 20 gave higher OR for glioma than in laterage groups.

Comment*: *Self-reported exposure.These studies confirm previous results demonstrating an association between heavy mobile and cordless phone use, with acoustic neuroma and glioma.

8. Coureau et al., 2014.

France. 2004-2006. CERENAT. Case-control study.

The objective was to analyse the association between mobile phone exposure and primary central nervous system tumours (gliomas and meningiomas) in adults. CERENAT is a multicenter case-control study carried out in four areas in France in 2004-2006. Data about mobile phone use were collected through a detailed questionnaire delivered in a face-to-face manner. Conditional logistic regression for matched sets was used to estimate adjusted ORs and 95% CIs. A total of 253 gliomas, 194 meningiomas and 892 matched controls selected from the local electoral rolls were analysed. No association with brain tumours was observed when comparing regular mobile phone users with non-users (OR=1.24; 95% CI 0.86 to 1.77 for gliomas, OR=0.90; 95% CI 0.61 to 1.34 for meningiomas). However, the positive association was statistically significant in the heaviest users when considering life-long cumulative duration (≥896 h, OR=2.89; 95% CI 1.41 to 5.93 for gliomas; OR=2.57; 95% CI 1.02 to 6.44 for meningiomas) and number of calls for gliomas (≥18,360 calls, OR=2.10, 95% CI 1.03 to 4.31). Risks were higher for gliomas, temporal tumours, occupational and urban mobile phone use. These additional data support previous findings concerning a possible association between heavy mobile phone use and brain tumours.

***Comment*: *Self reported exposure with face to face interview by trained personel.This study confirms previous results of a possible association between heavy mobile phone use and malignant brain tumours*.**

9. Pettersson et al., 2014.

Sweden, 2002-2007. Population-based case-control study.

A population-based, nation-wide, case-control study of acoustic neuroma in Sweden was conducted. Eligible cases were persons aged 20 to 69 years, who were diagnosed between 2002 and 2007. Controls were randomly selected from the population registry, matched on age, sex, and residential area. Postal questionnaires were completed by 451 cases (83%) and 710 controls (65%). Ever having used mobile phones regularly (defined as weekly use for at least 6 months) was associated with an odds ratio (OR) of

1.18 (95% confidence interval = 0.88 to 1.59). The association was weaker for the longest induction time (≥10 years) (1.11 [0.76 to 1.61]) and for regular use on the tumour side (0.98 [0.68 to 1.43]). The OR for the highest quartile of cumulative calling time (≥680 hours) was 1.46 (0.98 to 2.17). Restricting analyses to histologically confirmed cases reduced all ORs; the OR for ≥680 hours was 1.14 (0.63 to 2.07). A similar pattern was seen for cordless land-line phones, although with slightly higher ORs. Analyses of the complete history of laterality of mobile phone revealed considerable bias in laterality analyses. The findings do not support the hypothesis that long-term mobile phone use increases the risk of acoustic neuroma. The study suggests that phone use might increase the likelihood that an acoustic neuroma case is detected and that there could be bias in the laterality analyses performed in previous studies

Comment: Self-reported exposure. Weak evidence of association between heavy mobile phone use and acoustic neuroma.

10. Yoon et al., 2015.

Korea; 2002- 2007; case- control study.

Study methods were based on the International Interphone study that aimed to evaluate possible adverse effects of mobile phone use. This study included 285 histologically-confirmed Korean patients 15 to 69 years of age, with gliomas diagnosed between 2002 and 2007 in 9 hospitals. The 285 individually matched controls were healthy individuals that had their medical check-up in the same hospitals. Unconditional logistic regression was used to calculate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for use of mobile phones. For the entire group, no significant relationship was investigated between gliomas and regular use of mobile phones, types of mobile phones, lifetime years of use, monthly service fee, and the other exposure indices. Analyses restricted to self-respondents showed similar results. For ipsilateral users, whose body side for usual mobile phone use matched the location of glioma, the aORs (95% CIs) for lifetime years of use and cumulative hours of use were 1.25 (0.55 to 2.88) and 1.77 (0.32 to 1.84), respectively. However, contralateral users showed a slightly lower risk than ipsilateral users. Results do not support the hypothesis that the use of mobile phones increases the risk of glioma; however, we found a non-significant increase in risk among ipsilateral users. These findings suggest further evaluation for glioma risk among long-term mobile phone users.

Comment: Self reported exposure. Weak evidence of association between mobile phone use and brain tumour is found among ipsilateral users.

11. Al-Qahtani, 2016.

Saudi Arabia; 1996-2013; Retrospective case-control study.

A total of 26 patients diagnosed with parotid gland tumours and 61 healthy controls were enrolled through a hospital-based retrospective case-control study. The patients were referred and admitted to a tertiary hospital from January 1996 to March 2013. The Odds of exposure were 3.47 times higher among patients compared to their controls. 95% CI suggested that the true Odds Ratio (OR) at the population level could be somewhere between 1.3 and 9.23 and so the observed OR was statistically significant at 5% level of significance. Overall, an association between the exposure of cellular phone use for more than 1 hour daily and parotid tumour was observed. This association should be interpreted with caution because of the relatively small sample size.

Comment: Small sample size; poor methodology. Inconclusive study.

12. Satta et al., 2018.

Italy; 1998–2004; Population-based case-control study as part of the European multicenter study EPILYMPH.

A case-control study comprised of 322 patients and 444 individuals serving as controls in Sardinia, Italy in 1998-2004. Questionnaire information included the self-reported distance of the three longest held

residential addresses from fixed radio-television transmitters and mobile phone base stations. For each address within a 500-meter radius from a mobile phone base station, RF-EMF intensity using predictions from spatial models was estimated, and RF-EMF measurements performed at the door in the subset of the longest held addresses within a 250-meter radius. Risk of lymphoma and its major subtypes associated with the RF-EMF exposure metrics with unconditional logistic regression, adjusting by age, gender and years of education. Risk associated with residence in proximity (within 50 meters) to fixed radio-television transmitters was likewise elevated for lymphoma overall [odds ratio = 2.7, 95% confidence interval = 1.5-4.6], and for the major lymphoma subtypes. With reference to mobile phone base stations, the authors did not observe an association with either the self-reported, or the geocoded distance from mobile phone base stations. RF-EMF measurements did not vary by case-control status. By comparing the self-reports to the geocoded data, cases tended to underestimate the distance from mobile phone base stations differentially from the controls (P = 0.073). The interpretation of findings is compromised by the limited study size, particularly in the analysis of the individual lymphoma subtypes, and the unavailability of the spatial coordinates of radio-television transmitters. Nonetheless, our results do not support the hypothesis of a link between environmental exposure to RF-EMF from mobile phone base stations and risk of lymphoma subtypes.

Comment*: *Limited study size, exposure assessment unclear (far field, radiobase-stations). The study does not support the hypothesis of a link between environmental exposure to RF-EMF from mobile phone base stations and risk of lymphoma subtypes.

13. Balekouzou et al., 2017.

Central Africa. Case- control study.

Breast cancer is recognized as a major public health problem in developing countries; however, there is very little evidence of behavioral factors associated with breast cancer risk. This study was conducted to identify lifestyles as risk factors for breast cancer among Central African women. A case-control study was conducted with 174 cases confirmed histologically by the pathology unit of the National Laboratory and 348 age-matched controls. Data collection tools included a questionnaire with interviews and medical records of patients. Data were analyzed using SPSS software version 20. Odd ratio (OR) and 95% confidence intervals (95% CI) were obtained by unconditional logistic regression. In total, 522 women were studied with a mean age of 45.8 (SD = 13.4) years. By unconditional logistic regression model, women with breast cancer were more likely to have attained illiterate and elementary education level [11.23 (95% CI, 4.65±27.14) and 2.40 (95% CI, 1.15±4.99)], married [2.09 (95% CI, 1.18±3.71)], positive family history [2.31 (95% CI, 1.36±3.91)], radiation exposure [8.21 (95% CI, 5.04±13.38)], consumption charcuterie [10.82 (95% CI, 2.39±48.90)], fresh fish consumption [4.26 (95% CI, 1.56±11.65)], groundnut consumption [6.46 (95% CI, 2.57± 16.27)], soybean consumption [16.74 (95% CI, 8.03±39.84)], alcohol [2.53 (95% CI, 1.39± 4.60)], habit of keeping money in bras[3.57 (95% CI, 2.24±5.69)], overweight [5.36 (95% CI, 4.46±24.57)] and obesity [3.11(95% CI, 2.39±20.42)]. However, decreased risk of breast cancer was associated with being employed [0.32 (95% CI, 0.19±0.56)], urban residence [0.16 (95% CI, 0.07±0.37)], groundnut oil consumption [0.05 (95% CI, 0.02±0.14)], wine consumption [0.16 (95% CI, 0.09±0.26)], non habit of keeping cell phone in bras [0.56 (95% CI, 0.35±0.89)] and physical activity [0.71(95% CI, 0.14±0.84)]. The study showed that little or no education, marriage, positive family history of cancer, radiation exposure, charcuterie, fresh fish, groundnut, soybean, alcohol, habit of keeping money in bras, overweight and obesity were associated with breast cancer risk among Central African women living in Bangui. Women living in Bangui should be more cautious on the behavioral risk associated with breast cancer.

Comment*: *Limitations in self reporting of data. Many confounders. Any conclusive finding for an association beetween keeping cell phone in bras and mammary cancer.

14. Vila et al., 2018.

Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom; 2000-2004; INTEROCC study: international case-control study on mobilephone use and brain cancer risk in seven countries.

This study examines the relation between occupational RF and intermediate frequency (IF) EMF exposure and brain tumour (glioma and meningioma) risk in the INTEROCC multinational population-based case-control study (with nearly 4000 cases and over 5000 controls), using a novel exposure assessment approach. Individual indices of cumulative exposure to RF and IF-EMF (overall and in specific exposure time windows) were assigned to study participants using a source-exposure matrix and detailed interview data on work with or nearby EMF sources. Conditional logistic regression was used to investigate associations with glioma and meningioma risk. Overall, around 10% of study participants were exposed to RF while only 1% were exposed to IF-EMF. There was no clear evidence for a positive association between RF or IF-EMF and the brain tumours studied, with most results showing either no association or odds ratios (ORs) below 1.0. The largest adjusted ORs were obtained for cumulative exposure to RF magnetic fields (as A/m-years) in the highest exposed category (≥90th percentile) for the most recent exposure time window (1-4 years before the diagnosis or 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). Despite the improved exposure assessment approach used in this study, no clear associations were identified. However, the results obtained for recent exposure to RF electric and magnetic fields are suggestive of a potential role in brain tumour promotion/progression and should be further investigated.

Comment*: *Study suggestive of a potential role in brain tumour promotion/progression.

15. Luo et al., 2019.

USA. 2010-2011. Population-based case-control study.

This study aims to investigate the association between cell phone use and thyroid cancer. A population-based case-control study was conducted in Connecticut between 2010 and 2011 including 462 histologically confirmed thyroid cancer cases and 498 population-based controls. Multivariate unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for associations between cell phone use and thyroid cancer. Cell phone use was not associated with thyroid cancer (OR: 1.05, 95% CI: 0.74–1.48). A suggestive increase in risk of thyroid microcarcinoma (tumour size ≤10mm) was observed for long-term and more frequent users. Compared to cell phone non-users, several groups had nonstatistically significantly increased risk of thyroid microcarcinoma: individuals who had used a cell phone >15 years (OR: 1.29, 95% CI: 0.83–2.00), who had used a cell phone >2 hours per day (OR: 1.40, 95% CI: 0.83–2.35), who had the most cumulative use hours (OR: 1.58, 95% CI: 0.98–2.54), and who had the most cumulative calls (OR: 1.20, 95% CI: 0.78–1.84) Cumulative cell phone use was estimated by multiplying cell phone use hours or calls per day with the duration of use. Each variable was categorized into tertiles based on its distribution among controls.. This study found no significant association between cell phone use and thyroid cancer. A suggestive elevated risk of thyroid microcarcinoma associated with long-term and more frequent uses warrants further investigation.

Comment*: *Self reported exposure. No significant association was found, but a suggestive elevated risk of thyroid microcarcinoma associated with long-term and more frequent users.

ECOLOGICAL STUDIES (Table 2, a)

16. Gonzalez Rubio et al., 2017.

Spain. 2012-2015. Case-control ecological study.

This paper presents the results of a preliminary epidemiological study, combining Epidemiology, Statistics and Geographical Information Systems (GIS), in which the correlation between exposure to RF-EMF in the city of Albacete (166,000 inhabitants, southeast Spain) and the incidence of several cancers with unspecific

causes (lymphomas, and brain tumours) are analysed. Statistical tools to analyze the spatial point patterns and aggregate data so as to study the spatial randomness and to determine the zones with the highest incidence from 95 tumours studied (65 lymphomas, 12 gliomas and 18 meningiomas) were used. A correlation (Spearman) study between the personal exposure to RF-EMF in 14 frequency bands, recorded by an EME Spy 140 (Satimo) exposimeter in the city's administrative regions, and the incidence of the tumours registered from January 2012 to May 2015. The cancer cases studied have a random spatial distribution inside the city. On the other hand, and by means of an ecological study, the exposure to RF-EMF registered in the city of Albacete shows little correlation with the incidence of the tumours studied (gliomas (ρ=0.15), meningiomas (ρ=0.19) and lymphomas (ρ=-0.03)). The proposed methodology inaugurates an unexplored analysis path in this field.

***Comment*: *Little correlation between environmental exposure to RF-EMF and glioma, meningioma and lymphomas. Exposure assessment not clear*.**

COHORT STUDIES (Tables 3, a-d)

17. Frei et al., 2011.

Denmark. Subscribers and non-subscribers of mobile phones before 1995.

All Danes aged ≥30 and born in Denmark after 1925, subdivided into subscribers and non-subscribers of mobile phones before 1995. Main outcome measures Risk of tumours of the central nervous system, identified from the complete Danish Cancer Register. Sex specific incidence rate ratios estimated with log linear Poisson regression models adjusted for age, calendar period, education, and disposable income. Results 358,403 subscription holders accrued 3.8 million person years. In the follow-up period 1990-2007, there were 10,729 cases of tumours of the central nervous system. The risk of such tumours was close to unity for both men and women. When restricted to individuals with the longest mobile phone use—that is, ≥13 years of subscription—the incidence rate ratio was 1.03 (95% confidence interval 0.83 to 1.27) in men and 0.91 (0.41 to 2.04) in women. Among those with subscriptions of ≥10 years, ratios were 1.04 (0.85 to 1.26) in men and 1.04 (0.56 to 1.95) in women for glioma and 0.90 (0.57 to 1.42) in men and 0.93 (0.46 to 1.87) in women for meningioma. There was no indication of dose-response relation either by years since first subscription for a mobile phone or by anatomical location of the tumour—that is, in regions of the brain closest to where the handset is usually held to the head. Conclusions In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association.

Comment*: *Limits in exposure assessment. No increased risks of tumours of the central nervous system.

18. Benson et al., 2013.

UK. Million Women Study. 1999-2005 and 2005-2009. Prospective cohort study.

The relation between mobile phone use and incidence of intracranial central nervous system (CNS) tumours and other cancers was examined in 791,710 middle-aged women in a UK prospective cohort, the Million Women Study. Cox regression models were used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs). Women reported mobile phone use in 1999 to 2005 and again in 2009. Results During 7 years' follow-up, 51 680 incident invasive cancers and 1 261 incident intracranial CNS tumours occurred. Risk among ever vs never users of mobile phones was not increased for all intracranial CNS tumours (RR=1.01, 95% CI=0.90–1.14, P=0.82), for specified CNS tumour types nor for cancer at 18 other specified sites. For longterm users compared with never users, there was no appreciable association for glioma (10þ years: RR¼0.78, 95% CI¼0.55–1.10, P¼0.16) or meningioma (10+ years: RR=1.10, 95% CI=0.66–1.84, P=0.71). For acoustic neuroma, there was an increase in risk with long term use vs never use (10+ years: RR=2.46, 95% CI=1.07– 5.64, P=0.03), the risk increasing with duration of use (trend among users, P=0.03). Conclusions In this large prospective study, mobile phone use was not associated with increased incidence of glioma, meningioma or non-CNS cancers.

Comment*: *Self reported exposure. For acoustic neuroma, there was an increase in risk with long term use vs never use; the risk increasing with duration of use.

19. Poulsen et al., 2013.

Denmark, 1982-1995, follow up until 2007. Cohort study: CANULI study of social inequality and cancer incidence and survival.

In a nationwide cohort study, 355,701 private mobile phone subscribers in Denmark from 1987 to 1995 were followed up through 2007. We calculated incidence rate ratios (IRRs) for melanoma, basal cell carcinoma, and squamous cell carcinoma by using Poisson regression models adjusted for age, calendar period, educational level, and income. Separate IRRs for head/neck tumours and torso/leg tumours were compared (IRR ratios) to further address potential confounders. We observed no overall increased risk for basal cell carcinoma, squamous cell carcinoma, or melanoma of the head and neck. After a follow-up period of at least 13 years, the IRRs for basal cell carcinoma and squamous cell carcinoma remained near unity. Among men, the IRR for melanoma of the head and neck was 1.20 (95% confidence interval: 0.65, 2.22) after a minimum 13-year follow-up, whereas the corresponding IRR for the torso and legs was 1.16 (95% confidence interval: 0.91, 1.47), yielding an IRR ratio of 1.04 (95% confidence interval: 0.54, 2.00). A similar risk pattern was seen among women, though it was based on smaller numbers. In this large, population-based cohort study, little evidence of an increased skin cancer risk was observed among mobile phone users.

Comment*: *Extent of exposure not assessed. Little evidence of an increased skin cancer risk was observed among mobile phone users.

20. Hauri et al., 2014.

Switzerland. 2000-2008. Census-based cohort study (far field, radiobase stations).

The association between exposure to radio-frequency electromagnetic fields (RF-EMFs) from broadcasting transmitters and childhood cancer was investigated. Time-to-event analysis including children under age 16 years living in Switzerland on December 5, 2000 was performed. Follow-up lasted until December 31, 2008. All children living in Switzerland for some time between 1985 and 2008 were included in an incidence density cohort. RF-EMF exposure from broadcasting transmitters was modeled. Based on 997 cancer cases, adjusted hazard ratios in the time-to-event analysis for the highest exposure category (>0.2 V/m) as compared with the reference category (<0.05 V/m) were 1.03 (95% confidence interval (CI): 0.74, 1.43) for all cancers, 0.55 (95% CI: 0.26, 1.19) for childhood leukemia, and 1.68 (95% CI: 0.98, 2.91) for childhood central nervous system (CNS) tumours. Results of the incidence density analysis, based on 4,246 cancer cases, were similar for all types of cancer and leukemia but did not indicate a CNS tumour risk (incidence rate ratio = 1.03, 95% CI: 0.73, 1.46). This large census-based cohort study did not suggest an association between predicted RF-EMF exposure from broadcasting and childhood leukemia. Results for CNS tumours were less consistent, but the most comprehensive analysis did not suggest an association.

Comment: Limits in the assessment of residential exposure. No association between RF-EMF and cancer in children is suggested.

Table 1 – Cancer in epidemiological case-control studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
1. Aydin et al. 2011. Denmark, Sweden, Norway, and Switzerland; 2004-2008; CEFALO-Multicenter case-control study.	352 cases; 646 population-based matched controls (M and F). Age 7-19 years. Data from reports from pediatric, oncology, and neurosurgery departments and from national population-based registries.	Use of mobile phones, assessed by face-to-face interviews with the subjects and their parents.	Mobile phone use.	Intracranial central nervous system tumours..	**Odds ratio (OR) and 95% confidence intervals (95% CI) from conditional logistic regression. Trend from two-sided Wald testOR (95% CI) for brain tumours**	**p-value for trend**	Education, family history of cancer, past medical radiation exposure to the head, maternal smoking during pregnancy, past head injuries, use of baby monitors near the head, use of cordless phones, contact with animals, location where the child lived before age, having siblings, birth weight, born premature, ever doctor-diagnosed asthma, ever doctor-diagnosed atopic eczema, and ever doctor-diagnosed hay fever.	Adequate/ Equivocal (brain tumour) Children and adolescent
			Regular use (at least once per week, > 6 months)					
			No		1.0 (ref.)			
			Yes		1.36 (0.92 -2.02)			
			Time since first use (years)					
			Never regular user		1.0 (ref.)	0.37		
			≤3.3		1.35 (0.89 to 2.04)			
			3.3–5.0		1.47 (0.87 to 2.49)			
			>5.0		1.26 (0.70 to 2.28)			
			Cumulative duration of calls (hours)					
			Never regular user		1.0 (ref.)	0.42		
			≤35		1.33 (0.89 to 2.01)			
			36-144		1.44 (0.85 to 2.44)			
			>144		1.55 (0.86 to 2.82)			

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
2. Atzmon et al 2012. Israel, diagnosis between 1989 and 2007. Population-based case-control study/ The present analysis is a retrospective follow up study at diagnosis.	307 subjects, of whom 47 cases (M and F), median age 48. Cases from medical documents with confirmed diagnosis of cancer. Face-to-face interviews in the participant's home.	Exposure to radio and cellular transmitters located in the village prior to 2000. Individual exposure (E) was estimated using the following formula: E=1/D2, where D is distance (in meters) between a house and the closest transmitter.	Individual exposure and years of residence.	Cancer: colorectal (11), breast cancer (10), lymphoma (6), leukemia (3), lungs (2), uterine (2), liver (2), stomach (2), ovarian (2), pancreas (2), prostate (2), cervix (1), brain (1), and bladder (1). Odds ratios and confidence intervals (OR, 95% CI) from binary logistic regression model.	**OR (95% CI), Colorectal**	**OR (95% CI), Lymphoma**	**OR (95% CI), Uterine**	**OR (95% CI), Prostate**	**OR (95% CI), Brain**	Duration of residence in the same house; alcohol consumption; nutritional habits; frequency of physical exercise; use of cellular phones; exposure to wireless equipment in the house; use of oral contraceptives or hormones replacement therapy and income	**Inadequate**
			Radiation intensity		1.03 (1.01-1.05)	0.95 (0.86-1.06)	0.99 (0.91-1.07)	1.67 (0.04-61.04)	12.45 (0.34–453.54)	**No appropriate measurement of RF exposure**	
			Years of exposure to radiation		0.97 (0.877-1.082)	0.95 (0.82-1.11)	1.12 (0.88-1.42)	0.97 (0.86-1.10)	0.96 (0.84–1.11)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued c)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
3. Li et al. 2012. Taiwan; 2003-2007; Population-based case-control study.	2606 childhood neoplasm cases (M and F), 78180 matched controls (939-28170 for leukemia; 394- 11820 for brain neoplasms). Age < 15 years. Clinical data from the National Health Insurance Research Database (NHIRD).	RF exposure metric was estimated from the averaged Annual Power Density for the five-year period prior to the neoplasm diagnosis in the township where the subject lived at the time of neoplasm diagnosis. Information on MPBS from the Taiwan National Communication Council (NCC).	Exposure to mobile phone base stations (MPBS): 800-900 MHz; 1800-2200 Mhz. Estimate APD	All neoplasms; Leukemia; Brain neoplasms. Odds ratio (OR) and 95% confidence intervals (95% CI) from multiple unconditional logistic regression models	**OR (95% CI) for all neplasms**	**OR (95% CI) for leukemia**	**OR (95% CI) for brain neplasms**	age, gender, calendar year of neoplasm diagnosis, urbanisation level of township, and high-voltage (69/161/345 kV) transmission line (HVTL) density of the township. Limits in exposure assessment	Inadequate
			Level of exposure (compared to median= 167.02 WYs/km2						
			<Median		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			≥Median		1.13 (1.01–1.28)	1.23 (0.99-1.52)	1.14 (0.83-1.55)		
			p-value		0.048	0.052	0.426		
4. Soderqvist et al. 2012. Sweden, 2000-2003. Case–control study.	78 cases; 312 controls (M and F), age 22–80, median 69. Patients were recruited as reported by the Regional Oncology Centre of Uppsala/Orebro and Linkoping, including nine of 21 Swedish counties. Controls were drawn from the population registry at random.	Use of wireless phones, i.e. both mobile and cordless phones. Self-reported exposure from postal questionnaire.	The cumulative number of hours of use was calculated using the number of years and average time used per day. Cumulative hours of use was also divided into three groups, 1–1000, 1001–2000 and more than 2000 h. Use of wireless phones within 1 year before diagnoses were treated as unexposed.	Salivary gland tumour. Odds ratios and 95% confidence intervals from unconditional logistic regression.	**OR (95% CI) for Mobile phones**	**OR (95% CI) for cordless phones**	**OR (95% CI) for wireless phones, total**	No information available Limits in exposure assessment	Inadequate
			Cumulative use (h)						
			Unexposed		1 (Ref.)	1 (Ref.)	1 (Ref.)		
			1–1000		0.9 (0.4–1.7)	0.6 (0.3–1.3)	0.8 (0.5-1.6)		
			1001–2000		0.7 (0.1–3.6)	1.2 (0.2–7.8)	0.7 (0.2–2.7)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued d)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
5. Carlberg et al. 2013. Sweden; 2007-2009; Case-control study.	709 cases; 1368 population-based matched controls (M and F). Age 18-75 years. Data from a cancer register.	Use of wireless phones (mobile and cordless phones), assessed by a self-administered structured phone questionnaire.	Mobile phone use (UMTS, 4G); cordless phone use (1900 MHz).	Meningioma. Odds ratio (OR) and 95% confidence intervals (95% CI) from unconditional logistic regression.	**OR (95% CI) for meningioma, Digital (2G)**	**OR (95% CI) for meningioma, Digital (UMTS, 3G)**	**OR (95% CI) for meningioma, Cordless phone**	**OR (95% CI) for meningioma, Digital type**	Gender, age, year of diagnosis, socio-economic index (SEI).	Adequate/ Positive (meningioma)
			Cumulative use of wireless phones (h)							
			<39-405		1.0 (0.7-1.4)	0.7 (0.3-1.3)	1.0 (0.7-1.4)	1.1 (0.8-1.6)		
			406–1091		1.0(0.7-1.5)	0.4 (0.1-1.2)	0.9 (0.6-1.3)	0.9 (0.6-1.3)		
			1092-2376		0.9 (0.6-1.4)	0.6 (0.2-1.8)	1.2 (0.8-1.8)	0.9 (0.6-1.3)		
			>2376		1.5 (0.9-2.3)	7.3 (1.2-46)	1.8 (1.2-2.8)	1.4 (0.96-2.6)		
			P for trend		0.06	0.04	0.0003	0.002		
6. Hardell et al. 2013a. Sweden, 2007-2009. Case-control study.	593 cases, 1368 controls (M and F), age 18-75. Newly diagnosed brain tumour cases from the regional and national Swedish cancer registers. The Swedish Population Registry was used for identification of controls.	Use of wireless phones, i.e. both mobile and cordless phones. Self-reported exposure from self-administered questionnaire supplemented by a phone interview.	Frequency of use; Duration of exposure.	Malignant brain tumours. Odds ratio (OR) and 95% confidence interval (CI) from unconditional logistic regression analysis.	**OR (95% CI) for Mobile phone use (Analogue, 2G, 3G)**	**OR (95% CI) for digital phone use (2G, 3G, cordless)**	**OR (95% CI) for all wireless phones**		Occupational history, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionising radiation.	Adequate/ Positive (Malignant brain tumours)
			Frequency of use							
			Non users (<1 years)		1 (Ref.)	1 (Ref.)	1 (Ref.)			
			Users (>1 years)		1.6 (0.99 - 2.7)	1.7 (1.04 - 2.8)	1.7 (1.04 - 2.8)			
			Duration of use (years)							
			1-5		1.8 (1.002 - 3.4)	2.6 (1.4 - 4.9)	2.6 (1.4 - 5.0)			
			5-10		1.7 (0.98 - 2.8)	1.6 (0.9 - 2.7)	1.6 (0.98 - 2.8)			
			10-15		1.3 (0.8 - 2.2)	1.4 (0.8 - 2.3)	1.3 (0.8 - 2.2)			
			15-20		1.5 (0.8 - 2.6)	2.2 (1.3 - 3.6)	1.7 (1.02 - 3.0)			
			20-25		1.9 (1.1 - 3.5)	1.5 (0.5 - 4.6)	1.9 (1.04 - 3.4)			
			>25		2.9 (1.4 - 5.8)	-	3.0 (1.5 - 6.0)			

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued e)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
7. Hardell et al. 2013b and Hardell and Carlberg 2015. Sweden, 1997-2003 and 2007-2009. Pooled case-control study.	316 cases of acoustic neuroma, 3530 controls (M and F), aged 20–80 years (1997–2003) and18–75 years (2007–2009) at the time of diagnosis. Cases reported from cancer registries.	Use of wireless phones, i.e. both mobile and cordless phones. Self-reported exposure from self-administered questionnaire supplemented by a phone interview.		Acoustic neuroma. Odds ratio (OR) and 95% confidence intervals (CI) from unconditional logistic regression analysis.	**OR (95% CI) for Mobile phone use (Analogue, 2G, 3G)**	**OR (95% CI) for digital phone use (2G, 3G, cordless)**	**OR (95% CI) for all wireless phones**	Occupational history, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionising radiation.	Adequate/ Positive (acoustic neuroma and glioma)
			Frequency of use						
			Non users (<1 years)		1 (Ref.)	1 (Ref.)	1 (Ref.)		
			Users (>1 years)		1.6 (1.2 - 2.2)	1.5 (1.1 - 2.0)	1.5 (1.1 - 2.0)		
			Duration of use (years)					Positive association in heavy users	
			1-5		1.3 (0.9 - 1.8)	1.4 (1.01 - 1.9)	1.2 (0.8 - 1.6)		
			5-10		2.3 (1.6 - 3.3)	1.6 (1.1 - 2.3)	1.9 (1.3 - 2.7)		
			10-15		2.1 (1.3 - 3.5)	1.6 (0.97 - 2.8)	2.0 (1.3 - 3.2)		
			15-20		2.1 (1.02 - 4.2)	1.1 (0.5 - 2.5)	1.7 (0.9 - 3.3)		
			>20		4.5 (2.1 - 9.5)	8.1 (2.0 - 32)	4.4 (2.2 - 9.0)		
	1380 cases of glioma, 3530 controls (M and F), aged 20–80 years (1997–2003) and18–75 years (2007–2009) at the time of diagnosis. Cases reported from cancer registries.	Use of wireless phones, i.e. both mobile and cordless phones. Self-reported exposure from self-administered mailed questionnaire.		Glioma. Odds ratio (OR) and 95% confidence intervals (CI) from unconditional logistic regression analysis.	**OR (95% CI) for Mobile phone use (Analogue, 2G, 3G)**	**OR (95% CI) for digital phone use (2G, 3G, cordless)**	**OR (95% CI) for all wireless phones**	Occupational history, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionising radiation.	)
			Frequency of use						
			Non users (<1 years)		1 (Ref.)	1 (Ref.)	1 (Ref.)		
			Users (>1 years)		1.6 (1.2 - 2.0)	1.3 (1.1- 1.6)	1.3 (1.1- 1.6)		
			Duration of use (years)						
			1-5		1.1 (0.7- 1.7)	1.2 (0.9- 1.4)	1.1 (0.9- 1.4)		
			5-10		1.1 (0.8- 1.6)	1.6 (1.3 - 2.0)	1.5 (1.2- 1.9)		
			10-15		2.2 (1.5 - 3.7)	1.4 (1.1- 1.9)	1.4 (1.1- 1.8)		
			15-20		2.4 (1.5- 3.7)	2.0 (1.5- 2.8)	1.7 (1.2- 2.3)		
			20- 25		3.2 (1.9- 5.5)	1.6 (0.6- 4.4)	1.9 (1.3- 2.9)		
			> 25		4.8 (2.5- 9.1)	-	3.0 (1.7- 5.2)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued f)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
8. Coureau et al.2014. France. 2004-2006. CERENAT. Case-control study.	596 cases and 1192 controls (M and F) over 16 years of age. Cases identified from populationbased cancer registries. Two controls with no history of CNS tumour were randomly selected from the local electoral rolls matched on age (±2 years), sex and department of residence.	Exposure from mobile phone use. Self-reported exposure from standardised questionnaires delivered as face-to-face non-blinded structured interviews by trained interviewers.	Time since first use (years), Cumulative duration of calls (hours)	Gliomas, meningiomas. Conditional logistic regression for matched sets was used to estimate ORs and 95%Cis	**OR (95% CI) for glioma**	**OR (95% CI) for meningioma**	Level of education, smoking, alcohol consumption. Potential occupational confounders were identified from detailed job calendars, and from specific questions about exposure to pesticides, extremely low-frequency electromagnetic fields (ELF-EMF), RF-EMF, and ionising radiation	Adequate/ Positive (glioma, meningioma)
			Regular mobile phone use					
			Not regular user		1 (Ref.)	1 (Ref.)	Positive association in heavy users	
			Regular user		1.24 (0.86 - 1.77)	0.90 (0.61 - 1.34)		
			Time since first use (years)					
			1-4		0.88 (0.56 - 1.39)	0.79 (0.49 - 1.27)		
			5-10		1.34 (0.87 - 2.06)	0.97 (0.58 - 1.61)		
			>10		1.61 (0.85 - 3.09)	1.57 (0.64 - 3.86)		
			Cumulative duration of calls (hours)					
			<43		0.83 (0.48 - 1.44)	1.12 (0.61 - 2.04)		
			43-112		0.77 (0.42 - 1.41)	0.85 (0.45 - 1.61)		
			113-338		1.07 (0.60 - 1.90)	0.52 (0.25 - 1.07)		
			339-895		1.78 (0.98 - 3.24)	0.52 (0.18 - 1.45)		
			>896		2.89 (1.41 - 5.93)	2.57 (1.02 - 6.44)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued g)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
9. Pettersson et al. 2014. Sweden, 2002-2007. Population-based case-control study.	422 cases with acoustic neuroma, 643 controls for analyses of mobile phone use. 417 cases with acoustic neuroma, 635 controls for analyses of cordless phone use (M and F), age 20-69 years. Cases identified in clinics, the Swedish Regional Cancer Registers and local acoustic neuroma registries. Two matched controls per case randomly selected from the Swedish population register.	Use of mobile phone and cordless phone . Self-reported exposure from mail questionnaire.	Frequency of use; Duration of exposure; Cumulative hours of use	Acoustic Neuroma. Odds Ratios (OR) with 95% CIs from conditional logistic regression	**OR (95% CI) for Mobile phone users**	**OR (95% CI) for Cordless phone users**	Smoking, education, marital status, and parity; for cordless phone analyses: hands-free use. Limits in exposure assessment. Positive association in heavy users.	Adequate/ Equivocal (Acoustic neuroma)
			Frequency of use					
			Never or rarely		1 (Ref.)	1 (Ref.)		
			Regular use		1.18 (0.88 - 1.59)	1.41 (1.07 - 1.86)		
			Duration of use (years)					
			<5		1.06 (0.73 - 1.54)	1.35 (0.97 - 1.89)		
			5 to 9		1.39 (0.97 - 1.97)	1.74 (1.22 - 2.46)		
			=>10		1.09 (0.75 - 1.59)	1.10 (0.73 - 1.64)		
			Cumulative use (hours)					
			<38		1.09 (0.73 - 1.62)	1.22 (0.82 - 1.82)		
			39-189		1.12 (0.74 - 1.69)	1.27 (0.85 - 1.89)		
			190-679		1.13 (0.75 - 1.70)	1.42 (0.96 - 2.09)		
			=>680		1.46 (0.98 - 2.17)	1.67 (1.13 - 2.49)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued h)

Study information	Population	Type of Exposure and assessment method		Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)	Any Other Co-Exposure/adjustments	Comments
10 Yoon et al. 2015. Korea; 2002- 2007; case-control study.	285 cases, 285 controls (M and F), mean age 42.3 (±14.1) cases; 42.5 (±14.0) controls. Patients recruited from five areas including Seoul and checked at department of neurosurgery in nine hospitals. The control group persons who received health screenings at the same hospitals.	Exposure from mobile phone use. Self-reported exposure from questionnaires.		Cumulative hours and lifetime years of use; average daily receiving call and the average daily sending call; average call duration time	Glioma; adjusted odds ratios (aORs) and 95% CIs were calculated using logistic regression	**OR (95% CI) for glioma**	adjusted for sex, age, type of respondent, five residential regions, educational achievement, the use of dye, alcohol drinking, the use of computer, and the use of electric blanket	Adequate/ Equivocal (Glioma)
				Use of mobile phone				
				Non users		1 (Ref.)		
				Users		1.17 (0.63 - 2.14)		
				Lifetime years of use (months)				
				< 48		1.28 (0.62 - 2.64)		
				48-84		1.27 (0.63 - 2.56)		
				>48		1.04 (0.52 - 2.09)		
				Cumulative hours of use (h)				
				< 300		1.25 (0.64 - 2.45)		
				300-900		1.59 (0.72 - 3.21)		
				>900		0.64 (0.30 - 1.34)		
				Average duration time (min)				
				<2		1.18 (0.62 - 2.24)		
				3-4		1.31 (0.65 - 2.63)		
				>5		1.00 (0.45 - 2.24)		
11. Al-Qahtani 2016. Saudi Arabia; 1996-2013; Retrospective case-control study.	26 cases, 61 controls (M and F). <30 years: 28; 30-39 years: 23; 40-49 years: 15; >50 years: 21. Hospital records.	Exposure from mobile phone use. Self-reported exposure from telephone and in-person interviews using standardized questionnaire.		Everyday use: <=1 h/day: unexposed; >1 h/day: exposed. Latency: <10 years of use; =>10 years of use	Parotid gland tumour. OR and 95% confidence interval	**OR (95% CI) for parotid gland tumour**	Smoking Other confounding not considered. Small sample.	Inadequate
				Everyday use				
				Non exposed		1 (Ref.)		
				Exposed		3.47 (1.30 - 9.23)		
				Duration of exposure				
				< 10 years		3.6 (0.97 - 13.36)		
				10 years or more		3.46 (0.77 - 15.56)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued i)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
12. Satta et al. 2018. Sardinia, Italy; 1998–2004; Population-based case-control study as part of the European multicenter study EPILYMPH.	322 lymphoma cases; 444 matched controls (M and F). Cases aged 25 to 74 years. In person interviews using a standardized questionnaire.	Exposure from radio-television transmitter or mobile phone base station near the three most prolonged residential addresses at any time of the life. Distance used as proxy for intensity of exposure; RF-EMF measurements at the door of the longest residential addresses available for the subset of subjects residing within 250 m of the closest transmitter base station, using a Microrade broadband detector.	Radiofrequency field estimates (V/m):	Lymphoma subtypes: B-cell; T-cell; Hodgkin; not otherwise specified NHL; OR and 95% confidence interval from logistic regression.	**OR for all lymphomas**	**OR for B-cell lymphoma**	**OR for Chronic lymphocytic leukemia**		Age, gender, years of education (categorized as 8 years, 9–13 years, 14 years), level of education and quartiles of vehicular traffic in proximity to the residential addresses of study subjects.	Inadequate
			RF field estimates (V/m):							
			<0.01		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		Uncertain exposure assessment	
			0.01- 1.23		0.7 (0.4 - 1.5)	0.8 (0.4 - 2.0)	1.5 (0.5 - 4.4)			
			1.24- 1.50		0.7 (0.3 - 1.5)	0.9 (0.4 - 2.1)	-			
			1.51- 1.7401		1.0 (0.5 - 2.1)	1.1 (0.5 - 2.7)	0.6 (0.1 - 3.1)			
			>1.7401		1.2 (0.6 - 2.6)	1.4 (0.6 - 3.4)	0.9 (0.2 - 4.6)			
13. Balekouzou et al. 2017. Central African Republic; 2003-2015; Case-control study.	174 cases; 348 age-matched controls (F). Age >15 years. Data from a cancer register.	Use of mobile phones,radiation exposure. Trained interviewers administered a standardized in person interview.	Exposure to radiation; habit to keep mobile phone in the bra.	Breast cancer. Odds ratio (OR) and 95% confidence intervals (95% CI) from unconditional logistic regression.	**OR (95% CI) for Breast cancer, univariate analysis**	**p-value**	**OR (95% CI) for Breast cancer, multivariate analysis**	**p-value**	Age, occupation, economic status, education, residence, ethnic group and marital status, family history, radiation exposure, food consumption, physical activity, alcohol, tobacco, use of bra, habit to keep money or cell phones in bras, height, weight and BMI.	Inadequate
			Daily use (h/day)						Self reported habit to keep mobilphone in the bra	
			No		1.00 (ref.)		1.00 (ref.)			
			Yes		8.02 (5.16-12.47)	0.000	8.21 (5.04 – 13.38)	0.000		
			Habit of keeping cell phone in bras							
			Yes		1.00 (ref.)		1.00 (ref.)			
			No		0.45 (0.31-0.65)	0.000	0.56 (0.35-0.89)	0.01		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued j)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
14. Vila et al. 2018. Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom; 2000-2004; INTEROCC study: international case-control study on mobilephone use and brain cancer risk in seven countries. "	2054 glioma cases; 1924 meningioma cases; 5601 controls (M and F). Cases aged 30 to 59 years of age; up to 69 years in Germany; 18 years and above in Israel; 18 to 69 years in the United Kingdom. In person computer-assisted personal interview.	Self-reported occupational exposure or proximity to radars, telecommunication antennas, transmitters, equipment for semiconductors manufacturing, medical diagnosis and treatment, industrial heating or food heating. A source-exposure matrix (SEM) was used to assign average exposure levels to each RF and IF source reported. Field intensities for each EMF source were weighted using the frequency-dependent reference levels (RLs) by the International Commission on Non-Ionising Radiation Protection (ICNIRP) for occupational exposure. Frequency of exposure: 10 MHz- 300 GHz.	E-field (V/m, Arithmetic mean exposure levels from the SEM. RF sources organized by E-field exposure level)	Glioma and meningioma risk; adjusted OR and 95% confidence intervals.	**OR (95% CI) for Gliomas**	**OR for Meningiomas**	No information available Study suggestive of a potential role in brain tumour promotion/progression	Adequate/ negative (Glioma and meningioma)
			Duration of exposure: 1-4 years					
			Non exposed		1.00 (ref.)	1.00 (ref.)		
			<0.42		0.69 (0.49 - 0.98)	0.60 (0.38 - 0.96)		
			0.42–4.47		0.85 (0.54 - 1.35)	1.13 (0.60 - 2.14)		
			4.48–18.8		0.77 (0.44 - 1.37)	0.86 (0.35 - 2.13)		
			≥18.9		1.38 (0.75 - 2.54)	1.30 (0.58 - 2.91)		
			Duration of exposure: 5-9 years					
			Non exposed		1.00 (ref.)	1.00 (ref.)		
			<0.42		0.84 (0.61 - 1.17)	0.60 (0.38 - 0.97)		
			0.42–4.47		0.93 (0.60 - 1.44)	1.48 (0.84 - 2.61)		
			4.48–18.8		0.82 (0.46 - 1.47)	1.08 (0.66 - 2.39)		
			≥18.9		0.90 (0.44 - 1.83)	1.03 (0.45 - 2.63)		

Table 1 - Cancer in epidemiological Case-Control studies (450-6000 MHz) (Continued l)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
15. Luo et al. 2019. Connecticut, USA, 2010-2011; population-based case-control study.	462 cases and 498 population-based controls (M and F), 21-84 years of age.	Use of mobile phones,radiation exposure. Trained interviewers administered a standardized and structured questionnaire.	Use of mobile phones; Duration of exposure.	Thyroid cancer (papillary, follicular, medullary, anaplastic). Multivariate unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI).	**OR (95% CI) for Thyroid cancer, Overall**	**OR (95% CI) for Thyroid cancer, MM**	**OR (95% CI) for Thyroid cancer, FF**	age, sex, education, family history of thyroid cancer, alcohol consumption, body mass index, previous benign thyroid diseases, occupational radiation exposure, and radiation treatment.	Adequate/ Equivocal (Thyroid cancers)
			Use of mobile phone						
			Non users (< 6 months use)		1 (Ref.)	1 (Ref.)	1 (Ref.)		
			Users (< 6 months use)		1.05 (0.74, 1.48)	1.27 (0.62, 2.61)	0.99 (0.66, 1.47)		
			Daily use (h/day)						
			≤1		1.10 (0.72, 1.66)	1.76 (0.72, 4.32)	0.97 (0.60, 1.56)		
			1-2		1.51 (0.90, 2.53)	1.66 (0.57, 4.82)	1.45 (0.79, 2.65)		
			>2		1.40 (0.83, 2.35)	1.05 (0.35, 3.14)	1.52 (0.83, 2.80)		
			Age at first use (years)						
			≤20		1.08 (0.53, 2.20)	1.49 (0.34, 6.01)	0.95 (0.42, 2.18)		
			21-50		1.06 (0.72, 1.55)	1.44 (0.65, 3.17)	0.96 (0.62, 1.49)		
			>50		1.03 (0.62, 1.70)	0.99 (0.36, 2.70)	1.05 (0.58, 1.90)		
			Duration of use (years)						
			≤12		0.99 (0.66, 1.49)	0.99 (0.39, 2.48)	0.97 (0.61, 1.53)		
			12-15		0.94 (0.63, 1.42)	0.82 (0.34, 1.97)	0.97 (0.61, 1.55)		
			>15		1.29 (0.83, 2.00)	2.11 (0.91, 4.89)	1.03 (0.62, 1.73)	Some evidence in long term users	

Table 2 – Cancer in epidemiological ecological case-control studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
16. Gonzalez Rubio et al. 2017. Spain. 2012-2015. Case-control ecological study.	95 cases: 65 lymphomas, 12 gliomas, 18 meningiomas (30 brain tumours); 390 anonymous controls (M and F). Resident population data in the 110 administrative districts from the Spain's National Statistics Institute (INE). Addresses for all cancer cases of gliomas, meningiomas and lymphomas from Oncology Service of the University Hospital of Albacete. Representative random sample of 390 anonymous addresses for the control group from the Statistics Service of the Town Council of Albacete.	Residential exposure to any RF. 14 frequency bands (FM, TV3, TETRA, TV4and5, GSMTx, GSM Rx, DCS Tx, DCS Rx, DECT, UMTS Tx, UMTS Rx,WiFi 2G,WiMAX y WiFI 5G), ranging from 88MHz up to 6 GHz. Personal exposure assessed using an EME Spy 140 (Satimo)exposimeter, conveying the exposimeter in a bicycle. 168266 total measurement, 12019 measurements per frequency, 1540 average measurement records per administrative region.	Average total exposure to RF-EMF (V/m) per administrative region: Min 0.07, max 1.03	Gliomas, meningiomas and lymphomas; Spearman correlation test between exposure and incidence of tumours. Effect estimate not appropriate	**ρ of Spearman for Meningioma, (p-value)**	**ρ of Spearman for Glioma, (p-value)**	**ρ of Spearman for all brain, (p-value)**	**ρ of Spearman for Lymphoma, (p-value)**	**ρ of Spearman for all tumours, (p-value)**	Smoking Other counfounders not analysed Design not clear, particularly given that there seems to be personal exposure assessment	inadequate
	Design not clear, particularly given that there seems to be personal exposure assessment	Not clear exposure assessment			0,19 (0,04)	0,15 (0,13)	0,28 (0,003)	-0,03 (0,72)	0,13 (0,19)		

Table 3 – Cancer in epidemiological cohort studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
17. Frei et al. 2011. Denmark; 1990-2007. Nationwide cohort study.	All Danes aged ≥30 and born in Denmark after 1925, subdivided into subscribers and non-subscribers of mobile phones before 1995.	Use of mobile phones as mobile phone subscription; records for 1982-95 were obtained from the Danish network operators.	Mobile phone use, duration of subscription.	Tumours in the central nervous system. Sex-specific incidence rate ratios (IRR) and 95% confidence intervals from log-linear Poisson regression models.	**IRR (95% CI) for Central nervous system tumours, MM**	**IRR (95% CI) for Central nervous system tumours, FF**	**IRR (95% CI) for Central nervous system tumours, MM with >12 years of education**	Age, calendar period, education, and disposable income.	Inadequate
			Use of mobile phones						
			Non-subscribers		1.0 (ref.)	1.0 (ref.)	1.0 (ref.)		
			Subscribers		1.02 (0.94 to 1.10)	1.02 (0.86 to 1.22)	1.00 (0.83 to 1.22)	Exposure assessment only by subscriptions	
			Years of subscription						
			Non-subscribers		1.0 (ref.)	1.0 (ref.)	1.0 (ref.)		
			1-4		1.07 (0.92 to 1.24)	0.97 (0.69 to 1.36)	1.29 (0.92 to 1.79)		
			5-9		0.95 (0.83 to 1.08)	1.05 (0.81 to 1.37)	0.95 (0.70 to 1.29)		
			10-12		1.08 (0.93 to 1.25)	1.05 (0.75 to 1.47)	0.82 (0.55 to 1.24)		
			≥13		1.03 (0.83 to 1.27)	0.91 (0.41 to 2.04)	0.94 (0.55 to 1.60)		

Table 3 – Cancer in epidemiological cohort studies (450-6000 MHz) (Continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
18. Benson et al. 2013. United Kingdom,; prospective Cohort study , the Million Women Study.	1.3 million middle-aged women recruited for Breast Screening Programme	Use of mobile phone. Postal questionnaire; questions on mobile phone use were asked in 1999–2005, and again in 2009	Use of mobile phone.	Intracranial central nervous system tumours. Cox regression models to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs)	**RR (95% CI) for all intracranial CNS tumours**	**RR (95% CI) for glioma**	**RR (95% CI) for meningioma**	**RR (95% CI) for pituitary**	**RR (95% CI) for acoustic neuroma**	Socioeconomic status, region, age at baseline, height, BMI, smoking, alcohol intake, exercise, use of menopausal hormone therapy.	Adequate/ Positive (acoustic neuroma, pituitary gland)
			Ever used a mobile phone							Overadjusted for several outcomes.	
			No		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			Yes		1.01 (0.90-1.14)	0.91 (0.76-1.08)	1.05 (0.81-1.38)	1.52 (0.99-2.33)	1.44 (0.91-2.28)		
			Frequency of use								
			Never user		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<Daily use		1.02 (0.90-1.15)	0.92 (0.77-1.10)	1.05 (0.80-1.37)	1.53 (0.99-2.36)	1.45 (0.91-2.31)		
			Daily use		1.00 (0.80-1.26)	0.80 (0.56-1.14)	1.11 (0.67-1.85)	1.45 (0.68-3.10)	1.37 (0.61-3.07)		
			Duration of exposure (years)					*p-value for trend = 0.23*	*p-value for trend = 0.03*		
			Never user		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<5		1.00 (0.84-1.20)	0.93 (0.71-1.21)	0.88 (0.60-1.31)	2.31 (1.31-4.06)	1.00 (0.54-1.82)		
			5-9		1.02 (0.89-1.17)	0.92 (0.75-1.13)	1.21 (0.89-1.65)	1.08 (0.64-1.82)	1.80 (1.08-3.03)		
			10+		1.02 (0.81-1.27)	0.78 (0.55-1.10)	1.10 (0.66-1.84)	1.61 (0.78-3.35)	2.46 (1.07-5.64)		

Table 3 – Cancer in epidemiological cohort studies (450-6000 MHz) (Continued c)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
19. Poulsen et al. 2013. Denmark, 1982-1995, follow up until 2007. Cohort study: CANULI study of social inequality and cancer incidence and survival	355701 (M and F), 30 years to date of the first cancer diagnosis, death, emigration.	Use of mobile phones. Mobile phone subscriptions in Denmark during the period from 1982 until the end of 1995. Person-time within the first year of subscription was defined as unexposed.	Use of mobile phones; Duration of exposure.	Basal Cell Carcinoma of the head and neck, Squamous Cell Carcinoma and Melanoma on the head and neck. Incidence rate ratios (IRRs) and 95% confidence intervals from log-linear Poisson regression models.	**IRR (95% CI) for Basal Cell Carcinoma of the head and neck, FF**	**IRR (95% CI) for Basal Cell Carcinoma of the head and neck, MM**	**IRR (95% CI) for Squamous Cell Carcinoma and Melanoma of the head and neck, FF**	**IRR (95% CI) for Squamous Cell Carcinoma and Melanoma of the head and neck, MM**	Age, calendar year, educational level, and income. Exposure assessment by mobile phone subscription only	Inadequate
			Use of mobile phone							
			Non users (< 1 year subscription)		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)		
			Users (>1 year subscription)		0.93 (0.82 - 1.05)	0.98 (0.93 - 1.03)	1.01 (0.88 - 1.16)	1.05 (0.80 - 1.37)		
			Duration of use (years)							
			1–4		1.02 (0.80 - 1.30)	1.01 (0.91 - 1.13)	0.86 (0.61 - 1.21)	1.16 (0.69 - 1.94)		
			5-9		0.78 (0.64 - 0.95)	0.96 (0.89 - 1.04)	1.01 (0.81 - 1.26)	1.01 (0.65 - 1.57)		
			10-12		1.02 (0.83 - 1.26)	0.96 (0.87 - 1.05)	1.17 (0.93 - 1.48)	0.92 (0.55 - 1.54)		
			>=13		1.20 (0.79 - 1.82)	1.02 (0.90 - 1.15)	0.91 (0.66 - 1.27)	1.20 (0.65 - 2.22)		

Table 3 – Cancer in epidemiological cohort studies (450-6000 MHz) (Continued d)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
20. Hauri et al. 2014. Switzerland. 2000-2008. Census-based cohort study.	997 cancer cases from Swiss National Cohort: 283 leukemia, 258 CNS tumours, 456 other cancers; 117 cases from Swiss Childhood Cancer Registry, not linked with SNC: 27 leukemia, 26 CNS tumours, 64 other cancers (M and F); ≤15 years.	Residential exposure to broadcast transmitters emitting medium-wave (0.5–1.6 MHz), short-wave (6–22 MHz), very high frequency (VHF; 174–230 MHz), and ultra-high frequency (UHF; 470–862 MHz) EMFs. RF-EMF levels from VHF and UHF transmitters ... were modeled by the Federal Office of Communications for an area with a radius of 10 km around each transmitter for the years 1990 and 2000.	A priori chosen cutpoints to differentiate between low, medium, and high exposure. V/m	Leukemia, acute lymphoblastic leukemia, and Central Nervous System tumours, including benign tumours. Hazard Ratio from time-to-event analysis (Cox Regression), 2000–2008. Incidence Rate Ratio from Poisson regression analysis, 1985–2008.	**HR (95% CI), IRR (95% CI), All cancers**	**HR (95% CI), IRR (95% CI), All leukemias**	**HR (95% CI), IRR (95% CI), CNS tumours**	Sex, benzene, natural background ionising γ radiation, distance to the nearest high-voltage power line, and degree of urbanisation.	Adequate/ Negative (Childood cancers)
			Residential exposure						
			Low		1 (Ref.)	1 (Ref.)	1 (Ref.)		
			Medium		1.14 (0.94 - 1.38) 1.09 (1.00 - 1.20)	0.70 (0.46 - 1.07) 0.92 (0.77 - 1.10)	1.35 (0.94 - 1.95) 1.16 (0.95 - 1.42)		
			High		1.03 (0.74 - 1.43) 0.90 (0.76 - 1.06)	0.55 (0.26 - 1.19) 0.76 (0.55 - 1.05)	1.68 (0.98 - 2.91) 1.03 (0.73 - 1.46)		

Table 4 (summary 1-3) – Collected data on cancer in epidemiological studies (450-6000 MHz)

Total studies FR1*	20			
Adequate studies	11			
Observed Tumour	Total adequate studies	Positive results	Equivocal results	Negative results
Glioma	8	3	2	3
Acoustic neuroma	3	2	1	
Meningioma	4	2		2
Lymphoma	1			1
Thyroid gland	1		1	
Pituitary gland	1	1		

*Some of the studies include more than one tumour site.

1. SUMMARY OF THE RESULTS OF EPIDEMIOLOGICAL STUDIES (FR1: 450 to 6000 MHz) (Table 4)

The epidemiological evidence on possible associations of exposure to RF-EMF with cancer comes from studies of diverse design that assessed a range of exposure sources: the populations included people exposed in occupational settings, people exposed through sources in the general environment, e.g. radio-base stations, and people exposed through use of wireless (mobile and cordless) telephones.

In chapter 4 (Limitations) general methodological concerns related to the assessment of individual studies are covered. The total number of epidemiological studies published after the IARC 2011 evaluation (IARC, 2013) and up to 2020, as selected for the present review for FR1, was 20.

After further deep analyses of the 20 original papers, 11 studies proved to be adequate on the basis of exposure assessment, sample size and appropriateness of confounding analyses.

Gliomas, acoustic neuromas, meningiomas, lymphomas, thyroid and pituitary gland tumours were analysed in the 11 adequate studies for a possible association with exposure to RF-EMF, related to the use of mobile phone, or for environmental/occupational exposure to emissions from radiobase stations. The association of the different neoplasias to RF-EMF exposure is reported below. Between brackets numbers assigned to the various studies are reported.

Glioma: out of 7 adequate studies regarding this outcome, 3 showed a positive association with RF-EMF exposure (Ref: 6, 7, 8), 2 were equivocal (1,10) and 3 negative (Ref: 14,18, 20).

Acoustic neuroma: out of 3 adequate studies regarding this outcome, 2 showed a positive association with the RF-EMF exposure (Ref: 7, 18), 1 was equivocal (Ref:9).

Meningioma: out of 4 adequate studies regarding this outcome, 2 showed a positive association with the RF-EMF exposure (Ref: 5,8), and 2 were negative (Ref: 14, 18).

Lymphoma/leukaemia: the only adequate study (childhood) regarding this outcome was negative (Ref: 20).

Thyroid tumour: the only adequate study regarding this outcome showed equivocal results (Ref: 15).

Pituitary gland tumour: the only adequate study regarding this outcome was positive (Ref: 18).

The results of the different studies for the same outcome are mixed (showing conflicting findings) , as summarized in Table 4. The tumours with more robust evidence of association are glioma and acoustic neuroma. The association of glioma and acoustic neuroma is stronger among long-term heavy users of mobile phones, which is also the most extensively investigated exposure source, and in some cases the onset of tumours was related to the side on which the device was handled.

The IARC evaluation of *limited evidence* of cancerogenicity of RF-EMF in epidemiological studies as regards FR1 is confirmed.

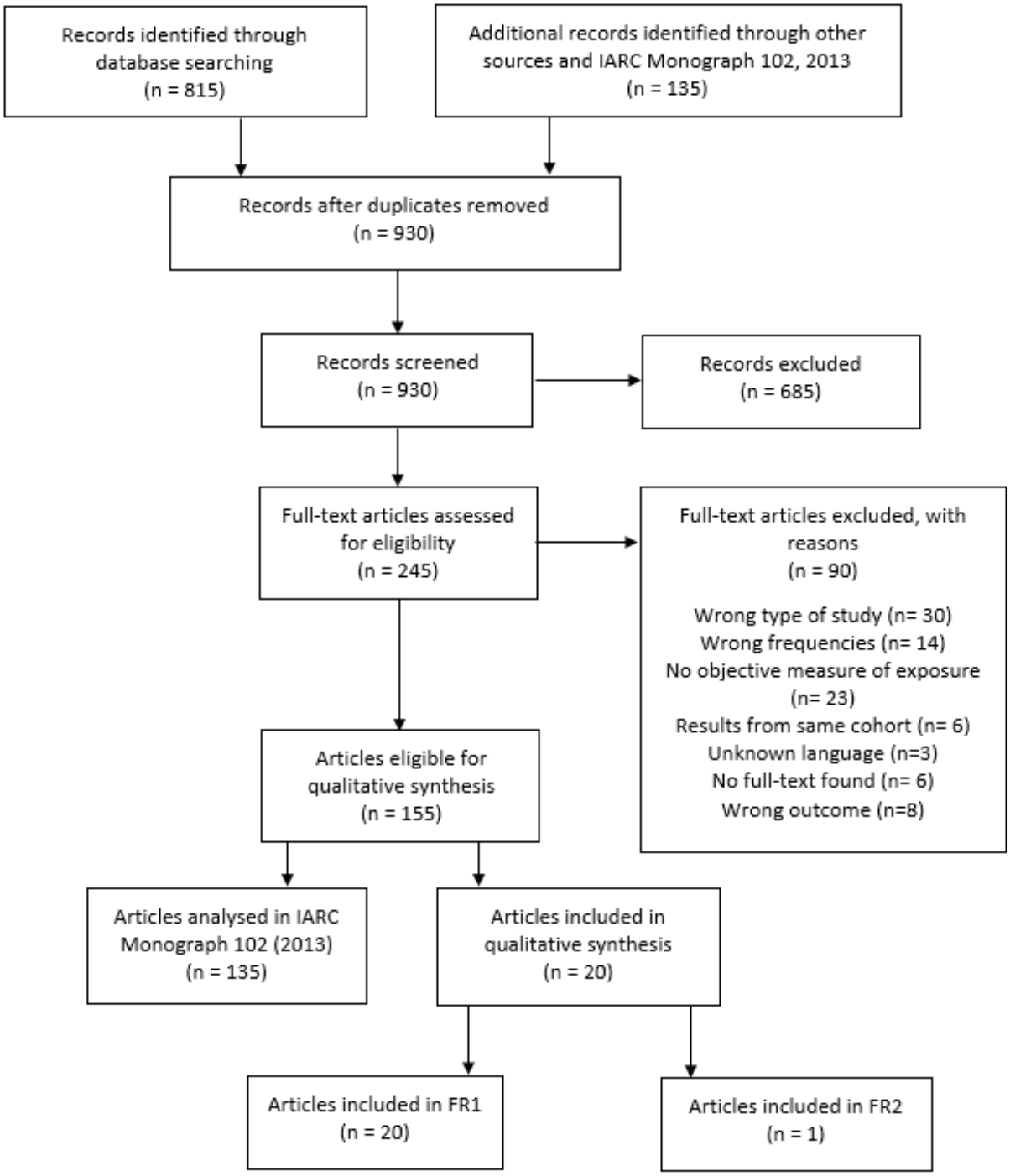
4.1.2 Cancer in epidemiological studies: Studies evaluating health effects due to RF at a higher frequency range (FR2: 24 to 100 GHz, MMW).

The stream of selection of the relevant literature is the same as for FR1, as highlighted in the PRISMA flowchart, 930 articles were screened based on title and abstract and 685 were excluded at this stage; 245 were screened based on full-texts and 90 were excluded at this stage, and after a more thorough assessment, only one published article was eligible for inclusion in the scoping review for the highest range of frequencies (this article reported occupational exposures for both FR1 and FR2, so this doesn't add up to the overall number of included studies) (Fig. 10).

Two articles that were included in IARC Monograph 102 (IARC, 2013) (and are therefore not described here) presented exposures related to FR2 range: it was decided to provide the most important information in the summary tables, since these novel frequencies are the real focal point of this scoping review.

Again, for each article, the abstract is presented, together with a table summarising the most important information; furthermore, a senior expert evaluated their adequacy for assessing carcinogenic effects (adequate/inadequate), and an overall synthesis of the results (positive/negative/equivocal), following the criteria used to assess the adequacy described in the methodology section.

Figure 10 – Flow diagram. Epidemiological studies on cancer for FR2



In conclusion, search on PubMed e EMFPortal databases for epidemiological studies considering exposures from 24GHz to 100 GHz (FR2) included 3 studies. Two were already described in the IARC Monograph 102 (Stang et al., 2001 (1); Baumgardt-Elms et al., 2002 (2)) , one was published after 2011 (Vila et al, 2018 (3)); the latter was also studied in the lower frequencies analysis included in the review.The 3 studies regard occupational exposures of radar operators or workers nearby radar stations. The range of frequencies used by radar telecommunications are represented in Table 5 (IEEE 521-2002). Exposure of workers is not well assessed, as the RF-EMF exposure is self reported, usually quantified by distance from the radar or simply job title:

Table 5 – Range of frequencies used by radar communication.

Range name	Frequency
L	1 - 2 GHz
S	2 – 4 GHz
C	4 – 8 GHz
[3]	8 – 12 GHz
Ku	12 – 18 GHz
K	18 – 27 GHz
Ka	27 – 40 GHz
V	40 – 75 GHz
W	75 – 110 GHz

Summaries of the analysed studies for these frequencies are presented in Tables 6a,b. The epidemiological study not included in the 2011 IARC Working group evaluation is the following:

3. Vila et al., 2018.

Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom; 2000-2004; INTEROCC study: international case-control study on mobilephone use and brain cancer risk in seven countries.

In 2011, the International Agency for Research on Cancer classified radiofrequency (RF) electromagnetic fields (EMF) as possibly carcinogenic to humans (group 2B), although the epidemiological evidence for the association between occupational exposure to RF-EMF and cancer was judged to be inadequate, due in part to limitations in exposure assessment. This study examines the relation between occupational RF and intermediate frequency (IF) EMF exposure and brain tumour (glioma and meningioma) risk in the INTEROCC multinational population-based case-control study (with nearly 4000 cases and over 5000 controls), using a novel exposure assessment approach. Methods: Individual indices of cumulative exposure to RF and IF-EMF (overall and in specific exposure time windows) were assigned to study participants using a source-exposure matrix and detailed interview data on work with or nearby EMF sources. Conditional logistic regression was used to investigate associations with glioma and meningioma risk. Overall, around 10% of study participants were exposed to RF while only 1% were exposed to IF-EMF. There was no clear evidence for a positive association between RF or IF-EMF and the brain tumours studied, with most results showing either no association or odds ratios (ORs) below 1.0. The largest adjusted ORs were obtained for cumulative exposure to RF magnetic fields (as A/m-years) in the highest exposed category (≥90th percentile) for the most recent exposure time window (1–4 years before the diagnosis or 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). Despite the improved exposure assessment approach used in this study, no clear associations were identified. However, the results obtained for recent exposure to RF electric and magnetic fields are suggestive of a potential role in brain tumour promotion/progression and should be further investigated.

Comment*: *Improved exposure assessment. No clear associations were identified for glioma and meningioma, potential role in brain tumour promotion/progression.

Table 6 – Cancer in epidemiological case-control studies (24 to 100 GHz, MMW) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
1.Stang et al. 2001. Germany. 1994-1997. Hospital-based and population-based case-control study.	118 cases, 475 controls (M and F). 35-74 years. Hospital-based case-control study at the Division of Ophthalmology, University of Essen; Controls in the population-based study were selected randomly from mandatory lists of residence.	Occupational sources of electromagnetic radiation. Self-reported exposure from face-to-face interview.	Lifetime exposure: source of exposure, duration, beginning of exposure.	Uveal Melanoma. Odds ratios (ORs) and 95% CI from conditional logistic regression models.	**OR (95% CI), Uveal Melanoma**		Medical history, phenotypic characteristics, life-style factors, Few participants reported exposure to radar	Adequate/negative (Uveal melanoma)
			EMF Source					
			Radar units		0.4 (0.0-2.6)			
2. Baumgardt-Elms et al. 2002. Germany. 1995-1997. Population-based case–control study.	269 cases, 797 controls (M). 15-69 years. Cases were ascertained through an active reporting system of clinical and pathology departments in the study regions. Controls were selected at random from the mandatory registries of residents.	Occupational exposure to EMF. Self-reported exposure from face-to-face interview.	At least 6 months of exposure. Exposures grouped according to the electromagnetic spectrum and assumptions on the strength of the electric and magnetic fields measured in specific workplaces.	Testicular cancer; Odds ratio and 95% confidence intervals (OR, 95% CI) from conditional logistic regression.	**OR (95% CI), testicular cancer**		Matching factors age (ten 5-year age groups since there were no cases in the highest age group) and region of residence (five strata) through stratification; subgroup analysis for blue- and white-collar workers.	Adequate/negative (Tumours of the testis)
			EMF Source					
			Working near radar units		1.0 (0.60-1.75)			

Table 6 – Cancer in epidemiological case control studies (24 to 100 GHz, MMW) (continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
3. Vila et al. 2018. Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom; 2000-2004; INTEROCC study: international case-control study on mobilephone use and brain cancer risk in seven countries.	2054 glioma cases; 1924 meningioma cases; 5601 controls (M and F). Cases aged 30 to 59 years of age; up to 69 years in Germany; 18 years and above in Israel; 18 to 69 years in the United Kingdom. In person computer-assisted personal interview.	Self-reported occupational exposure or proximity to radars, telecommunication antennas, transmitters, equipment for semiconductors manufacturing, medical diagnosis and treatment, industrial heating or food heating. A source-exposure matrix (SEM) was used to assign average exposure levels to each RF and IF source reported. Field intensities for each EMF source were weighted using the frequency-dependent reference levels (RLs) by the International Commission on Non-Ionising Radiation Protection (ICNIRP) for occupational exposure. Frequency of exposure: 10 MHz-300 GHz.	E-field (V/m, Arithmetic mean exposure levels from the SEM. RF sources organized by E-field exposure level)	Glioma and meningioma risk; adjusted OR and 95% confidence intervals.	**OR (95% CI) for Gliomas**	**OR for Meningiomas**	No information available Improved exposure assessment. No clear associations were identified for glioma and meningioma, potential role in brain tumour promotion/progression.	Adequate/negative (glioma and meningioma)
			Duration of exposure: 1-4 years					
			Non exposed		1.00 (ref.)	1.00 (ref.)		
			<0.42		0.69 (0.49-0.98)	0.60 (0.38-0.96)		
			0.42–4.47		0.85 (0.54-1.35)	1.13 (0.60-2.14)		
			4.48–18.8		0.77 (0.44-1.37)	0.86 (0.35-2.13)		
			≥18.9		1.38 (0.75-2.54)	1.30 (0.58-2.91)		
			Duration of exposure: 5-9 years					
			Non exposed		1.00 (ref.)	1.00 (ref.)		
			<0.42		0.84 (0.61-1.17)	0.60 (0.38-0.97)		
			0.42–4.47		0.93 (0.60-1.44)	1.48 (0.84-2.61)		
			4.48–18.8		0.82 (0.46-1.47)	1.08 (0.66-2.39)		
			≥18.9		0.90 (0.44-1.83)	1.03 (0.45-2.63)		

Table 7 (Summary 6 a, b) – Summary table for epidemiological studies on Cancer, FR2: 24-100 GHz

Total studies*	3			
Adequate studies	3			
Observed Tumour	Total adequate studies	Positive results	Equivocal results	Negative results
Glioma	1			1
Meningioma	1			1
Uveal melanoma	1			1
Testicular cancer	1			1

*one of the studies includes more than one tumour site.

➢ SUMMARY OF THE RESULTS EPIDEMIOLOGICAL STUDIES ON CANCER (FR2: 24 to 100 GHz, MMW) (Table 6a, b)

All 3 adequate studies reviewed did not show any clear association between exposure to higher frequencies (FR2) and the selected cancer (table 7).

The IARC Working group in the summary of data reported for occupational exposure regarding also FR2, concluded:

"Tumours of the brain*: "…exposure misclassification and insufficient attention to possible confounding limit the interpretation of findings. Thus, there is no clear indication of an association of occupational exposure to RF radiation with risk of cancer of the brain. "*

*"*Leukaemia/Lymphoma*: In summary, while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF radiation, the limited exposure assessment and possible confounding make these results difficult to interpret".*

Other kinds of tumour emerged as potentially associated with exposure to high frequencies (uveal melanoma, cancer of the testis, breast, lung, and skin), but many of the studies showed methodological limitations and the results were inconsistent (IARC 2013). Afterwards, any other adequate study was performed regarding the association of these types of tumours with the exposure to RF-EMF (FR2).

The present review bears out these remarks, so we must confirm that, where the highest 5G (FR2) frequency is concerned, the only 3 epidemiological studies examined for FR2 exposure are *not adequate* to assess the impact on health.

4.1.3 Cancer in experimental animals: Studies evaluating health effects due to RF at a lower frequency range (FR1: 450 to 6000 MHZ), which also includes the frequencies used in previous generations' broadband cellular networks (1G, 2G, 3G and 4G).

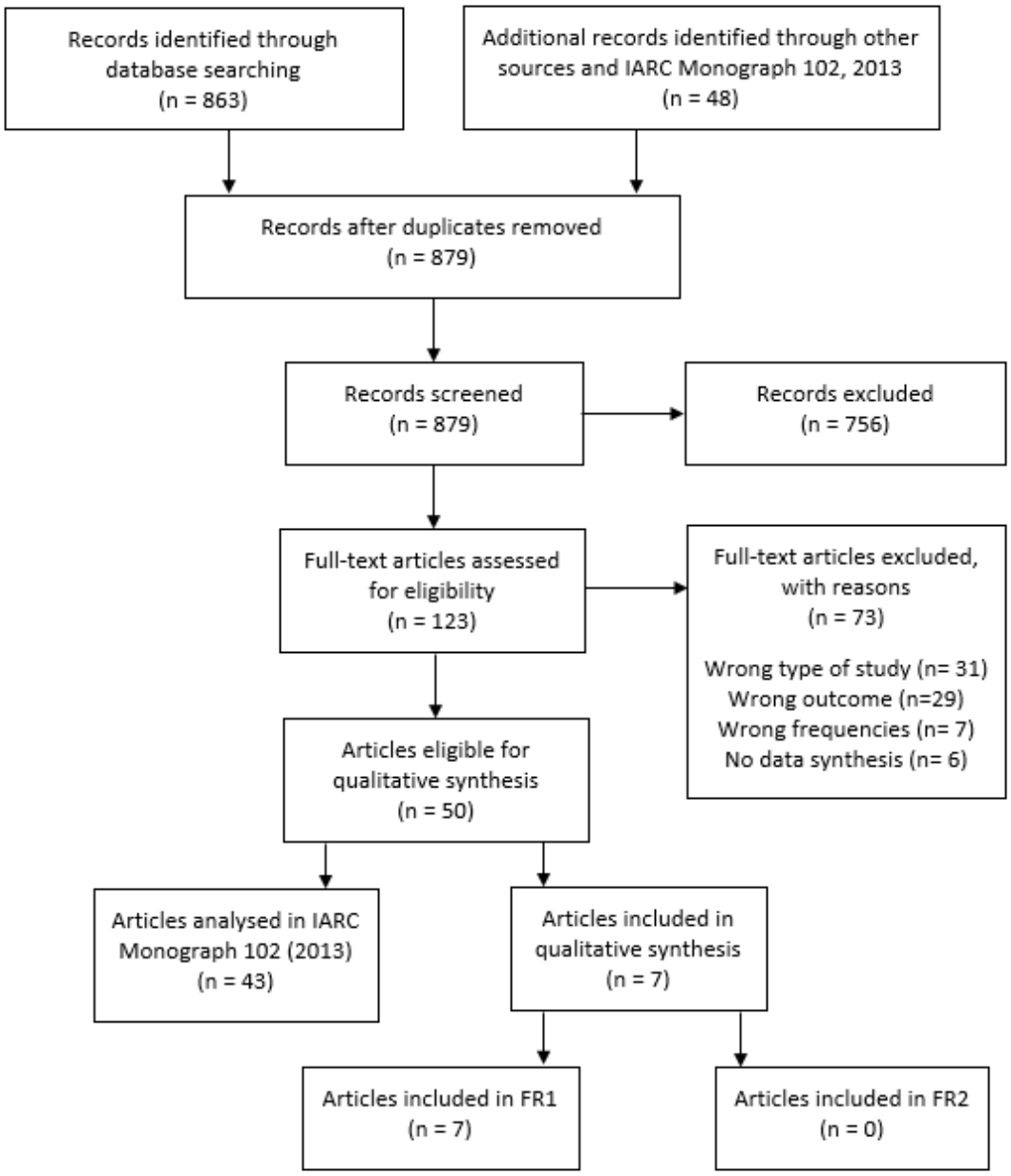
The articles identified through database searching and other sources were 911. After removing duplicates (32) and excluding non-pertinent articles (756) based on title and abstracts, 123 articles remained. Based on full-text screening, 73 papers were further excluded, so that the articles with frequencies appropriate for inclusion in this qualitative synthesis were 50.

As further explained in the methodology section, we considered IARC Monograph 102 (IARC, 2013) as our key reference for all studies on cancer in experimental animals published until 2011: all original papers (43) that were included in the IARC monograph were analysed and referenced in this report as well; of course, we considered for this report only the final IARC classification. Seven adequate studies were published after 2011.

At this stage, a separation based on frequency range was also performed: of the 7 papers included, all reported exposures belonging to the band considered in FR1, and none reported exposures regarding FR2 (Fig. 11).

For each article selected, the abstract is presented, together with the tables summarising the most important information; furthermore, a senior expert evaluated their adequacy for assessing carcinogenic effects adequate/inadequate), and expressed an overall synthesis of the results (positive/negative/equivocal), following the criteria described in the methodology chapter.

Figure 11 – Flow diagram. Cancer in experimental animal studies FR1



KEY REFERENCE: IARC 2013 (43 studies)

The IARC Monograph 102 is the key reference for the present review. The evaluation of the adequate available studies at that time is reported below (IARC, 2013).

In May, 2011, 30 scientists from 14 countries met at the International Agency for Research on Cancer(IARC) in Lyon, France, to assess the carcinogenicity of radiofrequency electromagnetic fields (RF-EMF). These assessments was published as Volume 102 of the IARC Monographs (IARC, 2013).

Four classes of cancer bioassays in animals were reviewed and assessed by the Working Group. These studies involved a variety of animal models, exposure metrics, duration of exposure, and other criteria on which the evaluation of carcinogenicity was based.

The Working Group evaluated:

- 7 two-year cancer bioassays of RF radiation, two in mice and five in rats; six studies were performed to examine the effects of exposure to mobile-phone RF metrics, and one study involved exposure to pulsed RF radiation. When compared with sham controls, no statistically significant increases in the incidence of benign or malignant neoplasms at any organ site were identified in animals exposed to mobilephone RF radiation in any study. In the study with exposure to pulsed RF radiation, an increased incidence of total malignant tumours (all sites combined) was observed in rats; however, the Working Group considered this finding to be of limited biological significance since it resulted from pooling of non-significant changes in tumour incidence at several sites. Exposure to RF radiation did not increase total tumour incidence in any of the other six studies that were evaluated. The Working Group concluded that the results of the 2-year cancer bioassays provided no evidence that long-term exposure to RF radiation increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats.

- 12 studies that used four different tumour-prone animal models; two of these studies demonstrated an increased incidence of tumours in animals exposed to RF radiation. The first study with positive results demonstrated an increased incidence of lymphoma in *Eμ-Piml-transgenic* mice exposed to GSM mobile-phone RF radiation at 900 MHz; however, two subsequent studies by other investigators using the same model system failed to confirm this finding. In the second study with positive results, an increased incidence of tumours of the mammary gland was observed in C3H/HeA mice exposed to RF radiation at 2450 MHz; although two later studies using the same exposure metric did not confirm this finding, these follow-on studies were performed at lower levels of exposure. The Working Group concluded that the results of studies in three tumour-prone animal models (the *Eμ-Piml* mouse model of lymphoma, the *AKR* mouse model of lymphoma, and the *Patchedr -1* mouse model of brain cancer) do not support the hypothesis that the incidence of tumours in the brain or lymphoid tissue would increase as a result of exposure to RF radiation.

- 16 studies of initiation and promotion that were performed with animal models of tumourigenesis in skin, mammary gland, brain, and lymphoid tissue. None of the five studies in models of skin cancer and none of the six studies in models of brain cancer showed an association with exposure to RF radiation. One of four studies with the model of mammary-gland tumour in Sprague-Dawley rats gave positive results; the other three studies - one with a nearly identical protocol - did not show an association, although they used the same experimental model and the same conditions of exposure to RF radiation. Likewise, the study with the model of lymphoma was negative. The Working Group concluded that the evidence from these studies of initiation and promotion failed to demonstrate a consistent pattern of enhancement of carcinogenesis by exposure to RF radiation in any of the tissues studied.

- 6 co-carcinogenesis studies involving five different animal models. Four positive responses were reported. Two studies giving positive results, one in Wistar rats continuously exposed to drinking-water containing MX - a by-product of water disinfection - and another study in pregnant B6C3F1 mice given a single dose of ethyl-nitrosourea, involved exposures to mobile-phone RF radiation at 900 and 1966 MHz, respectively. The other two studies with positive results involved coexposure of BALB/c mice to RF radiation at 2450 MHz and benzo[a]pyrene. Although the value of two of these studies was weakened by their unknown relevance to cancer in humans, the Working Group concluded that they did provide some additional evidence supporting the carcinogenicity of RF radiation in experimental animals.

The conclusion for the animal studies evaluation was: "*There is limited evidence in experimental animals for the carcinogenicity of radiofrequency radiation*" (IARC, 2013).

- REVIEW OF THE ANIMAL STUDIES 2011-2020

Starting from 2011, the present review evaluates by type of study and by year of publication (2011-2020) the animal studies also summarized in Table 3 (a, b, c, d). The author adds to short abstracts her own brief comments on the results of the different studies.

TWO YEAR CANCER BIOASSAY IN MICE (Table 8a)

1. NTP TR 596, 2018.

GSM-modulated RFR, B6C3F1/N mice (M, F), for 24 months, Carcinogenicity study.

Groups of 105 male and 105 female mice were housed in reverberation chambers and received whole-body exposures to GSM-modulated cell phone RFR at power levels of 0 (sham control), 2.5, 5, or 10 W/kg, 9 hours and 10 minutes per day, 7 days per week for 106 (males) or 108 (females) weeks with continuous cycling of 10 minutes on and 10 minutes off during a period of 18 hours and 20 minutes each day. The sham control animals were housed in reverberation chambers identical to those used for the exposed groups, but were not exposed to RFR; shared groups of unexposed mice of each sex served as sham controls for both RFR modulations. Fifteen mice per group were randomly selected from the core group after 10 weeks of study; 10 of those 15 mice per group were used for interim evaluation at 14 weeks, and five mice per group were used for genetic toxicity testing at 14 weeks. The remaining 90 animals per group were exposed up to 2 years. In the 2-year study, percent survival was significantly higher for the 5 W/kg males than the sham control group. Survival of the other exposed groups of males and females was generally similar to that of the sham controls. Mean body weights of exposed groups of males and females were similar to those of the sham controls throughout the study. The combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma of the skin were increased in 5 and 10 W/kg males, although not significantly or in a SAR-related manner; however, the incidences exceeded the overall historical control ranges for malignant fibrous histiocytoma. In the lung, there was a significant positive trend in the incidences of alveolar/ bronchiolar adenoma or carcinoma (combined) in males. Compared to the sham controls, all exposed groups of females had increased incidences of malignant lymphoma and the incidences in the 2.5 and 5 W/kg groups were significantly increased. The sham control group had a low incidence of malignant lymphoma compared to the range seen in historical controls. There were no nonneoplastic lesions that were considered related to exposure to GSM-modulated cell phone RFR.

2. NTP TR 596, 2018.

CDMA-modulated RFR, B6C3F1/N mice (M, F), for 24 months, Carcinogenicity study.

Groups of 105 male and 105 female mice were housed in reverberation chambers and received whole-body exposures to CDMA-modulated cell phone RFR at power levels of 0 (sham control), 2.5, 5, or 10 W/kg, 9 hours and 10 minutes per day, 7 days per week for 106 (males) or 108 (females) weeks with continuous cycling of 10 minutes on and 10 minutes off during a period of 18 hours and 20 minutes each day. The sham control animals were housed in reverberation chambers identical to those used for the exposed groups, but were not exposed to RFR; shared groups of unexposed mice of each sex served as sham controls for both RFR modulations. Fifteen mice per group were randomly selected from the core group after 10 weeks of study; 10 of those 15 mice per group were used for interim evaluation at 14 weeks, and five mice per group were used for genetic toxicity testing at 14 weeks. The remaining 90 animals per group were exposed up to 2 years. Percent survival was significantly higher in 2.5 W/kg males compared to that in the sham controls in the 2-year study. Survival of males and females in all other exposed groups was generally similar to that of the sham controls. Mean body weights of exposed groups of males and females were similar to those of the sham controls throughout the study. There was a significantly increased incidence of hepatoblastoma in 5 W/kg males. Compared to the sham controls, the incidences of malignant lymphoma were increased in all exposed groups of females, and the increase was significant in the 2.5 W/kg group. As noted for the GSM study, the shared sham control group had a low incidence of malignant

lymphoma compared to the range observed in historical controls.There were no nonneoplastic lesions that were considered related to exposure to CDMA-modulated cell phone RFR.

Comprehensive summary: Under the conditions of these 2-year studies, there was equivocal evidence of carcinogenic activity of GSM-modulated cell phone RFR at 1,900 MHz in male B6C3F1/N mice based on the combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin, and the incidences of alveolar/ bronchiolar adenoma or carcinoma (combined) in the lung. There was equivocal evidence of carcinogenic activity of GSM-modulated cell phone RFR at 1,900 MHz in female B6C3F1/N mice based on the incidences of malignant lymphoma (all organs). There was equivocal evidence of carcinogenic activity of CDMA-modulated cell phone RFR at 1,900 MHz in male B6C3F1/N mice based on the incidences of hepatoblastoma of the liver. There was equivocal evidence of carcinogenic activity of CDMA-modulated cell phone RFR at 1,900 MHz in female B6C3F1/N mice based on the incidences of malignant lymphoma (all organs).

Comprehensive comment*: *Equivocal evidence of carcinogenicity in mice for GSM and CDMA-modulated RFR.

TWO YEAR CANCER BIOASSAY IN RATS (Table 9 a)

3. NTP TR 595, 2018.

GSM-modulated RFR, Harlan SD rats (M, F), prenatal exposure for 24 months, carcinogenicity study.

Beginning on GD 5, groups of 56 time-matched F0 female rats were housed in specially designed reverberation chambers and received whole-body exposures to GSM-modulated cell phone RFR at power levels of 0 (sham control), 1.5, 3, or 6 W/kg for 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. There were seven exposure groups per sex, including a shared sham control and three exposure groups for each modulation. At weaning, three males and three females per litter from 35 litters were randomly selected per exposure group for continuation. Weaning occurred on the day the last litter reached PND 21, marking the beginning of the 2-year studies. Groups of 105 male and 105 female F1 offspring continued to receive whole-body exposures to GSM-modulated cell phone RFR at the same power levels and under the same exposure paradigm, 7 days per week for up to 104 weeks. After 14 weeks of exposure, 10 rats per group were randomly selected for interim histopathologic evaluation and five were designated for genetic toxicity evaluation. In the heart at the end of the 2-year studies, malignant schwannoma (synonymous neurinoma) was observed in all exposed male groups and the 3 W/kg female group, but none occurred in the sham controls. Endocardial Schwann cell hyperplasia also occurred in a single 1.5 W/kg male and two 6 W/kg males. There were also significantly increased incidences of right ventricle cardiomyopathy in 3 and 6 W/kg males and females. In the brain of males, there were increased incidences of malignant glioma and glial cell hyperplasia in all exposed groups, but none in the sham controls. There was also increased incidences of benign or malignant granular cell tumours in all exposed groups. There were significantly increased incidences of benign pheochromocytoma and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla in males exposed to 1.5 or 3 W/kg. In the adrenal medulla of females exposed to 6 W/kg, there were significantly increased incidences of hyperplasia. In the prostate gland of male rats, there were increased incidences of adenoma or adenoma or carcinoma (combined) in 3 W/kg males and epithelium hyperplasia in all exposed male groups. In the pituitary gland (pars distalis), there were increased incidences of adenoma in all exposed male groups. There were also increased incidences of adenoma or carcinoma (combined) of the pancreatic islets in all exposed groups of male rats, but only the incidence in the 1.5 W/kg group was significant. In female rats, there were significantly increased incidences of C-cell hyperplasia of the thyroid gland in all exposed groups, and significantly increased incidences of hyperplasia of the adrenal cortex in the 3 and 6 W/kg groups.

GSM-modulated RFR: Under the conditions of this 2-year whole-body exposure study, there was clear evidence of carcinogenic activity of GSM-modulated cell phone RFR at 900 MHz in male Hsd:Sprague Dawley SD rats based on the incidences of malignant schwannoma of the heart. The incidences of malignant glioma of the brain and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla were also related to RFR exposure. The incidences of benign or malignant granular cell tumours of the brain, adenoma or carcinoma (combined) of the prostate gland, adenoma of the pars distalis of the pituitary gland, and pancreatic islet cell adenoma or carcinoma (combined) may have been related to RFR exposure. There was equivocal evidence of carcinogenic activity of GSM-modulated cell phone RFR at 900 MHz in female Hsd:Sprague Dawley SD rats based on the incidences of schwannomas of the heart. Increases in nonneoplastic lesions of the heart, brain, and prostate gland in male rats, and of the heart, thyroid gland, and adrenal gland in female rats occurred with exposures to GSM-modulated RFR at 900 MHz.

Comment: Positive evidence of carcinogenicity for malignant Schwannoma (neurinoma) of the heart associated to RF-EMF exposure in the near field (GSM-modulated RFR); the incidences of malignant glioma of the brain and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla were also related to RFR exposure. Note: brain tumours and neurinomas are also increased in epidemiological studies.

4. Falcioni et al., 2018.

SD rats (M, F), prenatal exposure until spontaneous death, Carcinogenicity study.

Male and female Sprague-Dawley rats were exposed from prenatal life until natural death to a 1.8 GHz GSM far field of 0, 5, 25, 50 V/m with a whole-body exposure for 19 h/day. A statistically significant increase in the incidence of heart Schwannomas was observed in treated male rats at the highest dose (50 V/m). Furthermore, an increase in the incidence of heart Schwann cells hyperplasia was observed in treated male and female rats at the highest dose (50 V/m), although this was not statistically significant. An increase in the incidence of malignant glial tumours was observed in treated female rats at the highest dose (50 V/m), although not statistically significant. The RI findings on far field exposure to RFR are consistent with and reinforce the results of the NTP study on near field exposure, as both reported an increase in the incidence of tumours of the brain and heart in RFR-exposed Sprague-Dawley rats. These tumours are of the same histotype as those observed in some epidemiological studies on cell phone users. These experimental studies provide sufficient evidence to call for re-evaluation of the IARC conclusions regarding the carcinogenic potential of RFR in humans.

Comment : Positive evidence for an association of RF-EMF in the far field (environmental) exposure with an increase in heart Schwannoma (neurinoma is a synonymous) [pubblication of the whole study is ongoing]. Note: brain tumours and neurinomas are also increased in epidemiological studies.

TUMOUR-PRONE MICE (Table 10 a)

5. Lee et al., 2011

AKR/J mice (M, F), 42 weeks (~10 months), Lymphoma-prone.

Carcinogenic effects of combined signal RF-EMFs on AKR/J mice, which were used for the lymphoma animal model, were investigated. Six-week-old AKR/J mice were simultaneously exposed to two types of RF signals: single code division multiple access (CDMA) and wideband code division multiple access (WCDMA). AKR/J mice were exposed to combined RF-EMFs for 45 min/day, 5 days/week, for a total of 42 weeks. The whole-body average specific absorption rate (SAR) of CDMA and WCDMA fields was 2.0 W/kg each, 4.0 W/kg in total. When we examined final survival, lymphoma incidence, and splenomegaly incidence, no differences were found between sham- and RF-exposed mice. However, occurrence of metastasis infiltration to the brain in lymphoma-bearing mice was significantly different in RF-exposed

mice when compared to sham-exposed mice, even though no consistent correlation (increase or decrease) was observed between male and female mice. However, infiltration occurrence to liver, lung, and spleen was not different between the groups. From the results, we suggested that simultaneous exposure to CDMA and WCDMA RF-EMFs did not affect lymphoma development in AKR/J mice.

Comment*: *Short period of exposure. Exposure did not affect lymphoma development in AKR/J mice.

PROMOTION STUDIES IN MICE (Table 11a)

6. Lerchl et al., 2015, B6C3F1 mice (F), 24 months, Promotion study.

(Tillmann et al., 2010) suggested tumour-promoting effects of RF-EMF. A replication study using higher numbers of animals per group and including two additional exposure levels (0 (sham), 0.04, 0.4 and 2 W/kg SAR) was performed. Numbers of tumours of the lungs and livers in exposed animals were significantly higher than in sham-exposed controls. In addition, lymphomas were also found to be significantly elevated by exposure. A clear dose-response effect was absent. We hypothesize that these tumour-promoting effects may be caused by metabolic changes due to exposure. Since many of the tumour-promoting effects in our study were seen at low to moderate exposure levels (0.04 and 0.4 W/kg SAR), thus well below exposure limits for the users of mobile phones, further studies are warranted to investigate the underlying mechanisms. Our findings may help to understand the repeatedly reported increased incidences of brain tumours in heavy users of mobile phones.

Comment: The study does not exactly replicate the Tillmann et al., (2010) study. It shows positive evidence of association between lung, liver tumours, and lymphomas with exposure to RF-EMF.

Table 8 – Cancer in experimental animals: two years cancer bioassays in mice (450-6000 MHz) (a)

Reference, Strain, Species (sex), Duration, Type of study	RF Exposure Level Frequencies, Intensities; Any Other Co-Exposure	Exposure time, No. of Animals	Increased Tumour Incidence (Significance)	Comments
1. NTP TR 596, B6C3F1/N mice (M, F), prenatal exposure for 24 months, carcinogenicity study, 2018	GSM, (1900 MHz), 2.5, 5, and 10 W/Kg	9 h/day, 7 days/week, 105/sex/group	Combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin and the incidences of alveolar/ bronchiolar adenoma or carcinoma (combined) in the lung. In females increased incidences of malignant lymphoma (all organs).	Adequate, equivocal
2. NTP TR 596, B6C3F1/N mice (M, F), prenatal exposure for 24 months, carcinogenicity study, 2018	CDMA (1900 MHz), 2.5, 5, and 10 W/Kg	9 h/day, 7 days/week, 105/sex/group	Hepatoblastoma of the liver. in female increased incidences of malignant lymphoma (all organs).	Adequate, equivocal

Table 9 – Cancer in experimental animals: two years cancer bioassays in rats (450-6000 MHz) (a)

Reference, Strain, Species (sex), Duration, Type of study	RF Exposure Level Frequencies, Intensities; Any Other Co-Exposure	Exposure time, No. of Animals	Increased Tumour Incidence (Significance)	Comments
3. NTP TR 595, SD rats (M, F), prenatal exposure for 24 months, carcinogenicity study, 2018	GSM, CDMA (900 MHz), 1.5, 3, 5 W/kg	9 h/day, 7 days/week, 105/sex/group	Male brain glioma, heart Schwannoma, and combined adrenal pheochromocytoma ($p < 0.05$)	Adequate, positive for heart Schwannomas and brain tumours; positive for adrenal tumours
4. NTP TR 595, SD rats (M, F),), prenatal exposure for 24 months, carcinogenicity study, 2018	GSM, CDMA (900 MHz), 1.5, 3, 5 W/kg	9 h/day, 7 days/week, 105/sex/group	Male brain glioma, heart Schwannoma, and combined adrenal pheochromocytoma ($p < 0.05$)	Adequate, positive for heart Schwannomas and brain tumours; positive for adrenal tumours
5. Falcioni et al., 2018, SD rats (M, F), prenatal exposure until spontaneous death, carcinogenicity study	GSM (1800 MHz), 0.1, 0.03, 0.001 W/Kg	19 h/day, 7 days/week, 200,400 /sex/group	Male heart Schwannoma ($p < 0.05$) and female brain glioma	Adequate, positive for heart Schwannomas; borderline for brain tumours

Table 10a - Cancer in experimental animals: tumour-prone mice (450-6000 MHz) (a)

Reference, Strain, Species (sex), Duration, Type of study	RF Exposure Level Frequencies, Intensities; Any Other Co-Exposure	Exposure time, No. of Animals	Increased Tumour Incidence (Significance)	Comments
6. Lee et al., 2011, AKR/J mice (M, F), 42 weeks (~10 months), Lymphoma-prone	CDMA (849 MHz) and WCDMA (1950 MHz), 4 W/kg (combined)	45 min/day, 5 days/week, 40/sex/group	No statistically significant increase in tumour incidence	Inadequate (Short daily exposure)

Table 10b - Cancer in experimental animals: promotion studies in mice (450-6000 MHz) (a)

Reference, Strain, Species (sex), Duration, Type of study	RF Exposure Level Frequencies, Intensities; Any Other Co-Exposure	Exposure time, No. of Animals	Increased Tumour Incidence (Significance)	Comments
7. Lerchl et al., 2015, B6C3F1 mice (F), 24 months, Promotion study	UMTS fields, 0.04, 0.4 and 2.0 W/kg; prenatal ENU 40mg/kg b.w.	23.5 h/day, 7 days/week, 96/group	Female lymphoma, lung adenoma and carcinoma, liver carcinoma (tumour promotion) ($p < 0.05$)	Adequate, positive

Table 11 (summary tables 8-10) - Collected data for experimental studies on Cancer (FR1: 450-6000 MHz)

Total studies FR1*	7							
Adequate studies	7							
	Rat				Mouse			
Observed Tumour	Total adequate studies[a]	Positive results	Equivocal results	Negative results	Total adequate studies[b]	Positive results	Equivocal results	Negative results
Glioma	3	2	1					
Heart Schwannoma	3	3						
Alveolar-bronchiolar adenoma, carcinoma					3	1	2	
Liver tumours	2		1		3	1	2	
Adrenal pheochromocytoma	2	2						
Pancreatic islet adenoma+carcinoma	2		2					
Prostate adenoma+carcinoma	2		2					
Pituitary gland adenoma	2		2					
Lymphoma					4	1	2	1
Fibrosarcoma, fibro-histiocitic sarcoma of the skin					3		2	

*Some of the studies include more than one tumour site. [a] 1 study published only partial results on brain and heart.[b]1 study on lymphoma prone mice

SUMMARY OF THE RESULTS OF CANCER IN EXPERIMENTAL ANIMALS STUDIES (FR1: 450 to 6000 MHZ)(Table 11)

Based on full-text screening, the articles with frequencies appropriate for inclusion in this qualitative synthesis were 50. As further explained in the methodology section, we considered IARC Monograph 102 (IARC, 2013) as our key reference for all studies on cancer in experimental animals published until 2011: all original papers (43) that were included in the IARC monograph were analysed and referenced in this report as well; of course, we considered for this report only the final IARC classification. Seven adequate studies were published after 2011. From the present review, 7 studies on carcinogenicity in experimental animals were selected. 4 studies were performed on mice, 3 were performed on rats. Summaries of the results are presented in Table 27.

Out of the 7 adequate studies, the results were:

- Carcinogenicity in mice:

Two adequate carcinogenicity studies were performed to investigate possible non-thermal adverse effects on carcinogenicity related to RF-EMF exposure in mice. The studies were performed by the NTP laboratory in the USA .

Ref: 1: GSM-modulated cell phone RFR at 1,900 MHz in male B6C3F1/N mice showed: *positive* association of RF-EMF exposure with combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin, and the incidences of alveolar/ bronchiolar adenoma or carcinoma (combined) in the lung. There was *equivocal* evidence of carcinogenic activity in female B6C3F1/N mice based on the incidences of malignant lymphoma (all organs).

Ref: 2: There was *equivocal* evidence of carcinogenic activity of CDMA-modulated cell phone RFR at 1,900 MHz in male B6C3F1/N mice based on the incidences of hepatoblastoma of the liver. There was equivocal evidence of carcinogenic activity of CDMA-modulated cell phone RFR at 1,900 MHz in female B6C3F1/N mice based on the incidences of malignant lymphoma (all organs).

Two studies with different animal model and design were also performed on mice:

Ref: 6: one study on lymphoma-prone mice did not show any increase in lymphoma (*no* evidence).

Ref: 7: one two-years promotion study showed a statistically significant increase of tumours of the lung and liver in exposed animals. In addition, lymphomas were also found to be significantly increased (*positive* ass0ciation)

- Carcinogenicity in rats

Three adequate carcinogenicity studies were performed to investigate possible non-thermal adverse effects on carcinogenicity related to RF-EMF exposure in rats. Two studies were performed by the NTP laboratory in the USA (Ref:3,4) , one study (partially published) by the Ramazzini Institute in Italy (Ref: 5).

The most convincing evidence for the 3 studies regards the statistically significant increase (positive association) of brain tumours (Ref: 3, 4) supported by the *equivocal* association of the same tumour in the third study (Ref: 5) and the statistically significant increase of a very rare tumour of the heart, malignant Schwannoma, in all 3 studies (*positive* association). The increase of adrenal pheochromocytoma was statistically significant (positive association), and pancreatic islet adenoma+carcinoma, prostate adenoma+carcinoma, pituitary gland adenoma were also increased in treated groups (Ref: 3, 4) (*equivocal* association).

FR1: Our review on experimental studies on rats and mice shows a sufficient evidence of carcinogenicity of RF-EMF at lower frequencies (FR1). The observation of tumours of the nervous system (central and peripheral) in male rats is of particular significance, because supporting findings of epidemiological studies.

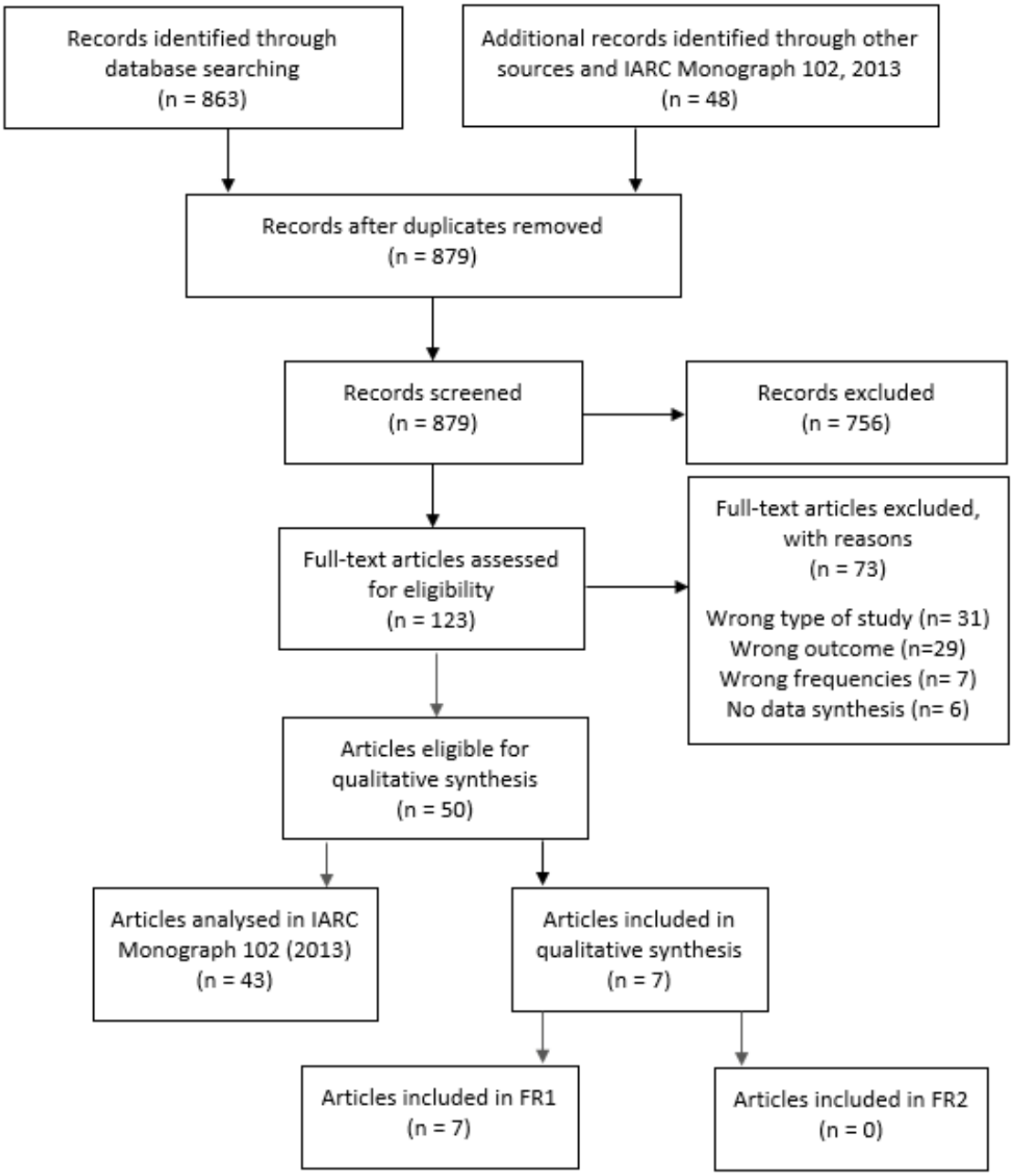
4.1.4 Cancer in experimental animals: Studies evaluating health effects due to RF at a higher frequency range (FR2: 24 to 100 GHz, MMW).

The articles identified through database searching and other sources were 911. After removing duplicates (32) and excluding non-pertinent articles (756) based on title and abstracts, 123 articles remained. Based on full-text screening, 73 papers were further excluded, so that the articles with frequencies appropriate for inclusion in this qualitative synthesis were 50 (Fig. 12).

As further explained in the methodology section, we considered IARC Monograph 102 (IARC, 2013) as our key reference for all studies on cancer in experimental animals published until 2011: all original papers (43) that were included in the IARC monograph were analysed and referenced in this report as well; of course, we considered for this report only the final IARC classification. Seven adequate studies were published after 2011.

At this stage, a separation based on frequency range was also performed: of the 7 papers included, all reported exposures belonging to the band considered in FR1, and none reported exposures regarding FR2. In conclusion, there is no available literature regarding the association between RF radiation at the range 24 to 100 GHz (MMW) in experimental carcinogenicity studies.

Figure 12 – Flow diagram. Cancer in experimental animal studies FR2



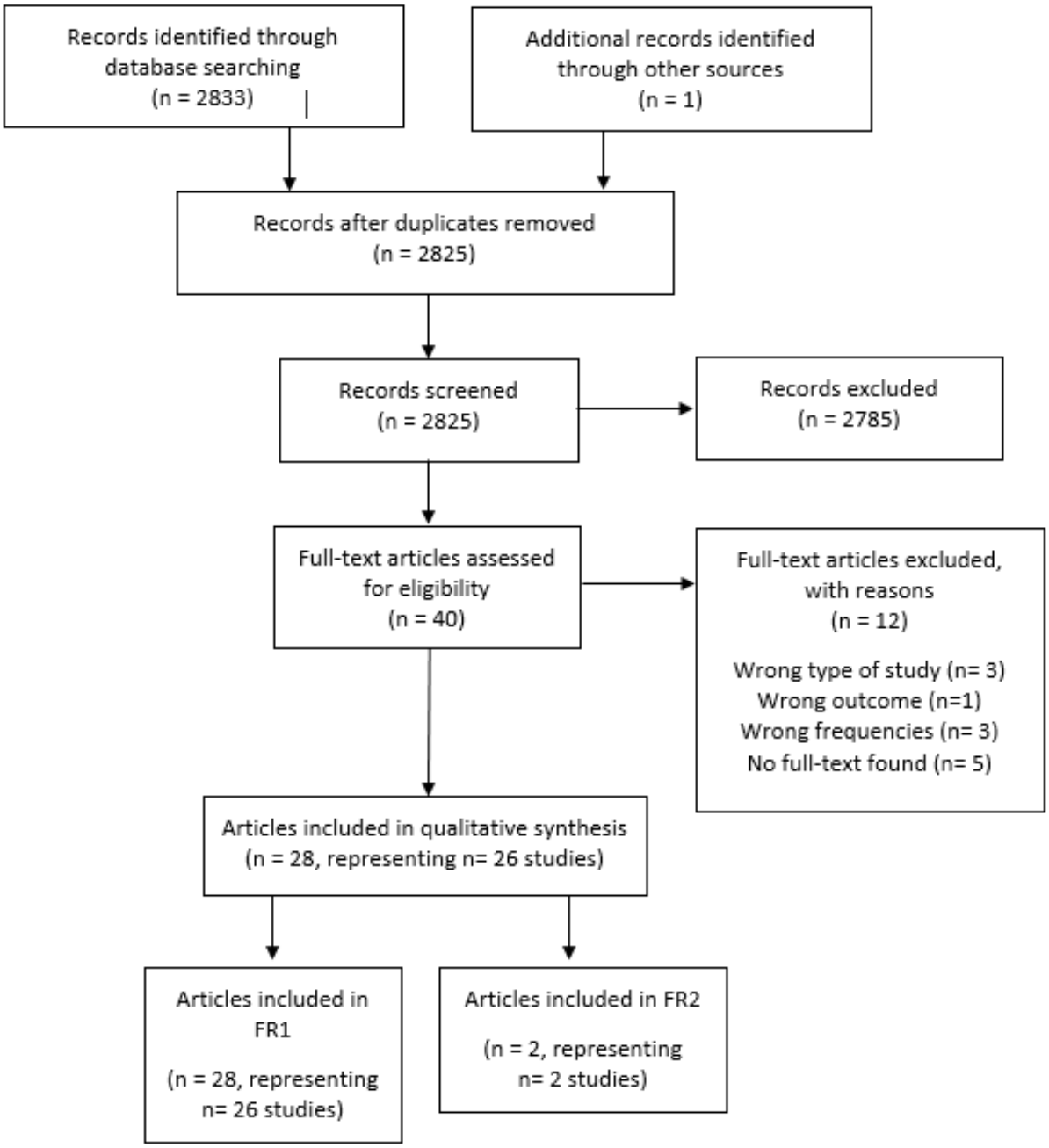
4.2 Reproductive/developmental adverse effects by frequency range

4.2.1 Reproductive/developmental effects in epidemiological studies: Studies evaluating health effects due to RF at a lower frequency range (FR1: 450 to 6000 MHZ), which also includes the frequencies used in previous generations' broadband cellular networks (1G, 2G, 3G and 4G).

The articles identified through database searching and other sources were 2834. After removing duplicates (9) and excluding non-pertinent articles (2785) based on title and abstracts, 40 articles remained. Based on full-text screening, 12 papers were further excluded, so that the published articles with appropriate frequencies to be included in this qualitative synthesis were 28, corresponding to 26 studies (in two cases, two papers were published reporting information on the same study) (Fig. 13).

At this stage, selection based on frequency range was also performed: 28 papers/26 studies referred to exposures belonging to the FR1 range, and 2 referred to FR2 as well. These 2 papers report exposures suitable for both FR1 and FR2, so they don't add up to the overall number of included studies; the same study is analysed therefore twice, once in every frequency range.

Figure 13 – Flow diagram. Epidemiological studies on reproductive/developmental effects FR1



MALE FERTILITY

Case-control studies (Tables 12a)

1. Al-Quzwini et al., 2016.

Iraq. Case-control study.

A seminal fluid analysis is clinical marker of male reproductive potential. To find out whether environmental hazard such as mobile phone tower has an effect on male reproductive ability. Two hundred couples were enrolled, one hundred subfertile couples as a study group (n=100), and one hundred fertile couples as a control group (n= 100). Environmental exposure to electromagnetic radiation from mobile phone towers and occupational state was assessed by standard questionnaire. Semen analysis was done for the subfertile males, because the fertile males (control group) refused to give semen samples. The occupational hazard expressed significant difference between the subfertile and the control groups (38% versus 12%) ($p< 0.05$), with odds ratio (OR) =4.5 and 95% Confidence Interval (CI): 2.175–9.288, and also the environmental factor (mobile tower within fifty meters from their house) showed significant difference (29% versus 12%) ($p< 0.05$), with OR= 3; 95% CI: 1.426–6.290. SFA of the subfertile males was 40% abnormal versus 60% normal semen analysis. These abnormalities were classified into 35% oligozoospermia, 55% asthenospermia, and 10% teratozoospermia. Oligozoospermia was associated with more occupational hazard (OR= 1.8, 95% CI: 0.569–5.527). Teratozoospermia was associated with more occupational hazard (OR= 5.23, 95% CI: 0.524–52.204), and with exposure to environmental hazard (OR = 2.6, 95% CI: 0.342– 19.070), and associated with smoking hazard (OR =1.7, 95% CI: 0.225–12.353). Male fertility represented by quality of semen might be affected by occupational and environmental exposures, so it seems that prevention of occupational and environmental risk factors, may lead to improvement of semen quality in subfertile men.

Comment*: *Inadequate/Inconclusive.

Cross-sectional studies (Tables 13, a-d)

2. Baste et al., 2008.

Norway. 2002-2004. Cross-sectional study, occupational exposure.

The authors performed a cross-sectional study among military men employed in the Royal Norwegian Navy, including information about work close to equipment emitting radiofrequency electromagnetic fields, one-year infertility, children and sex of the offspring. Among 10,497 respondents, 22% had worked close to high-frequency aerials to a ''high'' or ''very high'' degree. Infertility increased significantly along with increasing self-reported exposure to radiofrequency electromagnetic fields. In a logistic regression, the odds ratio (OR) for infertility among those who had worked closer than 10 m from high-frequency aerials to a ''very high'' degree relative to those who reported no work near high-frequency aerials was 1.86 (95% confidenceinterval (CI): 1.46–2.37), adjusted for age, smoking habits, alcohol consumption and exposure to organic solvents, welding and lead. Similar adjusted OR for those exposed to a ''high'', ''some'' and ''low'' degree were 1.93 (95% CI: 1.55–2.40), 1.52 (95% CI: 1.25–1.84), and 1.39 (95% CI: 1.15–1.68), respectively. In all age groups there were significant linear trends with higher prevalence of involuntary childlessness with higher self-reported exposure to radiofrequency fields. However, the degree of exposure to radiofrequency radiation and the number of children were not associated. For self-reported exposure both to high-frequency aerials and communication equipment there were significant linear trends with a lower ratio of boys to girls at birth when the father reported a higher degree of radiofrequency electromagnetic exposure.

Comment*: *Self-reported level of exposure. Higher degree of RF-EMF exposure associated to infertility and a lower ratio of boys to girls at birth.

3. Mollerlekken and Moen, 2008.

Norway. 2002. Cross-sectional, occupational exposure.

The aim of this study was to examine the relationship between workers exposed to electromagnetic fields and their reproductive health. We obtained data using a questionnaire in a cross-sectional study of naval military men, response rate 63% (n¼1487). The respondents were asked about exposure, lifestyle, reproductive health, previous diseases, work and education. An expert group categorized the work categories related to electromagnetic field exposure. We categorized the work categories ''tele/communication,'' ''electronics'' and ''radar/sonar'' as being exposed to electromagnetic fields. Logistic regression adjusted for age, ever smoked, military education, and physical exercise at work showed increased risk of infertility among tele/ communication odds ratio (OR≤1.72, 95% confidence interval 1.04–2.85), and radar/sonar odds ratio (OR≤2.28, 95% confidence interval 1.27–4.09). The electronics group had no increased risk. This study shows a possible relationship between exposure to radiofrequency fields during work with radiofrequency equipment and radar and reduced fertility. However, the results must be interpreted with caution.

Comment*: *Self-reported exposure. Possible increased risk of infertility among telecommunication and radar/sonar operators.

4. Fejez et al., 2005.

Hungary. Cross-sectional study.

The history-taking of men in our university clinic was supplemented with questions concerning cell phone use habits, including possession, daily standby position and daily transmission times. Semen analyses were performed by conventional methods. Statistics were calculated with SPSS statistical software. A total of 371 were included in the study. The duration of possession and the daily transmission time correlated negatively with the proportion of rapid progressive motile sperm (r = 0.12 and r = 0.19, respectively), and positively with the proportion of slow progressive motile sperm (r =0.12 and r = 0.28, respectively). The low and high transmitter groups also differed in the proportion of rapid progressive motile sperm (48.7% vs. 40.6%). The prolonged use of cell phones may have negative effects on the sperm motility characteristics.

Comment*: *Exposure self-reported. Confounding factors not analysed.

5. Jurewicz et al., 2014, Radwan et al., 2016 (they published the same study).

Poland. Cross-sectional study.

The aim of the study was to examine the association between modifiable lifestyle factors and main semen parameters, sperm morphology, and sperm chromatin structure. The study population consisted of 344 men who were attending an infertility clinic for diagnostic purposes with normal semen concentration of 20–300 M/ml or with slight oligozoospermia (semen total concentration of 15–20 M/ml) [WHO 1999]. Participants were interviewed and provided semen samples. The interview included questions about demographics, socio-economic status, medical history, lifestyle factors (consumption of alcohol, tobacco, coffee intake, cell phone and sauna usage), and physical activity. The results of the study suggest that lifestyle factors may affect semen quality. A negative association was found between increased body mass index (BMI) and semen volume (p≤0.03). Leisure time activity was positively associated with sperm concentration (p≤0.04) and coffee drinking with the percentage of motile sperm cells, and the percentage of sperm head and neck abnormalities (p≤0.01, p≤0.05, and p≤0.03, respectively). Drinking red wine 1–3 times per week was negatively related to sperm neck abnormalities (p≤0.01). Additionally, using a cell phone more than 10 years decreased the percentage of motile sperm cells (p≤0.02). Men who wore boxer shorts had a lower percentage of sperm neck abnormalities (p≤0.002) and percentage of sperm with DNA damage (p≤0.02). These findings may have important implications for semen quality and lifestyle.

Comment*: *Self-reported exposure. Different confounders could affect results.

6. Yildirim et al., 2015.

Turkey. Cross-sectional study.

Semen for analyses from the male patients coming to our infertility division and also asked them to fill out an anonymous questionnaire. We queried their mobile phone and wireless internet usage frequencies in order to determine their radiofrequency-electromagnetic radiation exposure. A total of 1082 patients filled the questionnaire but 51 of them were excluded from the study because of azoospermia. There was no significant difference between sperm counts and sperm morphology excluding sperm motility, due to mobile phone usage period, ($p = 0.074$, $p = 0.909$, and $p = 0.05$, respectively). The total motile sperm count and the progressive motile sperm count decreased due to the increase of internet usage ($p = 0.032$ and $p = 0.033$, respectively). In line with the total motile sperm count, progressive motile sperm count also decreased with wireless internet usage compared with the wired internet connection usage ($p = 0.009$ and $p = 0.018$, respectively). There was a negative correlation between wireless internet usage duration and the total sperm count ($r = - 0.089$, $p = 0.039$). We have also explored the negative effect of wireless internet use on sperm motility according to our preliminary results.

Comment*: *Exposure self-reported. Confounding factors were not analysed. Any difference between sperm parameters and cell phone and wireless internet usage is the authors conclusions.

7. Zilberlicht et al., 2015.

Israel. Cross-sectional.

Male infertility constitutes 30–40% of all infertility cases. Some studies have shown a continuous decline in semen quality since the beginning of the 20th century. One postulated contributing factor is radio frequency electromagnetic radiation emitted from cell phones. This study investigates an association between characteristics of cell phone usage and semen quality. Questionnaires accessing demographic data and characteristics of cell phone usage were completed by 106 men referred for semen analysis. Results were analysed according to WHO 2010 criteria. Talking for ≥1 h/day and during device charging were associated with higher rates of abnormal semen concentration (60.9% versus 35.7%, $P < 0.04$ and 66.7% versus 35.6%, $P < 0.02$, respectively). Among men who reported holding their phones ≤50 cm from the groin, a non-significantly higher rate of abnormal sperm concentration was found (47.1% versus 11.1%). Multivariate analysis revealed that talking while charging the device and smoking were risk factors for abnormal sperm concentration (OR = 4.13 [95% CI 1.28–13.3], $P < 0.018$ and OR = 3.04 [95% CI 1.14–8.13], $P < 0.027$, respectively). Our findings suggest that certain aspects of cell phone usage may bear adverse effects on sperm concentration. Investigation using largescale studies is thus needed.

Comment*: *Self-reported exposure. Some association was found.

8. Al-Bayyari, 2017.

Jordan. Cross-sectional observational study.

The objective was to study the effect of cell phone usage on semen quality and men's fertility. A cross-sectional observational study conducted on 159 men attending infertility clinics at North, Middle and South Governorates in Jordan and undergoing infertility evaluation were divided into two groups according to their active cell phone use: group A: ≤1 h/day and group B: >1 h/day. No interventions were given to patients and semen samples were collected by masturbation in a sterile container after an abstinence period of 5 days. The main outcome measures were sperm volume, liquefaction time, pH, viscosity, count, motility and morphology.

Time of talking by cell phone was recorded and the subjects were divided into 2 groups; group A ≤ 1 h/day (n = 104); group B > 1 h/day (n = 52) and participants who did not use cell phone (n = 3) were excluded from the statistical analysis regarding studying the effect of time spent in calling or receiving calls.There were no statistical significance differences (p > 0.05) between both groups regarding sperm quality parameters according to cell phone use, but there were statistical differences in the frequencies of sperm concentration, volume, viscosity, liquefaction time and means of immotile sperms and abnormal morphology. In addition, time spend on watching television and using wireless phones were significantly (p ≤0.05) associated with decreasing mean percentages of normal morphology. The distance from telecommunication tower was significantly (p ≤0.05) associated with decreasing sperms volume. Meanwhile, the time spent on sending or receiving messages was significantly (p ≤ 0.05) associated with decreasing sperms count and carrying mobile phone in trouser pocket was significantly associated with increasing means of immotile sperms. Cell phone use might have a negative effect on semen quality parameters and further research is needed.

Comment*: *Self-reported exposure. Cell phone use might have a negative effect on semen quality parameters.

9. Shi et al., 2018.

Cross-sectional study.

Three hundred and twenty-eight subjects who underwent semen analysis were recruited. Routine SA, sperm vitality, acrosome reaction (AR) assay and sperm DNA fragmentation index (DFI) were analyzed. Demographic and lifestyle information, including (1) BMI, (2) current smoking and alcohol drinking frequency, (3) sleep habits, (4) daily fluid intake, (5) weekly meat intake, (6) sports frequency, (7) trouser cell phone use, (8) age, and (9) abstinence time, were collected. Generalized additive models were used to analyze the possible non-linear association. The results showed that total sperm count (TSC) was significantly associated with age (P = 0.001), abstinence time (P = 0.001) and daily coffee intake (P = 0.044). Semen volume was significantly associated with age (P < 0.001) and daily coffee intake (P < 0.001). Sperm concentration was significantly associated with abstinence time (P = 0.011) and average sleep duration (P = 0.010). Sperm motility was significantly associated with age (P = 0.002) and daily juice intake (P = 0.001). Total motile sperm count was significantly associated with age (P = 0.003) and abstinence time (P = 0.009). DFI was significantly associated with age (P = 0.002), irregular sleeping habit (P = 0.008) and abstinence time (P = 0.032). The percentage of AR sperm was significantly associated with daily juice intake (P = 0.013). In conclusion, DFI and TSC were the most sensitive semen parameters for demographic and lifestyle features, whereas age had more influence on semen parameters than other demographic and lifestyle features. Trouser cell phone use was not significantly associated with any alteration of the sperm parameters examined.

Comment*: *Self-reported exposure. Many confounders in age and lifestyle. Any association with sperm alteration.

10. Blay et al., 2020.

Ghana. Cross-sectional study.

Male infertility is known to contribute about half of all infertility cases. In Ghana, the prevalence of male infertility is higher (15.8%) than in females (11.8%). Sperm quality is associated with the likelihood of pregnancy and known to be the cause of male fertility problems 90% of the time. Exposure to certain environmental factors reduces semen quality in men. The study examined the effects of environmental and lifestyle factors on semen quality in Ghanaian men. Materials and Methods. This was a cross-sectional study involving 80 apparent healthy adult males in their reproductive age. Participants were males referred to the laboratory (Immunology Unit of the Korle-Bu Teaching Hospital) for semen analysis test and/or culture and sensitivity. Participants were made to fill out a questionnaire which entailed selected environmental factors (accidents or trauma, exposure to chemicals, radiation, and heat) and lifestyle habits (including alcohol consumption, smoking, and whether participants sat more or less than 4 hours per day).

Semen samples were then collected by masturbation into sterile containers and analysed in accordance with WHO guidance for semen analysis within 60 minutes after ejaculation and collection. Results. About 69% of participants had semen pH within the normal range compared to 15% whose pH were lower than 7.2. There was a significantly high number of immotile sperm cells (p value = 0.017) in participants who sat for more than 4 hours as compared to those that sat for less than 4 hours in a day. Active sperm motility and viability showed significant increase (p value = 0.002 and 0.009, respectively) in participants who kept their cell phones in their side pockets. Smoking produced a twofold decrease in sperm count as smokers had a significantly lower sperm count (12:28 ± 10:95 × 106/ml) compared to the smoke-free (23:85 ± 22:14 × 106/ml). For exposure to STDs, no significant differences were recorded among study groups concerning semen quality. Conclusion. Sperm quality in Ghanaian men is associated with lifestyle habits. Smoking and sitting for long hours influenced sperm motility and count, respectively. Knowledge of the factors that influence sperm quality in this geographical region can contribute to informed decisions on effective management of infertility in Ghanaian men.

Comment*: *Self-reported exposure, uncertain. Increased activity and viability associated to cell phone in their side pockets. Many confounders.

Cohort studies (Tables 14, a-c)

11. Zhang, 2016.

China. 2013-2015. Cohort study.

Recruiting participants from infertility clinic not from general population may raise the possibility of a selection bias. To investigate effects of cell phone use on semen parameters in a general population. We screened and documented the cell phone use information of 794 young men from the Male Reproductive Health in Chongqing College students (MARHCS) cohort study in 2013, followed by 666 and 568 in 2014 and 2015, respectively. In the univariate regression analyses, we found that the daily duration of talking on the cell phone was significantly associated with decreased semen parameters, including sperm concentration [β coefficient = −6.32% per unit daily duration of talking on the cell phone (h); 95% confidence interval (CI), −11.94, −0.34] and total sperm count (−8.23; 95% CI, −14.38, −1.63) in 2013; semen volume (−8.37; 95% CI, −15.93, −0.13) and total sperm count (−16.59; 95% CI, −29.91, −0.73) in 2015]. Internet use via cellular networks was also associatedwith decreased sperm concentration and total sperm counts in 2013 and decreased semen volume in 2015. Multivariate analyseswere used to adjust for the effects of potential confounders, and significant negative associations between internet use and semen parameters remained. Consistent but nonsignificant negative associations between talking on the cell phone and semen parameters persisted throughout the three study years, and the negative association was statistically significant in a mixed model that considered all three years of data on talking on the cell phone and semen quality. Our results showed that certain aspects of cell phone use may negatively affect sperm quality inmen by decreasing the semen volume, sperm concentration, or sperm count, thus impairing male fertility.

Comment*: *Self-reported exposure. Confounding not analysed. Association with impairment of male fertility.

12. Lewis et al., 2017.

USA. 2004-2015. Longitudinal cohort study, part of the EARTH Study.

This is a longitudinal cohort study that recruited couples seeking infertility treatment from the Massachusetts General Hospital (MGH) Fertility Center; difficulty conceiving may be related to a male factor, a female factor, or a combination of both male and female factors. The relationship between mobile phone use patterns and markers of semen quality was explored in a longitudinal cohort study of 153 men that attended an academic fertility clinic in Boston, Massachusetts. Men between the ages of 18–56 years

were eligible to participate. Information on mobile phone use duration (no use, <2 h/day,2–4 h/day, >4 h/day), headset or earpiece use (never, occasionally, some of the time, most of the time, all of the time), and location in which the mobile phone was carried (pants pocket, belt, bag, other) was ascertained via nurse-administered questionnaire. Semen samples (n = 350) were collected and analysed onsite. To account for multiple semen samples per man, linear mixed models with random intercepts were used to investigate the association between mobile phone use and semen parameters. Overall, there was no evidence for a relationship between mobile phone use and semen quality.

Comment*: *Self-reported exposure. No evidence for a relationship between mobile phone use and semen quality.

DEVELOPMENTAL STUDIES

Case-control studies (Tables 15 a-f)

13. Tan et al., 2014.

Singapore. Case-control study.

Threatened miscarriage occurs in 20% of pregnancies. We conducted a case-control study to assess the association between maternal lifestyle factors and risk of threatened miscarriage. Cases were 154 women presenting with threatened miscarriage in the 5th to 10th weeks of gestation; controls were 264 women without threatened miscarriage seen in antenatal clinic in the 5th to 10th week of pregnancy. Lifestyle variables were: current and past cigarette smoking, current second-hand cigarette smoke exposure, computer and mobile-phone use, perceived stress, past contraceptive use, past menstrual regularity and consumption of fish oils, caffeine and alcohol. Logistic regression was performed. In multivariate analysis, we found a positive association of threatened miscarriage with second-hand smoke exposure (OR 2.93, 95% CI 1.32–6.48), computer usage (>4 hours/day) (OR 6.03, 95% CI 2.82–12.88), mobile-phone usage (>1 hour/day) (OR 2.94 95% CI 1.32–6.53) and caffeine consumption (OR 2.95 95% CI 1.57– 5.57). Any fish oil consumption was associated with reduced risk of threatened miscarriage (OR 0.20, 95% CI 0.09–0.42). Prolonged mobile phone and computer use and fish oil supplementation are potential novel correlates of threatened miscarriage that deserve further study.

Comment*: *Self-reported exposure. Stress as a confounding variable not considered. Correlation between mobile phone and computer use and threatened miscarriage observed.

14. Mahmoudabadi et al., 2015.

Iran. Case-control study.

Exposure to electromagnetic fields of cell phones increasingly occurs, but the potential influence on spontaneous abortion has not been thoroughly investigated. Methods: In a case–control study, 292 women who had an unexplained spontaneous abortion at < 14 weeks gestation and 308 pregnant women > 14 weeks gestation were enrolled. Two data collection forms were completed; one was used to collect data about socioeconomic and obstetric characteristics, medical and reproductive history, and lifestyles. Another was used to collect data about the use of cell phones during pregnancy. For the consideration of cell phone effects, we measured the average calling time per day, the location of the cell phones when not in use, use of hands-free equipment, use of phones for other applications, the specific absorption rate (SAR) reported by the manufacturer and the average of the effective SAR (average duration of calling time per day × SAR). Analyses were carried out with statistical package state software (SPSS)v.16. The association between use of cell phones and the risk of spontaneous abortions against potential confounders was supported by evidence that despite adjustments for many known or suspected risk factors in logistic regression analyses, the estimation was not significantly altered. All the data pertaining to mobile phones

were different between the two groups except the use of hands-free devices ($p < 0.001$). Our result suggests that use of mobile phones can be related to the early spontaneous abortions.

Comment*: *Self-reported exposure. Use of mobile phones may be related to the early spontaneous abortions.

Cross-sectional studies (Tables 16, a,b)

15. Col-Araz, 2013.

Turkey. 2009. Cross-sectional study.

The study was conducted in Turkey at Gazintep University, Faculty of Medicine's Outpatient Clinic at the Paediatric Ward. It comprised 500 patients who presented at the clinic from May to December 2009. All participants were administered a questionnaire regarding their pregnancy history. SPSS 13 was used for statistical analysis. In the study, 90 (19%) patients had pre-term birth , and 64 (12.9%) had low birth weight rate Birth weight was positively correlated with maternal age and baseline maternal weight ($r= 0.115$, $p= 0.010$; $r= 0.168$, $p= 0.000$, respectively). Pre-term birth and birth weight less than 2500g were more common in mothers with a history of disease during pregnancy ($p=0.046$ and $p=0.008$, respectively). The habit of watching television and using mobile phones and computer by mothers did not demonstrate any relationship with birth weight. Mothers who used mobile phones or computers during pregnancy had more deliveries before 37 weeks ($p=0.018$, $p=0.034$; respectively). Similarly, pregnancy duration was shorter in mothers who used either mobile phone or computers during pregnancy ($p=0.005$, $p=0.048$, respectively). Mobile phones and computers may have an effect on pre-term birth.

Comment*: *Self-reported exposure. Mobile phones and computers may have an effect on pre-term birth.

16. Zarei S. et al., 2015.

Iran. 2014. Cross-sectional study.

The purpose of this study was to investigate whether the maternal exposure to different sources of electromagnetic fields affects the rate and severity of speech problems in their offspring. In this study, mothers of 35 healthy 3-5 years old children (control group) and 77 children diagnosed with speech problems who had been referred to a speech treatment centre in Shiraz, Iran were interviewed. These mothers were asked whether they had exposure to different sources of electromagnetic fields such as mobile phones, mobile base stations, Wi-Fi, cordless phones, laptops and power lines. A significant association between either the call time ($P=0.002$) or history of mobile phone use (months used) and speech problems in the offspring ($P=0.003$) was found. However, other exposures had no effect on the occurrence of speech problems. To the best of our knowledge, this is the first study to investigate a possible association between maternal exposure to electromagnetic fields and speech problems in the offspring. Although a major limitation in our study is the relatively small sample size, this study indicates that the maternal exposure to common sources of electromagnetic fields such as mobile phones can affect the occurrence of speech problems in the offspring.

Comment*: *Small sample size, limit in exposure assessment. Association between maternal use of mobile phone and speech problems in the offspring.

17. Abad et al., 2016.

Iran. Cross-sectional study.

Investigation of the associations between electromagnetic field exposure and miscarriage among women of Tehran. In this longitudinal study, 462 pregnant women with gestational age <12 wks from seven main regions of Teheran city in Iran with similar social and cultural status were participated. The mean age of women was 28.22±4.53 years old. The frequency of spontaneous miscarriage was 56 cases. The incidence of abortion was 12.3%. Women were interviewed face-to face to collect data. Reproductive information

was collected using medical file recorded in those hospitals the subjects had delivery. The measuring device measured electromagnetic waves, Narda safety test solutions with valid calibration date at the entrance door of their houses. A significant likelihood of miscarriage in women who exposed to significant level of electromagnetic wave. However, this association was not confirmed by Wald test. This study may not provide strong or consistent evidence that electromagnetic field exposure is associated or cause miscarriage. This issue may be due to small sample size in this study.

Comment* : *Self-reported exposure. Small sample. Uncertain association between miscarriage and use of mobile phone.

18. Lu et al., 2017.

Japan. 2012-2014. Cross sectional study from cohort data.

The aim of the study was to determine the associations of excessive mobile phone use with neonatal birth weight and infant health status. A sample of 461 mother and child pairs participated in a survey on maternal characteristics, infant characteristics, and information about maternal mobile phone usage during pregnancy. Results showed that pregnant women tend to use mobile phones excessively in Japan. The mean infant birth weight was lower in the excessive use group than in the ordinary use group, and the frequency of infant emergency transport was significantly higher in the excessive use group than in the ordinary use group. Excessive mobile phone use during pregnancy may be a risk factor for lower birth weight and a high rate of infant emergency transport.

Comment*: *Self-reported exposure. Limited sample size. Limited assessment of mothers' exposure. Inconclusive.

Cohort studies (Tables 17, a-f)

19. Mjøen et al., 2006.

Norway. 1976-1995. Cohort study on adverse pregnancy outcome, occupational exposure.

The objective was to assess associations between paternal occupational exposure to RF-EMF and adverse pregnancy outcomes including birth defects using population-based data from Norway. Data on reproductive outcomes derived from the Medical Birth Registry of Norway were linked with data on paternal occupation derived from the general population censuses. Maritime occupations, telephone repair and installation workers and welders were chosen as three separate groups. An expert panel categorized occupations according to exposure. Three occupational exposure levels were assessed, reflecting probability of exposure to RFR; one group was ''probably not exposed'' (376,837 births), one group of ''possibly exposed'' (139,871 births), and one group of ''probably exposed'' (24,885 births). Using logistic regression 24 categories of birth defects as well as other adverse outcomes were analysed. In the offspring of fathers most likely to have been exposed, increased risk was observed for preterm birth (OR: 1.08, 95% confidence interval (CI): 1.03, 1.15). In this group we also observed a decreased risk of cleft lip (OR: 0.63, 95% CI: 0.41, 0.97). In the medium exposed group, we observed increased risk for a category of ''other defects'' (OR: 2.40, 95% CI:1.22, 4.70), and a decreased risk for a category of ''other syndromes'' (OR: 0.75, 95% CI: 0.56, 0.99) and upper gastrointestinal defects (OR: 0.61, 95% CI: 0.40, 0.93). The study is partly reassuring for occupationally exposed fathers.

Comment*: *Level of exposure uncertain. No evidence for a relationship between occupational exposure to RF-EMF and adverse pregnancy outcome.

20. Divan at al., 2008; Divan et al., 2011.

Denmark. Children born between 1997 and 1999, then updated to 2002. Cohort study.

The association between prenatal and postnatal exposure to cell phones and behavioral problems in young children was examined. Mothers were recruited to the Danish National Birth Cohort early in pregnancy. When the children of those pregnancies reached 7 years of age in 2005 and 2006, mothers were asked to complete a questionnaire regarding the current health and behavioral status of children, as well as past exposure to cell phone use. Mothers evaluated the child's behavior problems using the Strength and Difficulties Questionnaire. Mothers of 13,159 children completed the follow-up questionnaire reporting their use of cell phones during pregnancy as well as current cell phone use by the child. Greater odds ratios for behavioral problems were observed for children who had possible prenatal or postnatal exposure to cell phone use. After adjustment for potential confounders, the odds ratio for a higher overall behavioral problems score was 1.80 (95% confidence interval 1.45–2.23) in children with both prenatal and postnatal exposure to cell phones. Exposure to cell phones prenatally—and, to a lesser degree, postnatally—was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry.

Comment*: *Self-reported exposure and other possible confounders. Exposure to cell phone prenatally—and, to a lesser degree, postnatally—was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry.

Denmark. Children born between 1996 and 2002. Cohort study.

The aim of the second study was to examine if prenatal use of cell phones by pregnant mothers is associated with developmental milestones delays among offspring up to 18 months of age.
Methods Our work is based upon the Danish National Birth Cohort (DNBC), which recruited pregnant mothers from 1996–2002, and was initiated to collect a variety of detailed information regarding in utero exposures and various health outcomes. At the end of 2008, over 41 000 singleton, live births had been followed with the Age-7 questionnaire, which collected cell-phone-use exposure for mothers during pregnancy. Outcomes for developmental milestones were obtained from telephone interviews completed by mothers at age 6- and 18-months postpartum. Results A logistic regression model estimated the odds ratios (OR) for developmental milestone delays, adjusted for potential confounders. Less than 5% of children at age 6 and 18 months had cognitive/language or motor developmental delays. At 6 months, the adjusted OR was 0.8 [95% confidence interval (95% CI) 0.7–1.0] for cognitive/ language delay and 0.9 (95% CI 0.8–1.1) for motor development delay. At 18 months, the adjusted OR were 1.1 (95% CI 0.9–1.3) and 0.9 (95% CI 0.8–1.0) for cognitive/language and motor development delay, respectively. Conclusions No evidence of an association between prenatal cell phone use and motor or cognitive/language developmental delays among infants at 6 and 18 months of age was observed. Even when considering dose–response associations for cell phone use, associations were null.

***Comment*: *Self-reported exposure. No evidence of an association between prenatal cell phone use and motor or cognitive/language developmental delays*.**

21. Guxens et al., 2013.

The Netherlands. 2003-2004 enrolment; 2008-2009 assessment of behavioural problems; 2010-2011 retrospective exposure assessment.

The study was embedded in a population-based prospective birth cohort study. Together with cell phones, cordless phones represent the main exposure source of radiofrequency-electromagnetic fields to the head. Therefore, we assessed the association between maternal cell phone and cordless phone use during pregnancy and teacher-reported and maternal-reported child behaviour problems at age 5. The study was embedded in the Amsterdam Born Children and their Development study, a population-based birth cohort study in Amsterdam, the Netherlands (2003–2004). Teachers and mothers reported child behaviour problems using the Strength and Difficulties Questionnaire at age 5. Maternal cell phone and cordless phone use during pregnancy was asked about when children were 7 years old. A total of 2618 children

were included. As compared to non-users, those exposed to prenatal cell phone use showed an increased but non-significant association of having teacher-reported overall behaviour problems, although without dose-response relationship. with the number of calls (OR=2.12 (95% CI 0.95 to 4.74) for <1 call/day, OR=1.58 (95% CI 0.69 to 3.60) for 1–4 calls/day and OR=2.04 (95% CI 0.86 to 4.80) for ≥5 calls/day). ORs for having teacher-reported overall behaviour problems across categories of cordless phone use were below 1 or close to unity. Associations of maternal cell phone and cordless phone use with maternal-reported overall behaviour problems remained non-significant. Non-significant associations were found for the specific behaviour problem subscales. Our results do not suggest that maternal cell phone or cordless phone use during pregnancy increases the odds of behaviour problems in their children.

***Comment*: *Self-reported exposure and other possible confounders. Use of mobile phone during pregnancy increases specific behaviour problems, non significant*.**

22. Choi et al., 2017.

South Korea. 2006-2016. Multi-centre prospective cohort study (the Mothers and Children's Environmental Health (MOCEH) study).

Studies examining prenatal exposure to mobile phone use and its effect on child neurodevelopment show different results, according to the child's developmental stages. To examine neurodevelopment in children up to 36 months of age, following prenatal mobile phone use and radiofrequency radiation (RF-EMF) exposure, in relation to prenatal lead exposure, we analyzed 1198 mother-child pairs from a prospective cohort study (the Mothers and Children's Environmental Health Study). Questionnaires were provided to pregnant women at ≤20 weeks of gestation to assess mobile phone call frequency and duration. A personal exposure meter (PEM) was used to measure RF-EMF exposure for 24 h in 210 pregnant women. Maternal blood lead level (BLL) was measured during pregnancy. Child neurodevelopment was assessed using the Korean version of the Bayley Scales of Infant Development- Revised at 6, 12, 24, and 36 months of age. Logistic regression analysis applied to groups classified by trajectory analysis showing neurodevelopmental patterns over time. The psychomotor development index (PDI) and the mental development index (MDI) at 6, 12, 24, and 36 months of age were not significantly associated with maternal mobile phone use during pregnancy. However, among children exposed to high maternal BLL in utero, there was a significantly increased risk of having a low PDI up to 36 months of age, in relation to an increasing average calling time (p-trend=0.008). There was also a risk of having decreasing MDI up to 36 months of age, in relation to an increasing average calling time or frequency during pregnancy (p-trend=0.05 and 0.007 for time and frequency, respectively). There was no significant association between child neurodevelopment and prenatal RF-EMF exposure measured by PEM in all subjects or in groups stratified by maternal BLL during pregnancy. No association between prenatal exposure to RF-EMF and child neurodevelopment during the first three years of life was found; however, a potential combined effect of prenatal exposure to lead and mobile phone use was suggested.

***Comment*: *Maternal blood lead level as main confounding factor. A potential combined effect is suggested*.**

23. Papadopoulou et al., 2017.

Norway. 1999-2008. Prospective population-based pregnancy cohort study MoBa, Norwegian Institute of Public Health.

The association between maternal cell phone use in pregnancy and child's language, communication and motor skills at 3 and 5 years was studied. This prospective study includes 45,389 mother-child pairs, participants of the MoBa, recruited at mid-pregnancy from 1999 to 2008. Maternal frequency of cell phone use in early pregnancy and child language, communication and motor skills at 3 and 5 years, were assessed by questionnaires. Logistic regression was used to estimate the associations. Results: No cell phone use in early pregnancy was reported by 9.8% of women, while 39%, 46.9% and 4.3% of the women were categorized as low, medium and high cell phone users. Children of cell phone user mothers had 17% (OR = 0.83, 95% CI: 0.77, 0.89) lower adjusted risk of having low sentence complexity at

3 years, compared to children of non-users. The risk was 13%, 22% and 29% lower by low, medium and high maternal cell phone use. Additionally, children of cell phone users had lower risk of low motor skills score at 3 years, compared to children of non-users, but this association was not found at 5 years. We found no association between maternal cell phone use and low communication skills. 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 neurodevelopmental effects of prenatal cell phone use was reported.

Comment*: *Self-reported exposure. No evidence of adverse neurodevelopmental effects of prenatal cell phone use was reported.

24. Sudan et al., 2018.

Denmark DNBC, Spain INMA, and Korea MOCEH.

The relationship between maternal cell phone use during pregnancy and cognitive performance in 5-years old children is studied. This study included data from 3 birth cohorts: the Danish National Birth Cohort (DNBC) (n=1209), Spanish Environment and Childhood Project (INMA) (n=1383), and Korean Mothers and Children's Environment Health Study (MOCEH) (n=497). All cohorts collected information about maternal cell phone use during pregnancy and cognitive performance in children at age 5. Linear regression to compute mean differences (MD) and 95% confidence intervals (CI) in children's general, verbal, and non-verbal cognition scores comparing frequency of maternal prenatal cell phone use with adjustments for numerous potential confounding factors were performed. Models were computed separately for each cohort and using pooled data in meta-analysis. No associations were detected between frequency of prenatal cell phone use and children's cognition scores. Scores tended to be lower in the highest frequency of use category; MD (95% CI) in general cognition scores were 0.78 (−0.76, 2.33) for none, 0.11 (−0.81, 1.03) for medium, and −0.41 (−1.54, 0.73) for high compared to low frequency of use. This pattern was seen across all cognitive dimensions, but the results were imprecise overall. Patterns of lower mean cognition scores among children in relation to high frequency maternal prenatal cell phone use were observed. The causal nature and mechanism of this relationship remain unknown.

Comment*: *Self-reported exposure. Patterns of lower mean cognition scores among children in relation to high frequency maternal prenatal cell phone use were observed.

25. Tsarna et al., 2019.

Denmark, Netherlands, Spain, South Korea. 1996-2011. Four population-based birth cohort studies participating in the GERoNiMO Project—namely, the Danish National Birth Cohort (DNBC), the Amsterdam Born Children and Their Development Study (ABCD), the Spanish Environment and Childhood Project (INMA), and the Korean Mothers and Children's Environment Health Study (MOCEH).

Results from studies evaluating potential effects of prenatal exposure to radio-frequency electromagnetic fields from cell phones on birth outcomes have been inconsistent. Using data on 55,507 pregnant women and their children from Denmark (1996–2002), the Netherlands (2003–2004), Spain (2003–2008), and South Korea (2006–2011), we explored whether maternal cell-phone use was associated with pregnancy duration and fetal growth. On the basis of self-reported number of cell-phone calls per day, exposure was grouped as none, low (referent), intermediate, or high. Pregnancy duration (gestational age at birth, preterm/post-term birth), fetal growth (birth weight ratio, small/large size for gestational age), and birth weight variables (birth weight, low/ high birth weight) and meta-analysed cohort-specific estimates were examined. The intermediate exposure group had a higher risk of giving birth at a lower gestational age (hazard ratio = 1.04, 95% confidence interval: 1.01, 1.07), and exposure response relationships were found for shorter pregnancy duration ($P < 0.001$) and preterm birth ($P = 0.003$). We observed no association with fetal growth or birth weight. Maternal cell-phone use during pregnancy may be associated with shorter pregnancy duration and increased risk of preterm birth, but these results should be interpreted with caution, since

they may reflect stress during pregnancy or other residual confounding rather than a direct effect of cell-phone exposure.

Comment: Stress as a confounding factor. Uncertain association.

26. Boileau et al, 2020.

France. 2014-2017.Prospective, longitudinal, multicenter observational cohort study

The aim of this study was to evaluate the association between mobile phone use by pregnant women and fetal development during pregnancy in the general population.Data came from the NéHaVi cohort ("prospective follow-up, from intrauterine development to the age of 18 years, for children born in Haute-Vienne"), a prospective, longitudinal, multicenter (three maternity units in Haute-Vienne) observational cohort focusing on children born between April 2014 and April 2017. Main objective was to investigate the association of mobile phone use on fetal growth. Univariate and multivariate models were generated adjusted for the socioprofessional category variables of the mother, and other variables likely to influence fetal growth. For the analysis 1378 medical charts were considered from which 1368 mothers (99.3 %) used their mobile phones during pregnancy. Mean phone time was 29.8 min (range: 0.0–240.0 min) per day. After adjustment, newborns whose mothers used their mobile phones for more than 30 min/day were significantly more likely to have an AUDIPOG score ≤10th percentile than those whose mothers used their mobile phones for less than 5 min/day during pregnancy (aOR = 1.54 [1.03; 2.31], p = 0.0374). For women using their cell phones 5–15 min and 15–30 min, there wasn't a significant association with an AUDIPOG score ≤ 10th, respectively aOR = 0.98 [0.58; 1.65] and aOR = 1.68 [0.99; 2.82]. Using a mobile phone for calls for more than 30 min per day during pregnancy may have a negative impact on fetal growth. A prospective study should be performed to further evaluate this potential link.

Comment: Fetal growth restriction observed when mother were using mobile phone more than 30'/day.

Table 12 - Reproductive/developmental effects in humans: man fertility, epidemiologic case-control studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
1. Al-Quzwini et al., 2016. Iraq, 2014-2015. Case-control study.	100 randomly selected subfertile couples that attended the infertility clinic of Babylon Teaching Hospital for Maternity and Pediatric in Al-Hilla city in Iraq; 100 volounteers fertile couples fro staff or relatives from same hospital as control group.	Environmental exposure to electromagnetic radiation from mobile phone towers and occupational state was assessed by standard questionnaire.	Living near to mobile phone base station (<50m) and with power intensity of 71.226 mW/m2, duration of exposure to the electromagnetic radiation. Occupational exposure to work hazard (ex. "driver" sitting for long period, "worker" painters and construction workers and "militaries")	Seminal fluid analysis of the subfertile males. Odds ratios and 95% CI, and Chi-square test for differences.	**Oligozoospermia among subfertile males, OR (95% CI)**	**Asthenospermia among subfertile males, OR (95% CI)**	**Teratozoospermia among subfertile males, OR (95% CI)**			Smoking	Inadequate Semen analysis was done for the subfertile males, because the fertile males (control group) refused to give semen samples.
			Type of hazard								
			Occupational		**1.8 (0.57-5.53)**	1.07 (0.87-1.32)	**5.23 (0.52-52.20)**				
			Environmental		1.03 (0.841.19)	1.19 (0.43-3.31)	**2.6 (0.34-19.07)**				

Table 13 - Reproductive/developmental effects in humans: man fertility, epidemiologic cross sectional -studies (450-6000 MHz) (occupational) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)						Any Other Co-Exposure/adjustments	Comments
2. Baste et al., 2008. Norway. 2002-2004. Cross-sectional study	9925 current and former male military employees in the Royal Norwegian Navy, defined by the military employment list (M); mean age 49.	High-frequency aerials, communication equipment, radar. Self-assessed occupational exposure and age categories assessed by mail questionnaire.	Exposure to radiofrequency electromagnetic fields: work closer than 10 m from high-frequency aerials, work closer than 3 m from communication equipment and work closer than 5 m from radar.	Infertility. Odds ratios and 95% CI from adjusted logistic regression models; Mantel–Haenszel test for linear trend.	**Total Infertility - <10 m from high-frequency aerials, OR (95% CI)**	**Test for linear trend (Mantel–Haenszel chi-square)**	**Total Infertility - <3 m from communication equipment, OR (95% CI)**	**Test for linear trend (Mantel–Haenszel chi-square)**	**Total Infertility - <5 m from radar, OR (95% CI)**	**Test for linear trend (Mantel–Haenszel chi-square)**	Infertility. Odds ratios and 95% CI from adjusted logistic regression models; Mantel–Haenszel test for linear trend.	**Adequate/ Positive**
			Age <29									
			Not exposed									
			Low		1.00 (ref.)	0.013	1.00 (ref.)	0.077	1.00 (ref.)	0.001	Self-reported level of exposure.	
			Some		1.10 (0.30–4.07)		1.86 (0.54–6.40)		0.87 (0.25–2.99)			
			High		0.71 (0.15–3.34)		3.56 (1.05–12.08)		2.13 (0.64–7.06)			
			Very high		3.84 (1.09–13.52)		3.50 (0.83–14.78)		1.11 (0.20–6.00)			
			Age 30-39		2.70 (0.76–9.53)		2.49 (0.60–10.42)		5.09 (1.59–16.30)			
			Not exposed									
			Low		1.00 (ref.)	0.011	1.00 (ref.)	0.007	1.00 (ref.)	0.005		
			Some		1.24 (0.83–1.87)		1.53 (1.04–2.26)		1.46 (0.99–2.15)			
			High		1.36 (0.90–2.04)		1.88 (1.25–2.82)		1.32 (0.87–2.02)			
			Very high		1.51 (0.97–2.37)		1.76 (1.11–2.80)		1.79 (1.14–2.82)			
			Age 40-49		1.72 (1.08–2.74)		1.80 (1.10–2.96)		1.91 (1.19–3.07)			
			Not exposed									
			Low		1.00 (ref.)	<0.001	1.00 (ref.)	<0.001	1.00 (ref.)	0.002		
			Some		1.46 (1.03–2.07)		1.04 (0.75–1.45)		1.22 (0.87–1.71)			
			High		1.43 (0.99–2.07)		1.28 (0.91–1.81)		1.24 (0.87–1.79)			
			Very high		1.82 (1.21–2.75)		1.37 (0.91–2.08)		1.59 (1.05–2.41)			
			Age >50		1.90 (1.20–3.01)		1.86 (1.18–2.94)		1.50 (0.95–2.35)			
			Not exposed									
			Low		1.00 (ref.)	<0.001	1.00 (ref.)	<0.001	1.00 (ref.)	0.001		
			Some		1.28 (0.96–1.69)		1.02 (0.78–1.34)		1.11 (0.84–1.46)			
			High		1.59 (1.20–2.11)		1.31 (0.99–1.73)		1.58 (1.20–2.09)			
			Very high		2.02 (1.45–2.81)		1.71 (1.23–2.37)		1.39 (0.98–1.97)			

Table 13 - Reproductive/developmental effects in humans: man fertility, epidemiologic cross- sectional studies (450-6000 MHz) (occupational) (continue b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
3. Møllerløkken et al., 2008. Norway. 2002. Cross-sectional study.	2265 (M) employees who were currently serving in the Navy, both military and civilians. Mean age of 36 years of age, range 20–62.	Occupational exposure from military communication equipment. Information on occupational history from mail questionnaire. An expert group determined work categories related to electromagnetic field exposure.	Workers in the radar/sonar-, the tele/communication, electronics, other jobs (unexposed).	Infertility, Biological Children, Anomalies, Chromosomal Errors, Preterm and Stillbirths or Infant Deaths. Incidence of outcome by exposure group (%); Chi2 or Fisher Exact Tests to assess significance of differences among groups.	**Infertility - % (p-value from Chi2 tests)**	**Having biological children - % (p-value from Chi2 tests)**	**Children with anomalies or chromosomal errors - % (p-value from Chi2 or Fisher's Exact tests)**	**Children with preterm births - % (p-value from Chi2 or Fisher's Exact tests)**	**Stillbirths and infant deaths within 1 year - % (p-value from Fisher's Exact tests)**	Age, ever smoked, military education, and physical exercise at work.	Adequate /positive
			Other jobs (unexposed group)		8.6	62.0	3.5	7.9	2.3		
			Tele/communication workers (communication equipment, radio)		**14.8 (0.01)**	63.5 (0.70)	6.0 (0.18)	10.8 (0.18)	3.6 (0.22)		
			Electronics (electronics for weapons and communication systems)		12.1 (0.15)	58.6 (0.40)	1.8 (0.19)	9.5 (0.44)	1.8 (0.47)		
			Radar/sonar workers (radar)		**17.5 (<0.01)**	70.4 (0.10)	7.1 (0.11)	9.1 (0.37)	2.0 (0.61)		

Table 13 - Reproductive/developmental effects in humans: man fertility, epidemiologic cross-sectional studies (450-6000 MHz) (continued c)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
4. Fejez et al. 2005. Hungary. Cross-sectional study.	611 consecutive Caucasian men of reproductive age from clinic for infertility problems.	Self reported	Duration of possession (in months), duration of standby position closer than 50 cm to the patient (in hours) and duration of daily transmission (in minutes).	Quality of semen. Parametric t-test and the Pearson correlation tests were applied.	**Volume (ml), correlation, p-value**	**Sperm concentration (mln/ml)**	**Total motility (%)**	**Total sperm count (mln/ ejaculate)**	**Total motile sperm count (mln/ ejaculate)**	Occupational exposure to some chemical pesticides, petroleum, solvents, lead and nitrosamines, tobacco consumption.	Inadequate
			Duration of possession (months)		-0.02, 0.64	-0.01, 0.91	-0.08, 0.14	-0.01, 0.81	-0.03, 0.53	Many confounders not analysed	
			Duration of daily standby (h)		0.05, 0.42	-0.01, 0.39	-0.03, 0.64	-0.05, 0.41	-0.07, 0.22		
			Duration of daily transmission (min)		-0.01, 0.84	0.04, 0.84	-0.07, 0.16	0.03, 0.58	0.00, 0.54		
5. Jurewicz et al. 2014, and Radwan et al. 2016. Poland. Cross-sectional study.	344 men, age <45 years, attending infertility clinics in Lodz, Poland in 2008-2011 for diagnostic purposes.	Modifiable lifestyle factors, among which use of cell phone, assessed using self-administered questionnaire.	Duration of exposure from use of cell phones, assessed in years.	Semen quality (WHO 1999 reference values) and DNA fragmentation. Multiple linear regressions were used to assess association.	**Coeff for cell phone use, 0-5 years (p-value)**	**Coeff for cell phone use, 6-10 years (p-value)**	**Coeff for cell phone use, 11-25 years (p-value)**			Using cell phone more than 10 years decreased the percentage of motile sperm cells	Adequate/ positive
				Volume	1.16 (ref.)	-0.06 (0.32)	-0.01 (0.84)				
				Concentration	3.03 (ref.)	0.29 (0.22)	0.42 (0.13)				
				Motility	60.77 (ref.)	-4.13 (0.30)	**-11.27 (0.01)**				
				Atypical	45.73 (ref.)	4.44 (0.42)	**19.00 (0.01)**				
				Sperm head abnormalities	32.42 (ref.)	2.28 (0.69)	**17.58 (0.01)**				
				Sperm neck abnormalities	12.04 (ref.)	-0.25 (0.86)	0.12 (0.94)				
				Sperm tail abnormalities	2.02 (ref.)	-0.01 (0.96)	-0.02 (0.93)				
				DNA fragmentation index	2.52 (ref.)	0.01 (0.97)	0.20 (0.22)				

Table 13 - Reproductive/developmental effects in humans: man fertility, epidemiologic cross-sectional studies (450-6000 MHz) (continued d)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate					Any Other Co-Exposure/adjustments	Comments
6. Yildirim et al., 2015. Turkey, 2013-2014. Cross-sectional study.	1031 healthy men from the Andrology subdivision of the Urology Dept (Turgut Ozal University)	Use of mobile cell (850-1800 MHz) and wireless internet (2400 MHz), assessed using an anonymous questionnaire.	Daily the cell phone usage duration, habits of carrying mobile phone, wireless internet usage duration, and type of internet use.	Sperm parameters. Pearson correlation Coefficients, Student t test (2-tailed) and one way analysis of variance (ANOVA).	**Volume**	**Total sperm count (mln)**	**Total motile sperm count (mln)**	**Progressive motile sperm count (mln)**	**Morphology**	-	Inadequate
		Self-reported	*Duration of cell phone use (h)*	One way analysis of variance, p-value	0.194	0.074	**0.05**	0.083	0.909	Confounding factors not analysed	
			< 0.5		2.9 ± 1.41	42.3 ± 16.3	61.1 ± 60.6	47.5 ± 50.8	2.8 ± 1.9		
			0.5-2		2.9 ± 1.19	39.2 ± 16.3	54.6 ± 50.6	42.5 ± 42.1	2.57 ± 1.76		
			>2		3.01 ± 1.45	37.8 ± 16.1	53.8 ± 59	41.6 ± 51.2	2.74 ± 1.72		
			Mobile phone carrying habits	One way analysis of variance, p-value	0.973	0.256	0.168	0.538	**0.034**		
			Trouser pocket		2.9 ± 1.37	39.1 ± 31.1	56.5 ± 60.1	43.8 ± 51	2.72 ± 1.81		
			Handbag		3.08 ± 1.4	45 ± 31.6	63 ± 48.6	49.6 ± 41.4	3.18 ± 2.47		
			Jacket pocket		3.02 ± 1.38	40.3 ± 27	53.6 ± 49.1	41.9 ± 41.1	2.43 ± 1.38		
			Duration of wireless internet use (h)	One way analysis of variance, p-value	0.43	0.093	**0.032**	**0.033**	0.305		
			< 0.5		2.99 ± 1.4	43 ± 33	61.7 ± 60.2	48.2 ± 53.7	2.73 ± 1.84		
			0.5-2		2.81 ± 1.32	41.8 ± 28.2	56.2 ± 57.5	43 ± 42.1	2.65 ± 1.75		
			>2		2.99 ± 1.36	37.4 ± 29.4	53.8 ± 57.5	41.8 ± 49.6	2.73 ± 1.85		
			Internet usage	Student t test, p-value	0.064	0.054	**0.009**	**0.018**	0.182		
			Cable		2.92 ± 1.25	42 ± 32.3	62.7 ± 61.3	48.9 ± 50.3	2.82 ± 1.72		
			Wireless		2.98 ± 1.43	38.8 ± 29.6	53.6 ± 55.2	41.1 ± 47.7	2.67 ± 1.88		
7. Zilberlicht et al, 2015. Israel, 2011–2012. Cross-sectional study.	80 male patients at infertility workup in the Fertility and IVF division of Carmel Medical Centre.	Daily habits of cell phone use assessed from self-administered questionnaire.	Daily habits of cell phone usage.	Semen quality was assessed using four parameters: volume, concentration, motility and morphology. Variables that were statistically significant in univariate analysis were included in a multivariate logistic regression analysis. OR were calculated with 95% confidence interval (CI).	**P-value of association of Sperm concentration, abnormal vs normal**	**OR (95% CI) for abnormal sperm concentration**	**p-value**			Smoking, age, residential area, occupation, n of children, years of education.	Adequate / positive
			Total daily talking time (≤1h / >1h)		0.040	Not reported	n.s.				
			Talk while charging the device (Yes/no)		0.020	4.13 (1.28-13.3)	0.018				

Table 13 - Reproductive/developmental effects in humans: man fertility, epidemiologic cross-sectional studies (450-6000 MHz) (continued e)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate	Any Other Co-Exposure/adjustments	Comments
8. Al-Bayyari, 2017. Jordan, 2015–2016. cross-sectional observational study.	159 men attending infertility clinics at North, Middle and South Governorates in Jordan.	Daily habits of cell phone use assessed from interviews using a structured questionnaire.	Time of talking by cell phone.	Semen quality. The Pearson's Chi-square (v2) and Fisher's exact tests were applied to assess the association.	**Total daily talking time (≤1 h/day vs >1h/day), p-value**	-	Inadequate
				Sperm concentration (cut-off 20 mln/ml)	0.494	All from an Infertility clinic	
				Volume (ctu-off 3 ml)	0.457		
				Viscosity (Normal vs abnormal)	0.556		
				Liquefaction time (cut-off 20 min)	0.534		
				Sperm motility (%)	n.s.		
				Sperm morphology (%)	n.s.		
9. Shi et al., 2018. China, 2015–2016. Cross-sectional study.	328 men <65 years, attending clinics for sperm analysis.	Use of cell phone assessed using self-report questionnaire.	Habit to carry phone in trousers.	SA, sperm vitality, acrosome reaction (AR) assay and sperm DNA fragmentation index (DFI). Generalized additive models were used to analyze the possible non-linear association.	**Duration of trousers pocket cell phone use (hours/day)**	BMI, smoking and alcohol drinking, sleep, daily fluid intake, weekly meat intake, sports frequency, trouser cell phone use, age, abstinence time.	Inadequate
				Volume	n.s.		
				Concentration	n.s.	All from an Infertility clinic	
				TSC	n.s.		
				Motility	n.s.		
				TMC	n.s.		
				Vitality	n.s.		
				DFI	n.s.		
				AR	n.s.		
10. Blay et al., 2020. Ghana. 2004-2015. Cross-sectional study.	80 men, 21-62 years, recruited from a fertility clinic in Accra, Ghana.	Lifestyle habits assessed using a structured questionnaire.	Mobile phones use and site of common storage on the body.	Parameters of semen quality. Independent Student t-test and Pearson's chi squared test were used to test the association between variables.	**Site of mobile phone storage (side pocket vs other place), p-value**	General characteristics, medical history, particularly disorders of the immune system, smoking habits.	Inadequate
				Volume	0.884	Increased activity and viability associated to cell phone in their side pocket	
				pH	0.741		
				Active motility (%)	**0.002**		
				Sluggish motility (%)	0.269		

				Sluggish motility (%)	0.486	All from an Infertility clinic	
				Viability (%)	**0.009**		
				Count (×106/ml)	0.109		

Table 14 - Reproductive/developmental effects in humans: man fertility epidemiologic cohort studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
11. Zhang et al., 2016. China, 2013-2015. MARHCS cohort study	794 (2013), 666 (2014) and and 568 (2015) young men, age < 18 years, college students, enrolled in the Male Reproductive Health in Chongqing College Students (MARHCS) study.	Use of mobile cell phones, assessed using a questionnaire.	Number of cell phones owned, presence of 3G function, duration of cell phone use, position in which they carry the cell phone, daily duration that the cell phone is turned on (within 50 cm near the body), daily internet time or monthly data traffic via cellular networks, and daily time spent talking on the cell phone in the last three months.	Sperm parameters. Mixed-effects linear regression model was used to globally assess all three years of data on cell phone use and semen parameters	**Volume (ml), Coeff from mixed effects model (95% CI), p-value**	**Sperm concentration (mln/ml), Coeff from mixed effects model (95% CI), p-value**	**Total sperm count (mln), Coeff from mixed effects model (95% CI), p-value**	**Progressive motile sperm (mln), Coeff from mixed effects model (95% CI), p-value**	Age, duration of abstinence, body mass index (BMI), smoking and drinking status, and the consumption of cola, coffee, and fried food	Adequate/ positive
			Duration of cell phone use (h)		-2.19 (-4.39, 0.06), 0.056	-2.90 (-6.91, 1.27), 0.170	**-4.87 (-9.27, -0.27), 0.038**	-0.77 (-2.71, 1.22), 0.445		
			Internet use via cellular network (h, 2013)		0.42 (-0.71, 1.56), 0.472	**-2.74 (-4.53, -0.91), 0.004**	**-2.75 (-4.76, -0.69), 0.009**	0.51 (-0.29, 1.32), 0.213		
			Monthly data traffic (GB, 2014-2015)		**-1.47 (-2.74, -0.19), 0.025**	-1.65 (-4.04, 0.80), 0.185	**-3.22 (-5.85, -0.52), 0.020**	0.19 (-1.08, 1.48), 0.770		

Table 14 - Reproductive/developmental effects in humans: man fertility epidemiologic cohort studies (450-6000 MHz) (continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)						Any Other Co-Exposure/adjustments	Comments
12. Lewis et al., 2017. USA. 2004-2015. Longitudinal cohort study.	384 (M); 18-56 years; Men recruited from a fertility clinic in Boston, Massachusetts, enrolled in the Environment and Reproductive Health (EARTH) Study.	Mobile phones radiofrequencies; Self - reported exposure from mobile phone.	Use, duration (no use, <2 h/day, 2–4 h/day, >4 h/day), headset or earpiece use (H/E, N H/E), and location in which the mobile phone was carried (pants pocket, belt, bag, other).	Sperm motility, total sperm count, total motile sperm count, sperm morphology. Strict Kruger scoring criteria was used to classify men as having normal or below normal morphology by blinded semen analysts. Linear mixed-effects models with random subject effects.	**Absolute differences [ß (95% CI)], Semen volume**	**Absolute differences [ß (95% CI)], Total motility**	**Relative differences [exp(ß) (95% CI)], Total sperm count**	**Relative differences [exp(ß) (95% CI)], Sperm concentration**	**Relative differences [exp(ß) (95% CI)], Total motile sperm count**	**Relative differences [exp(ß) (95% CI)], Normal sperm morphology**	General characteristics, medical history, particularly disorders of the immune system, smoking habits. All from an Infertility clinic	Adequate/ positive
			Category of use (h/day) and headset or earpiece use.									
			No Use		0 (ref.)	0 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<2 h/day, H/E		0.74 (0.08-1.41)	13.05 (1.57-24.53)	1.60 (1.04-2.46)	1.24 (0.81-1.89)	2.43 (1.17-5.07)	0.94 (0.68-1.31)		
			<2 h/day, N H/E		0.40 (-0.06-0.86)	4.47 (-3.53-12.46)	1.09 (0.80-1.47)	0.99 (0.74-1.33)	1.39 (0.83-2.31)	0.97 (0.77-1.22)		
			>2 h/day, H/E		0.29 (-0.43-1.01)	3.06 (-9.39-15.50)	1.14 (0.71-1.82)	1.03 (0.65-1.63)	1.44 (0.65-3.20)	0.84 (0.59-1.20)		
			>2 h/day, N H/E		-0.12 (-0.93-0.68)	4.10 (-9.72-17.93)	1.47 (0.87-2.47)	1.52 (0.91-2.53)	1.89 (0.78-4.58)	0.83 (0.56-1.23)		

Table 15 - Reproductive/developmental effects in humans: developmental effects, epidemiologic case-control studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
13. Tan et al., 2014. Singapore. November 2010 and February 2011. Case-control study	Women with threatened miscarriage during the 5th to 10th weeks of gestation seen at emergency clinic KK Womens and Childrens Hospital (KKH) in Singapore. (F). Mean age of cases and controls were 30.2 and 30.7, respectively.	Potentially modifiable lifestyle factors were assessed by face to-face interview with cases and controls, conducted at the time of recruitment. Mobile phone and computer usage were quantified as self-reported number of hours of use per day based on the most recent one week.	Exposure to radiofrequency electromagnetic fields of cell phone and television. Greater duration of mobile phone use or computer use was associated with higher risk of threatened miscarriage, with dose-response relationship	Association between potential lifestyle risk factors (cell phone and TV usage) and threatened miscarriage: results of adjusted logistic regression analysis. Multivariate analysis adjusting for all confounders and for gestational age.	**Adjusted odds ratio (95% Confidence Interval):**		Maternal age, paternal age, gestational age, ethnicity, height, weight, regularity of menstrual cycle, housing type, educational level, past medical/ pregnancy/ gynaecological/ psychiatric history, urrent and past cigarette smoking, exposure to second-hand cigarette smoke at home, current and past alcohol consumption, current and past caffeine Consumption, perceived stress levels, DHA consumption, and most recent contraceptive use	**Adequate/ positive**
			Handphone use					
			0 to <1 hour		1		Stress not considered as confounder	
			≥ 1 to <2 hours		2.94 (1.32–6.53)			
			≥ 2hours		6.32 (2.71–14.75)			
			Computer use					
			0 to <1 hour		1			
			≥1 to <4 hours		2.66 (1.16–6.09)			
			≥ 4 hours		6.03 (2.82–12.88)			
14. Mahmoudabadi et al., 2015. Iran. Before 2015. Case-control study	292 women who had an unexplained spontaneous abortion at < 14 weeks gestation and 308 matching pregnant women > 14 weeks gestation were enrolled. The subjects were recruited from 10 hospitals in Tehran.	Data collection form was completed to collect data about the use of cell phones during pregnancy.	Average calling time per day, the location of the cell phones when not in use, use of hands-free equipment, use of phones for other applications, the specific absorption rate (SAR) reported by the manufacturer and the average of the effective SAR (average duration of calling time per day × SAR).	Spontaneous abortions. Logistic regression model was used to calculate OR and 95% CI; *T student test, ** Chi square test or Fisher's exact test were used to assess association.	**OR (95% CI)**	**P(2-tailed)**	Effective SAR, maternal age, paternal age, history of abortion and family relationship Life style confounders not analysed	**Adequate /positive**
			Association of spontaneous abortions with the effective SAR (Specific Absorption Rate)		**1.11 (1.07-1.16)**			
			Calling time per day* (minutes) Mean ± SD			**<0.001**		
			Use of hands free** n (%)			0.09		
			location of phones when not in use** n (%)			**<0.001**		
			use of phone for other applications **n (%)			**<0.001**		
			Effective SAR* Mean ± SD			**<0.001**		

Table 16 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cross-sectional studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
15. Col Araz et al., 2013. Turkey, 2009. Cross-sectional study.	500 mothers from the Outpatient Clinic, Dept of Paediatrics, Gaziantep University.	Use of television, computer and mobile phones during pregnancy assessed using a self-administered questionnaire	Cell phone use, computer use (user vs non-user).	Birth weight and preterm birth. The Chi-square test, independent samples t-test, and OR and 95% CI from logistic regression analysis were used.	**Delivery before 37 weeks, χ^2 (p-value)**	**Delivery week, mean ±SD**	**Delivery week, p-value**	Socio-demographic information, mothers weight, height, weight gained, consumption of tobacco and alcohol during pregnancy, disease history, observance of religious fasting during pregnancy, consumption of tea, milk and yoghurt, birth week and birth weight of the other children, if any.	Adequate /positive
			Cell phone use		**5.584 (<0.018)**		**<0.005**		
			User			38.7±1.9			
			Non user			39.2±1.6			
			Duration of cell phone use				**<0.001**		
			≤1h/day			37.6±2.2			
			>1h/day			38.8±1.8			
			Computer use		**4.510 (<0.034)**		**<0.048**		
			User			38.5±1.8			
			Non user			38.9±1.8			
			Duration of cell phone use				n.s.		
			≤1h/day			Not reported			
			>1h/day			Not reported			
16. Zarei S. et al., 2015. Iran. 2014. Cross-sectional study.	Mothers of 35 healthy children (control group) and 77 children aged 3-5 year and diagnosed with speech problems (F).	Different sources of electromagnetic fields (both RF-EMF and ELF) such as mobile phones, mobile base stations, Wi-Fi, cordless phones, laptops and power lines. Self-assessed exposure to different sources of electromagnetic fields.	The mean daily (mobile phone) call time was about 20 min. Call time, history of mobile phone use (months used), average duration of daily call time, cordless phone use and CRT use during pregnancy.	Speech problems in offspring. A P-value of less than 0.05 was considered as significant.	**Speech problems, P-value of association measure**			Age, proportion of consanguineous marriage, smoking, dental radiography history, mean number of pregnancies	Inadequate
			call time		0.002				
			history of mobile phone use		0.003				
			average duration of daily call time during pregnancy		N.S.				
			cordless phone use		0.528				
			CRT use		0.990				

Table 16 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cross-sectional studies (450-6000 MHz) (continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
17. Abad et al., 2016. Iran, 2009. Cross-sectional study.	413 pregnant women (18-35 years of age) from the Tehran region. Reproductive information was collected using medical file recorded in those hospitals the subjects had delivery.	Environmental exposure to EMF (range 27 MHz-3 GHz) assessed using NARDA at the entrance door of their houses three times during the pregnancy (semesters 1, 2, 3). Other information assessed using a face-to face interview.	Environmental exposure to EMF.	Miscarriage (spontaneous abortion, LBW, preterm delivery, and Intra Uterine Fetal Death). Independent samples t-test.	**Miscarriage, p-value from t-test**				Inadequate
			Digital radio and television broadcast services in central frequency 650 MHz		0.85				
			Mobile communications services 1.5 GHz		0.67				
			Wi-Fi access and MISC in central frequency 2.45 GHz		0.42				
18 Lu et al. 2017. Japan. 2012-2014. Cross sectional study from cohort data.	461 mother and child pairs (M and F). Data from the Japan Environment and Children's Study (JECS) and JECS Adjunct Study in Kumamoto.	Mobile phones radiofrequencies; Self-assessed exposure from self-administered questionnaires on maternal mobile phone usage information during pregnancy. A short version of the Self-Perception of Text-Message Dependency Scale (STDS) was used in this study for assessing text message dependency.	Daily mobile phone use times, location of the phone during the day and at night, and power state (on/off) of the mobile phone during sleep). A cut-off of 15 points for the excessive use score in the STDS was used to determine excessive mobile phone use.	Birth weight and infant health status (birth height, birth head circumference, birth chest circumference, mode of delivery, weeks of pregnancy, placental weight, low birth weight), infant emergency transport, and premature birth; linear regression analysis was used.	**ß (95%CI) for Birth weight**	**Adjusted OR (95%CI), Infant emergency transport**	**Adjusted OR (95%CI), Premature birth**	Maternal age, birth height, maternal BMI before pregnancy, maternal age, birth head circumference, primiparity, maternal smoking.	Inadequate
			Daily mobile phone use						
			Normal users		0 (ref.)	1.00 (ref.)	1.00 (ref.)		
			Mobile excessive users		-66.46 (-114.46- -18.46)	7.93 (1.40-44.85)	0.67 (0.09-4.97)		

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)						Any Other Co-Exposure/adjustments	Comments
19. Mjøen et al., 2006. Norway. 1976-1995. Cohort study.	541593 births (M and F). Data on all births registered between 1976 and 1995 in Norway from the Medical Birth Registry of Norway; The Norwegian general population censuses contain data on occupations coded according to the Nordic Classification of Occupations.	Paternal occupation categorized as ''probably not exposed'', ''possibly exposed'' and ''probably exposed'', reflecting probability of exposure to RFR. An expert panel assessed exposure to radiofrequency fields in the various occupations.	Level of exposure assigned from experts.	Birth defects, the total number of CNS and musculoskeletal limb defects, and all categories combined, preterm delivery, low birth weight, sex ratio and perinatal mortality. Relative risks for each exposure category were calculated by approximating odds ratios (OR) with 95% confidence intervals (CI) from logistic regression models.	**Preterm delivery (<37 weeks) - OR (95% CI)**	**Low birth weight (<2,500 g) - OR (95%CI)**	**Early stillbirth (between 16 and 28 weeks) - OR (95% CI)**	**Late stillbirth (after 28 weeks) - OR (95% CI)**	**Male gender - OR (95% CI)**	**Any birth defect - OR (95% CI)**	Calendar year, place of birth and level of education.	Adequate/ negative
			Probably not exposed		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			Possibly exposed		0.99 (0.96-1.02)	1.03 (0.98-1.07)	1.01 (0.91-1.12)	1.01 (0.92-1.11)	1.01 (1.00-1.03)	0.98 (0.94-1.02)		
			Probably exposed		1.08 (1.03-1.15)	1.03 (0.94-1.13)	0.98 (0.79-1.22)	1.09 (0.89-1.29)	0.99 (0.97-1.02)	0.94 (0.86-1.01)		

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
					Cognitive/language development delay at 6 months- Adjusted OR (95% CI)	**Motor development delay at 6 months- Adjusted OR (95% CI)**	**Cognitive/language development delay at 18 months- Adjusted OR (95% CI)**	**Motor development delay at 18 months- Adjusted OR (95% CI)**	**Overall Behavioural Problems Score at 7 years- Adjusted OR (95% CI)**		
20. Divan at al., 2008 and Divan et al. 2011. Denmark. Children born between 1997 and 2002. Cohort study.	41541 children (F and M). Mothers and live-born children constitute 2 fixed cohorts. Child's health status assessed at 7th year of age using an internet-based Questionnaire.	Cell phone and cordless phone use, assessed via four telephone interviews.	Cell phone use among children, among mothers during pregnancy (mother's use of cell phone during pregnancy, use of hands-free equipment during pregnancy (proportion of time) and location of the phone when not in use (handbag or clothing pocket), and for children, current use of cellular and other wireless phones.	Cognitive/language development delays, motor development delays and behavioural problems assessed using the "Strengths and Difficulties Questionnaire". Odds ratios and 95% CI from adjusted logistic regression models.						Adjusted for gender of child, combined social-occupational status, mother's age at birth, gestational age, and child's birth weight, child care outside home at 18 months.	Adequate/ Negative Exposure to cell phones prenatally—and, to a lesser degree, postnatally—was associated with behavioral difficulties such as emotional and hyperactivity problems around the age of school entry.
			Prenatal Exposure Only			1.12 (0.97–1.30)		**1.21 (1.05–1.40)**	**1.58 (1.29–1.93)**		
			Postnatal Exposure Only			1.06 (0.92–1.23)		1.02 (0.89–1.18)	1.18 (0.96–1.45)		
			Both Prenatal and Postnatal Exposure			**1.25 (1.07–1.47)**		**1.49 (1.28–1.74)**	**1.80 (1.45–2.23)**		
			Prenatal: Times spoken per day								
			0-1		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			2-3		1.0 (0.7–1.4)	0.8 (0.5–1.0)	0.9 (0.6–1.3)	0.7 (0.5–1.0)	1.33 (0.99–1.79)		
			4+		0.8 (0.4–1.3)	0.6 (0.3–1.0)	0.9 (0.5–1.6)	1.2 (0.8–1.8)	**1.51 (1.02–2.22)**		
			Prenatal: Percentage of time turned on								
			0		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<50		1.1 (0.6–1.9)	1.3 (0.8–2.7)	1.2(0.7–2.3)	1.1 (0.7–1.8)	0.62 (0.35–1.11)		
			50-99		0.9 (0.5–1.6)	1.1 (0.6–1.8)	1.2 (0.5–2.2)	1.2 (0.8–2.0)	0.93 (0.58–1.48)		
			100		1.0 (0.5–2.0)	1.1 (0.6–2.0)	1.5 (0.7–3.0)	1.3 (0.8–2.3)	1.09 (0.70–1.70)		

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (continued c)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
21. Guxens et al., 2013. Netherlands. 2003-2004 enrollment; 2008-2009 assessment of behavioural problems; 2010-2011 retrospective exposure assessment. Study embedded in a population-based prospective birth cohort study.	8266 pregnant women, 2618 children (F and M). Pregnant women enrolled during their first prenatal visit to an obstetric care provider. Prenatal phone use assessed retrospectively with postal or via web questionnaire at children 7th year, and child behaviour problems assessed at children 5th year.	Cell phones and cordless phones use during pregnancy. Self-assessed exposure from questionnaire. Given the introduction of Universal Mobile Telecommunications System technology in the Netherlands in the beginning of 2004, mobile phone use reports were expected to be nearly exclusively Global System for Mobile Communications (GSM) 900/1800 technology.	Frequency of cell phone calls were set to 75% of the number of calls for those reporting to use the hands-free equipment 'less than half of the calls', to 25% for those reporting to use it 'more than half of the calls', and to 0 for those reporting to use it 'nearly always'.	Children's behaviour (emotional symptoms, conduct problems, hyperactivity/inattention problems, peer relationship problems and pro-social behaviour) reported by primary school teachers and mothers using the Strengths and Difficulties Questionnaire (SDQ) at age 5. Odds ratios and 95% CI from unadjusted and adjusted logistic regression models.	**Teacher-reported child overall behaviour problems, Unadjusted model - OR (95% CI)**	**Teacher-reported child overall behaviour problems, Adjusted model - OR 95% CI)**	**Mother-reported child overall behaviour problems, Unadjusted model - OR (95% CI)**	**Mother-reported child overall behaviour problems, Adjusted model - OR**	Maternal age, maternal educational level, maternal country of birth, maternal parity, maternal pre-pregnancy weight and height, maternal smoking, maternal second-hand smoke at home, maternal alcohol consumption during pregnancy, maternal pregnancy-related anxiety and maternal anxiety and depression during pregnancy, children's birth addresses as indicator of socioeconomic position. .	Adequate/ negative
			Prenatal frequency of cell phone call							
			None		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<1/day		2.09 (0.95 - 4.62)	2.12 (0.95 - 4.74)	0.95 (0.39 - 2.29)	0.89 (0.36 - 2.20)		
			1–4/day		1.53 (0.69 - 3.42)	1.58 (0.69 - 3.60)	0.78 (0.32 - 1.92)	0.73 (0.28 - 1.85)		
			≥5/day		1.88 (0.82 - 4.34)	2.04 (0.86 - 4.80)	0.77 (0.29 - 2.06)	0.75 (0.27 - 2.09)		
			Prenatal frequency of cordless phone call							
			None		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
			<1/day		0.89 (0.57 - 1.39)	1.19 (0.74 - 1.92)	0.27 (0.15 - 0.50)	0.35 (0.18 - 0.67)		
			1–4/day		0.76 (0.48 - 1.22)	1.07 (0.65 - 1.76)	0.55 (0.32 - 0.96)	0.73 (0.41 - 1.33)		
			≥5/day		0.50 (0.23 - 1.09)	0.61 (0.27 - 1.35)	0.40 (0.15 - 1.07)	0.43 (0.15 - 1.21)		

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (continued d)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
22. Choi et al., 2017. South Korea. 2006-2016. Multi-center prospective cohort study (the Mothers and Children's Environmental Health (MOCEH) study).	1198 mother-infant pairs (M and F). Participants were enrolled at ≤20 weeks gestation.	RFR sources of exposure, including cell phone, TV, radio, working on the internet, and mobile phone base stations. Self-assessed exposured from questionnaire regarding average calling frequency (≤2, 3–5, and ≥6 times/day) and average calling time (< 3, 3–10, 10–30, and ≥30 min/day) during pregnancy.	Heavy user defined as calling frequency >6 times per day or calling time >30 min per day. Categories by average calling time (min/day)	MDI: Mental development index, PDI: Psychomotor development index.	**OR (95% CI) for decreasing MDI (6–36 months)**				Occupational exposure to some chemical pesticides, petroleum, solvents, lead and nitrosamines, tobacco consumption.	Inadequate
			Average calling time (min/day)		**All**	**Low Maternal blood lead during pregnancy (< 75%)**	**High Maternal blood lead during pregnancy (<75%)**	**p-interaction**	Maternal blood lead level as main confounding factor	
			<3		0.50 (0.30-0.83)	0.71 (0.42-1.21)	0 (0-Inf)	0.02		
			3-10		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)			
			10-30		0.85 (0.60-1.19)	0.86 (0.57-1.28)	2.11 (0.67-6.68)			
			>30		0.63 (0.37-1.08)	0.76 (0.43-1.34)	0 (0-Inf)			
			P for trend		0.86	0.48	**0.05**			
					OR (95% CI)) for low PDI (6–36 months)					
			Average calling time (min/day)		**All**	**Low Maternal blood lead during pregnancy (< 75%)**	**High Maternal blood lead during pregnancy (<75%)**	**p-interaction**		
			<3		0.47 (0.24-0.94)	0.41 (0.19-0.92)	0.45 (0.23-0.89)	0.44		
			3-10		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)			
			10-30		0.77 (0.49-1.23)	0.81 (0.49-1.35)	1.10 (0.69-1.76)			
			>30		0.64 (0.32-1.29)	0.73 (0.36-1.48)	1.56 (0.74-3.26)			
			P for trend		0.54	0.26	**0.008**			

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (continued e)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)			Any Other Co-Exposure/adjustments	Comments
23. Papadopoulou et al., 2017. Norway, 1999-2008. Norwegian mother and child cohort study (MoBa).	45389 mother-child pairs (M and F), participants of the MoBa, recruited at mid-pregnancy. Information assessed by questionnaires.	Maternal frequency of cell phone use in early pregnancy, assessed by a questionnaire administered at 17th and 30th weeks of gestation.	Frequency of talking on the cell phone: "seldom/never" (no use), "few times a week" (low), "daily" (medium), and "more than an hour daily" (high use).	Child language, communication and motor skills at 3 (45389 mother-child pairs) and 5 years (17310 mother-child pairs). Adjusted OR and 95% C.I. from logistic regression to estimate the associations.	**Risk for lower sentence complexity at 3 years-Adjusted OR (95% C.I.)**			Parity, maternal age, education and year of delivery.	**Adequate /negative**
			Maternal cell phone use in early pregnancy						
			No use		1 (ref)				
			Any use		0.83 (0.77, 0.89)				
			Low		0.87 (0.81, 0.94)				
			Medium		0.78 (0.72, 0.84)				
			High		0.71 (0.62, 0.81)				
			P for trend		**<0.001**				
24. Sudan et al., 2018. Denmark 1996-2002, Spain 2003-2008, South Korea 2006-2011. Data from 3 birth cohorts, part of the Generalized EMF Research using Novel Methods (GERoNiMO) Project.	3089 mother-child pairs participating in the Danish National Birth Cohort (DNBC) (n=1209), the Spanish Environment and Childhood Project (INMA) (n=1383), and the Korean Mothers and Children's Environment Health Study (MOCEH) (n=497).	Maternal cell phone use during pregnancy, assessed during pregnancy (ES and KO) or 7 years after birth (DK).	Frequency of talking on the cell phone: "seldom/never" (no use), "few times a week" (low), "daily" (medium), and "more than an hour daily" (high use). In the DNBC, ABCD, and INMA cohorts, no exposure corresponded to no cell-phone use, low exposure to ≤1 calls/day, intermediate exposure to 2–3 calls/day, and high exposure to ≥4 calls/day. In the MOCEH cohort, no exposure corresponded to no cell-phone use, low exposure to ≤2 calls/day, intermediate exposure to 3–5 calls/day, and high exposure to ≥6 calls/day.	Cognitive performance in children at age 5. Linear regression to compute mean differences (MD) and 95% confidence intervals (CI).	**General cognition, Adjusted OR (95% C.I.)**	**Verbal cognition, Adjusted OR (95% C.I.)**	**Non-verbal cognition, Adjusted OR (95% C.I.)**	Sex of child, age of child, maternal IQ, maternal age, parity, mother's history of psychological distress, maternal education, paternal education, prenatal smoking, prenatal alcohol use, and maternal pre-pregnancy BMI	**Adequate /equivocal**
			Maternal cell phone use in early pregnancy						
			No use		0.78 (-0.76, 2.33)	1.42 (-1.12, 3.96)	0.72 (-0.85, 2.28)		
			Low		1 (ref)	1 (ref)	1 (ref)		
			Medium		0.11 (-0.81, 1.03)	-0.23 (-1.29, 0.83)	-0.12 (-1.60, 1.35)		
			High		-0.41 (-1.54, 0.73)	-0.42 (-1.73, 0.89)	-0.85 (-2.23, 0.53)		

Table 17 - Reproductive/developmental effects in humans: developmental effects, epidemiologic cohort studies (450-6000 MHz) (continued f)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)				Any Other Co-Exposure/adjustments	Comments
25. Tsarna et al., 2019. Denmark 1996-2002, Spain 2003-2008, South Korea 2006-2011. Data from 3 birth cohorts, part of the Generalized EMF Research using Novel Methods (GERoNiMO) Project.	55507 mother-child pairs (M and F) participating in the Danish National Birth Cohort (DNBC), the Spanish Environment and Childhood Project (INMA), and the Korean Mothers and Children's Environment Health Study (MOCEH).	Use of mobile phone s during pregnancy. Retrospective exposure assessment (DNBC and ABCD) or prospective exposure assessment (INMA and MOCEH) were used.	Exposure were classified into 4 categories (none, low, intermediate, and high) based on daily frequency of cell-phone calls during pregnancy.	Preterm/post-term birth, fetal growth (small or large size for gestational age). Modified Wald, $\chi 2$, and Fischer exact tests. The calculated adjusted cohort-specific estimates were meta-analysed using random-effects models.	**Preterm birth - Adjusted OR (95% C.I.)**	**Post term birth - Adjusted OR (95% C.I.)**	**SGA birth - Adjusted OR (95% C.I.)**	**LGA birth - Adjusted OR (95% C.I.)**	Maternal age at child's birth (a natural spline term with 3 degrees of freedom), parity, active and passive smoking during pregnancy, alcohol consumption during pregnancy, pre-pregnancy body mass index.	Adequate/ equivocal
			None		0.96 (0.86-1.07)	0.98 (0.89-1.07)	0.94 (0.86-1.03)	0.98 (0.92-1.04)		
			Low		1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	Stress not considered as confounding	
			Intermediate		1.12 (0.97-1.28)	0.85 (0.75-0.97)	1.03 (0.88-1.21)	0.97 (0.89-1.05)		
			High		1.28 (0.87-1.88)	0.98 (0.83-1.16)	0.94 (0.78-1.13)	0.93 (0.83-1.04)		
			P for trend		**0.003**	0.863	0.872	0.488		
26. Boileau et al., 2020. France, children born in 2014-2017. Prospective, longitudinal, multicenter observational cohort study (NéHaVi cohort)	1378 mothers-child pairs (M and F). Questionnaires completed during face-to-face interviews in the post-partum period during stay at the maternity unit, and the child's and parents' medical records.	Use of mobile phone s during pregnancy. Retrospective exposure assessment (DNBC and ABCD) or prospective exposure assessment (INMA and MOCEH) were used.	Phone time recorded in minutes per day.	Fetal growth, assessed using a personalized AUDIPOG score (growth restriction at birth, defined by an AUDIPOG score ≤ 10th percentile at birth)	**AUDIPOG score ≤10th percentile- Adjusted OR (95% C.I.)**	**P-value**			Socio-professional category variables of the mother likely to influence phone time, smoking, alcohol consumption, history of diabetes or high blood pressure, gestational diabetes, gestational hypertension, and potential confounding factors.	Adequate/ positive
			Phone time (min/day)							
			0-5		1.00 (ref.)					
			5-15		0.98 (0.58-1.65)	0.9423				
			15-30		1.68 (0.99-2.82)	0.0508				
			≥30		**1.54 (1.03-2.31)**	**0.0374**				

Table 18 (summary tables 12-17) - Collected data for epidemiological studies on reproductive/ developmental effects (FR1: 450-6000 MHz)

Total studies		26			
Adequate studies		16			
Type of study	**Observed Effect**	**Total* adequate studies**	**Positive studies**	**Equivocal studies**	**Negative studies**
Reproductive- man fertility	Decline in semen quality	6	6		
Developmental-mother-offspring effects	Miscarriage	2	2		
	Preterm/post-term birth, foetal growth; chromosomal anomalies	8	2	2	4
	Language/communication/ behavioural /cognitive problems	4		2	2

*Some of the studies include more than one outcome.

SUMMARY OF THE COLLECTED DATA FOR EPIDEMIOLOGICAL STUDIES ON REPRODUCTIVE/DEVELOPMENTAL EFFECTS (FR1: 450 to 6000 MHZ) (Table 18)

The epidemiological evidence on possible associations of exposure to RF-EMF with reproductive developmental effects comes from studies of diverse design that have assessed a range of sources of exposure: the populations included people exposed in occupational settings, people exposed through sources in the general environment, e.g. radio-base stations, and people exposed through use of wireless (mobile and cordless) telephones.

In chapter 4 (Limitations) of the present document, general methodological concerns related to the assessment of individual studies are covered. The total number of epidemiological studies selected for the present review for FR1, was 26. After further deep analyses of the 26 original papers, 16 studies proved to be adequate on the basis of exposure assessment, sample size and appropriateness of confounding analyses.

Decline in semen quality, risk of miscarriage, pre-term/post-term birth, foetal growth, language/communication/ behavioural /cognitive problems were analysed in the 16 adequate studies for a possible association with exposure to RF-EMF, related to the use of mobile phone or to environmental/occupational exposure to emissions from radiobase stations. With reference to the numbers given to the studies in the respective abstracts and tables, the association of the different adverse effects to RF-EMF exposure is:

Decline in semen quality: out of 6 adequate studies regarding this outcome, all showed a positive association with RF-EMF exposure (Ref: 2, 3, 5, 7, 11, 12).

Miscarriage: both of the 2 adequate studies regarding this outcome, showed a positive association with RF-EMF exposure (Ref: 13, 14).

Pre-term/post-term birth, foetal growth: out of 8 adequate studies regarding these outcomes, 2 showed a positive association with RF-EMF exposure (Ref: 15, 26), 2 equivocal association /Ref: 24,25) whilewhile 4 were negative (Ref: 19, 20, 21, 23).

Language/communication/ behavioural /cognitive problems: out of 4 adequate studies, 2 showed equivocal evidence of association to RF-EMF exposure (Ref: 20, 24) and 2 were negative (Ref: 21, 23).

We can conclude as follows:

FR1: 450 to 6000 MHZ:

There is sufficient evidence of adverse effects on fertility in man.

There is limited evidence of adverse effects on fertility in woman.

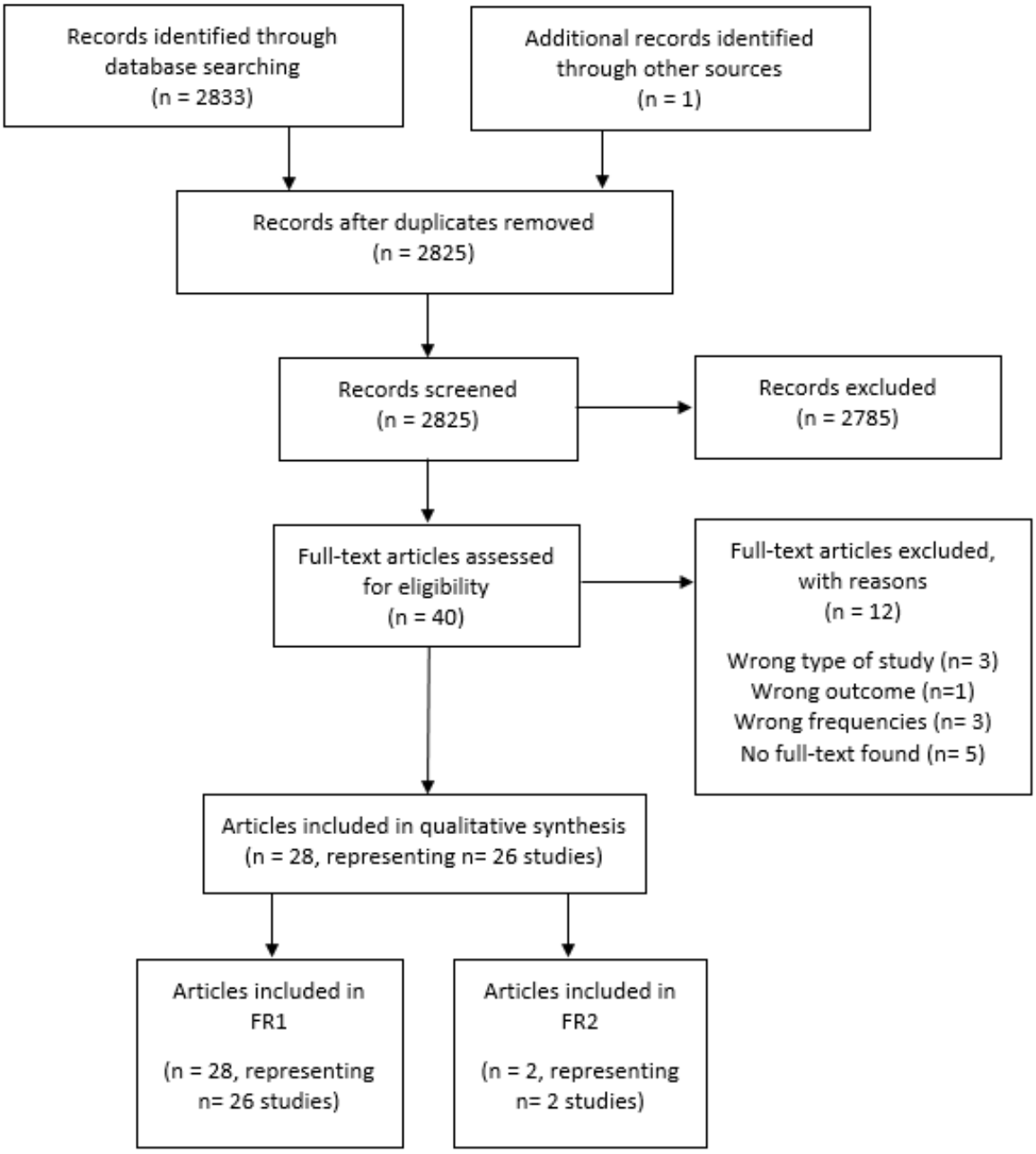
There is limited evidence for adverse effects in pregnant women and their offspring for all developmental end-point examined.

4.2.2 Reproductive/developmental effects in epidemiological studies: Studies evaluating health effects due to RF at a higher frequency range (FR2: 24 to 100 GHz, MMW).

The articles identified through database searching and other sources were 2834. After removing duplicates (9) and excluding non-pertinent articles (2785) based on title and abstracts, 40 articles remained. Based on full-text screening, 12 papers were further excluded, so that the published articles with frequencies appropriate for inclusion in this qualitative synthesis were 28, corresponding to 26 studies. Two papers were published reporting information on the same study (Fig. 14).

At this stage, a selection based on frequency range was also performed: 28 papers/26 studies referred to exposures belonging to the FR1 range, and 2 referred to FR2 as well. These papers reported exposures suitable for both FR1 and FR2, so they don't add up to the overall number of studies included; they are reported twice, once in each frequency range with related outcome.

Figure 14 – Flow diagram. Epidemiological studies on reproductive/developmental effects FR2



MALE FERTILITY

Cross-sectional studies (Table 19 a,b)

1. Baste et al., 2008.

Norway. 2002-2004. Case-control study , occupational exposure.

The authors performed a cross-sectional study among military men employed in the Royal Norwegian Navy, including information about work close to equipment emitting radiofrequency electromagnetic fields, one-year infertility, children and sex of the offspring. Among 10,497 respondents, 22% had worked close to high-frequency aerials to a ''high'' or ''very high'' degree. Infertility increased significantly along with increasing self-reported exposure to radiofrequency electromagnetic fields. In a logistic regression, the odds ratio (OR) for infertility among those who had worked closer than 10 m from high-frequency aerials to a ''very high'' degree relative to those who reported no work near high-frequency aerials was 1.86 (95% confidenceinterval (CI): 1.46–2.37), adjusted for age, smoking habits, alcohol consumption and exposure to organic solvents, welding and lead. Similar adjusted OR for those exposed to a ''high'', ''some'' and ''low'' degree were 1.93 (95% CI: 1.55–2.40), 1.52 (95% CI: 1.25–1.84), and 1.39 (95% CI: 1.15–1.68), respectively. In all age groups there were significant linear trends with higher prevalence of involuntary childlessness with higher self-reported exposure to radiofrequency fields. However, the degree of exposure to radiofrequency radiation and the number of children were not associated. For self-reported exposure both to high-frequency aerials and communication equipment there were significant linear trends with a lower ratio of boys to girls at birth when the father reported a higher degree of radiofrequency electromagnetic exposure.

Comment*: *Self-reported level of exposure. Higher degree of RF-EMF exposure associated to infertility and a lower ratio of boys to girls at birth.

2. Mollerlekken and Moen, 2008.

Norway. 2002. Case-control study, occupational exposure.

The aim of this study was to examine the relationship between workers exposed to electromagnetic fields and their reproductive health. We obtained data using a questionnaire in a cross-sectional study of naval military men, response rate 63% (n¼1487). The respondents were asked about exposure, lifestyle, reproductive health, previous diseases, work and education. An expert group categorized the work categories related to electromagnetic field exposure. We categorized the work categories ''tele/communication,'' ''electronics'' and ''radar/sonar'' as being exposed to electromagnetic fields. Logistic regression adjusted for age, ever smoked, military education, and physical exercise at work showed increased risk of infertility among tele/ communication odds ratio (OR≤1.72, 95% confidence interval 1.04–2.85), and radar/sonar odds ratio (OR≤2.28, 95% confidence interval 1.27–4.09). The electronics group had no increased risk. This study shows a possible relationship between exposure to radiofrequency fields during work with radiofrequency equipment and radar and reduced fertility. However, the results must be interpreted with caution.

Comment*: *Self-reported exposure. Possible increased risk of infertility among telecommunication and radar/sonar operators.

Table 19 - Reproductive/developmental effects in humans: man fertility, epidemiologic case-control studies (24-100 GHz)(a)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)		Any Other Co-Exposure/adjustments	Comments
1. Baste et al., 2008. Norway. 2002-2004. Case-control study	9925 current and former male military employees in the Royal Norwegian Navy, defined by the military employment list (M); mean age 49.	High-frequency aerials, communication equipment, radar. Self-assessed occupational exposure and age categories assessed by mail questionnaire.	Exposure to radiofrequency electromagnetic fields: work closer than 10 m from high-frequency aerials, work closer than 3 m from communication equipment and work closer than 5 m from radar.	Infertility. Odds ratios and 95% CI from adjusted logistic regression models; Mantel–Haenszel test for linear trend.	**Total Infertility - <5 m from radar, OR (95% CI)**	**Test for linear trend (Mantel–Haenszel chi-square)**	Infertility. Odds ratios and 95% CI from adjusted logistic regression models; Mantel–Haenszel test for linear trend.	**Adequate/ Positive for man infertility**
			Age <29					
			Not exposed					
			Low		1.00 (ref.)	0.001		
			Some		0.87 (0.25–2.99)			
			High		2.13 (0.64–7.06)			
			Very high		1.11 (0.20–6.00)			
			Age 30-39		5.09 (1.59–16.30)			
			Not exposed					
			Low		1.00 (ref.)	0.005		
			Some		1.46 (0.99–2.15)			
			High		1.32 (0.87–2.02)			
			Very high		1.79 (1.14–2.82)			
			Age 40-49		1.91 (1.19–3.07)			
			Not exposed					
			Low		1.00 (ref.)	0.002		
			Some		1.22 (0.87–1.71)			
			High		1.24 (0.87–1.79)			
			Very high		1.59 (1.05–2.41)			
			Age >50		1.50 (0.95–2.35)			
			Not exposed					
			Low		1.00 (ref.)	0.001		
			Some		1.11 (0.84–1.46)			
			High		1.58 (1.20–2.09)			
			Very high		1.39 (0.98–1.97)			

Table 19 - Reproductive/developmental effects in humans: man fertility, epidemiologic case-control studies (24-100 GHz)(continued b)

Study information	Population	Type of Exposure and assessment method	Exposure category or level	Health Outcome and measure	Risk estimate (95% CI)					Any Other Co-Exposure/adjustments	Comments
2. Møllerløkken et al., 2008. Norway. 2002. Case-control study.	2265 (M) employees who were currently serving in the Navy, both military and civilians. Mean age of 36 years of age, range 20–62.	Occupational exposure from military communication equipment. Information on occupational history from mail questionnaire. An expert group determined work categories related to electromagnetic field exposure.	Workers in the radar/sonar-, the tele/communication, electronics, other jobs (unexposed).	Infertility, Biological Children, Anomalies, Chromosomal Errors, Preterm and Stillbirths or Infant Deaths. Incidence of outcome by exposure group (%); Chi2 or Fisher Exact Tests to assess significance of differences among groups.	**Infertility - % (p-value from Chi2 tests)**	**Having biological children - % (p-value from Chi2 tests)**	**Children with anomalies or chromosomal errors - % (p-value from Chi2 or Fisher's Exact tests)**	**Children with preterm births - % (p-value from Chi2 or Fisher's Exact tests)**	**Stillbirths and infant deaths within 1 year - % (p-value from Fisher's Exact tests)**	Age, ever smoked, military education, and physical exercise at work.	**Adequate/ Positive for male infertility and developmental parameters in offspring**
			Other jobs (unexposed group)		8.6	62.0	3.5	7.9	2.3		
			Radar/sonar workers (radar)		**17.5 (<0.01)**	70.4 (0.10)	7.1 (0.11)	9.1 (0.37)	2.0 (0.61)		

Table 20 (summary tables 19 a,b) – Collected data for epidemiological studies on reproductive/ developmental effects (FR2: 24-100 GHz).

Total studies*	2				
Adequate studies	2				
Type of study	**Observed Effect**	**Total adequate studies**	**Positive results**	**Negative results**	**Equivocal results**
Reproduction- man fertility	Decline in sperm quality	2	2		
Developmental parameters	Children: preterm birth; chromosomal anomalies	1	1		

The epidemiological evidence on possible associations of exposure to RF-EMF with reproductive/ developmental effects comes from studies of diverse design that have assessed a range of sources of exposure. The studied populations for FR2 include people exposed in occupational settings, in particular military employees.

In chapter 4 (Limitations) of the present document, general methodological concerns related to the assessment of individual studies are covered. The total number of epidemiological studies up to 2020, selected for the present review for FR2, was 2, both considered adequate.

SUMMARY OF THE COLLECTED DATA FOR EPIDEMIOLOGICAL STUDIES ON REPRODUCTIVE/DEVELOPMENTAL EFFECTS (FR2: 24-100 GHz) (Table 20)

FR2 (24-100 GHz)

The two analysed studies on FR2 have limits in exposure assessment, so the real RF/ EMFs levels of exposure are uncertain. However, both studies show *sufficient* evidence of adverse effects on male fertility (Ref: 1, 2).

Limited evidence of developmental effects in offspring of exposed military workers is shown in one of the study (Ref: 2).

However, due to the small number of adequate studies available and the uncertainty about exposure assessment, these results do not allow to confirm or denie an association between exposure to FR2 and reproductive developmental outcome (*not classifiable*).

4.2.3 Reproductive/developmental effects in experimental animals: Studies evaluating health effects due to RF at a lower frequency range (FR1: 450 to 6000 MHZ), which also includes the frequencies used in previous generations' broadband cellular networks (1G, 2G, 3G and 4G).

The articles identified through database searching and other sources were 5052. After removing duplicates (77) and excluding non-pertinent articles (4886) based on title and abstracts, 89 articles remained. Based on full-text screening, 43 papers were further excluded, so that the published articles with appropriate frequencies for the inclusion in this qualitative synthesis were 46, corresponding to 39 studies. In three cases, more than one article was published reporting information on the same study for different reproductive/developmental end points (Fig. 15).

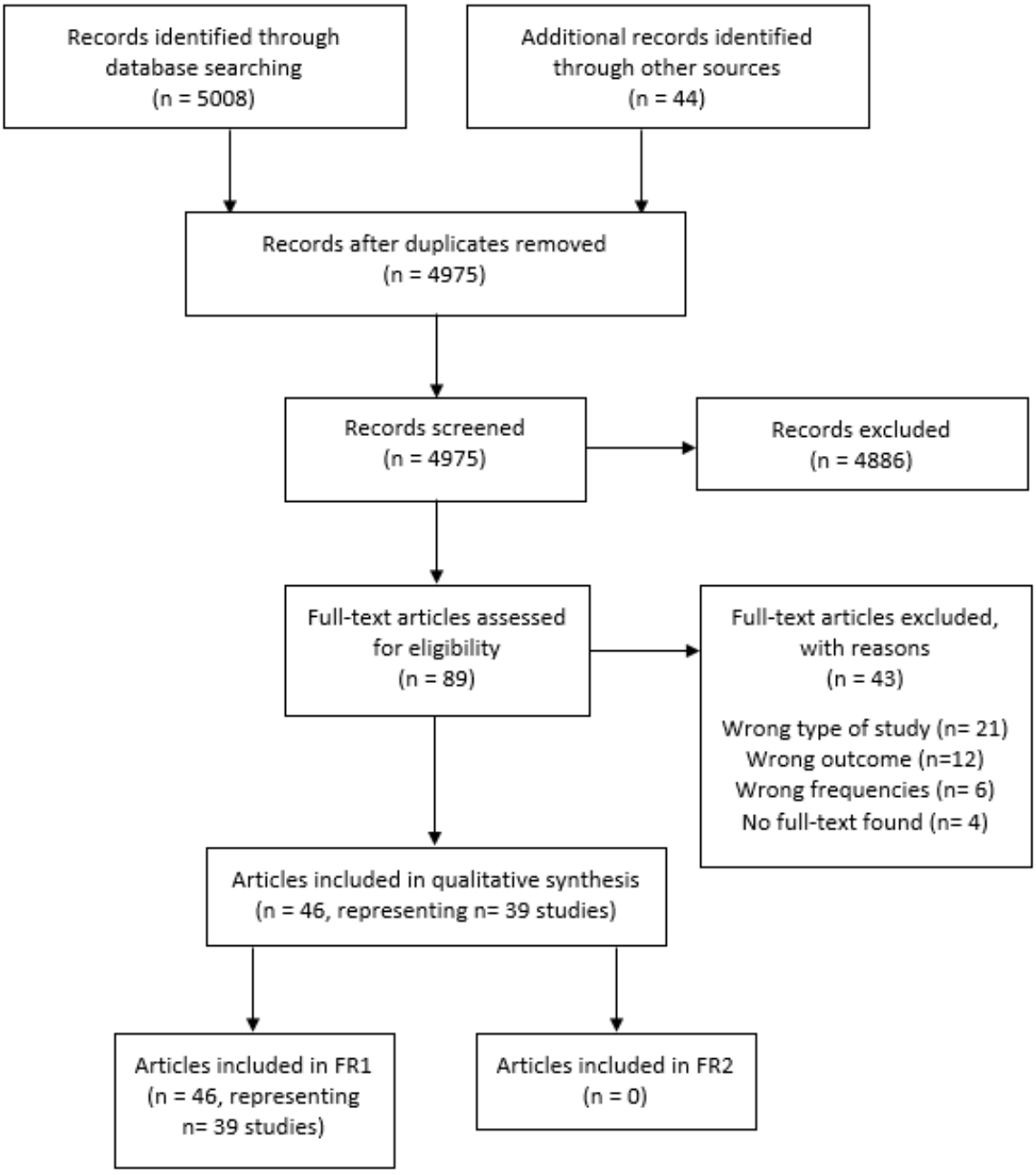
At this stage, a selection based on frequency range was also performed: out of 46 papers/39 studies, all reported exposures to the FR1 range, and none to FR2.

Another selection was based on the guidelines NTP Modified One Generation Study and OECD 443 from 2014 (Foster et al., 2014), which are globally recognised as the gold standard for the planning, conduct and monitoring of experimental bioassays on animals (rodents), aimed at finding effects on developmental pathology, endocrine disruptors, female reproduction, male reproduction, and effects on the reproductive system.

The guideline study design envisages at least 10 animals/sex/group in order to produce statistically robust results. Following this assumption, the papers were distributed by type of study, i.e., male reproduction, female reproduction, developmental pathology.

For each study, the abstract is reported, together with tables summarising the salient information; a senior expert evaluated their adequacy for assessing reproductive and developmental effects (adequate/inadequate), and expressed an overall synthesis of the results (positive/negative/equivocal), following the criteria described in the methodology section.

Figure 15 – Flow diagram. Reproductive/developmental effects in experimental animals FR1



REPRODUCTIVE TOXICITY

Male Mice (Tables 21, a, b)

1. Mugunthan et al., 2012.
India. Mice. Reproductive toxicity.

Mice (n=18) were exposed to 2G ultra-high frequency radiation, 48 minutes per day for a period of 30 to 180 days. The amount of electromagnetic field (EMF) exposed was calculated by the radiation frequency meter. Eighteen mice were exposed to 900-1900 MHz frequency radiation emitted from 2G cell phone and eighteen mice were sham control. The sham control mice (n=18) were exposed to similar conditions without 2G exposure. Each animal's weight was recorded before sacrifice. Three animals each were sacrificed at the end of 30, 60, 90,120,150 and 180 days of exposure in the experimental group after 24 hours of last exposure. Same numbers of control animals were sacrificed on similar period. We collected blood samples to measure plasma testosterone. We measured and analyzed the size, weight and volume of the testis. Testis sections were analysed under the light microscope for structural changes. Results: In 2G exposed group animal weight was lower at first, second and fourth month (p value ≤0.05). The mean testis weight of 2G exposed mice was significantly reduced in all months except fourth month (p value <0.05) and the mean testis volume was significantly reduced in the first three months (p value 0.02). The mean seminiferous tubule density per unit area was significantly lower (p value <0.001) in the 2G exposed testis. The mean seminiferous tubule diameter was significantly reduced in 2G exposed testis (p value is highly significant <0.001) except the second month. The mean number of Sertoli cells and Leydig cells were significantly reduced in 2G radiation exposed mice (p value is highly significant <0.001). While compared with control group, mean serum testosterone level of 2G exposed mice were significantly lower (p value 0.004). The following microscopic changes were found in the testis of 2G cell phone radiation exposed mice. 1. The interstitium appeared wide 2. Sertoli cells and spermatogonia were detached from the basal lamina. 3. Vacuolar degeneration and desquamation of seminiferous epithelium. Most of the peripheral tubules showed maturation arrest in the spermatogenesis. Seminiferous tubules scored between 8 and 9 using Johnson testicular biopsy score count. Chronic exposure to ultra-high frequency radiation emitted from a 2G cell phone could cause microscopic changes in the seminiferous tubules, reduction in the number of Sertoli and Leydig cells and decreased serum testosterone level. Long term use of cell phones could cause male infertility.

Comment*: *Adequate/positive.

2. Shahin et al., 2014.
India. Swiss mice (M). Reproductive toxicity.

Twelve-week-old mice were exposed to non-thermal low-level 2.45-GHz MW radiation (CW for 2/day for 30 days, power density = 0.029812 mW/cm2 and SAR = 0.018 W/Kg). Sperm count and sperm viability test were done as well as vital organs were processed to study different stress parameters. Plasma was used for testosterone and testis for 3b HSD assay. Immunohistochemistry of 3b HSD and nitric oxide synthase (i-NOS) was also performed in testis. We observed that MW irradiation induced a significant decrease in sperm count and sperm viability along with the decrease in seminiferous tubule diameter and degeneration of seminiferous tubules. Reduction in testicular 3b HSD activity and plasma testosterone levels was also noted in the exposed group of mice. Increased expression of testicular i-NOS was observed in the MW-irradiated group of mice. Further, these adverse reproductive effects suggest that chronic exposure to non-ionising MW radiation may lead to infertility via free radical species-mediated pathway.

Comment: Adequate/positive.

3. Zhu et al., 2015.

USA. ICR mice (M, SPF). Reproductive toxicity.

Adult male ICR mice were exposed to continuous wave 900 MHz radiofrequency fields (RF) After 7 days quarantine period, the animals were weighed (20 ± 2 gm) and randomized into three sep-arate groups of 10 mice each for different exposures.a. Continuous wave 900 MHzRf at 1.6 mW/cm2power intensity, 4 h/day for 15days. b. Sham exposure withoutRFtransmission (control mice. c. An acute dose of 2 Gy $_{\gamma}$-radiation (GR, positive controls). At the end of exposure, each mouse was caged with 3 mature virgin female mice for mating. After 7days, each male mouse was transferred to a fresh cage and mated with a second batch of 3 females. This process was repeated for a total of 4 consecutive weeks. Sham exposed male mice and those subjected to an acute 2 Gy -irradiation (GR) were handled similarly and used as un-exposed and positive controls,respectively. All females were sacrificed on the 18th day of gestation and presumptive mating and, the contents in their uteri were examined. The overall observations during the 4 weeks of mating indicated that the unexposed female mice mated to RF-exposed male mice showed no significant differences in the percentage of pregnancies, total implants, live implants and dead implants when compared with those mated with sham-exposed mice. In contrast, female mice mated with GR-exposed males showed a consistent pattern of significant differences in the above indices in each and all 4 weeks of mating. Thus, the data indicated an absence of mutagenic potential of RF exposure in the germ cells of male mice.

Comment*: *Adequate/negative.

4. Pandey et al., 2017.

India. Swiss mice (M). Reproductive toxicity.

Swiss albino mice were exposed to RFR (900 MHz) for 4 h and 8 h duration per day for 35 days. One group of animals was terminated after the exposure period, while others were kept for an additional 35 days post-exposure. RFR exposure caused depolarisation of mitochondrial membranes resulting in destabilized cellular redox homeostasis. Statistically significant increases in the damage index in germ cells and sperm head defects were noted in RFR-exposed animals. Flow cytometric estimation of germ cell subtypes in mice testis revealed 2.5-fold increases in spermatogonial populations with significant decreases in spermatids. Almost fourfold reduction in spermatogonia to spermatid turnover (1C:2C) and three times reduction in primary spermatocyte to spermatid turnover (1C:4C) was found indicating arrest in the premeiotic stage of spermatogenesis, which resulted in loss of post-meiotic germ cells apparent from testis histology and low sperm count in RFR-exposed animals. Histological alterations such as sloughing of immature germ cells into the seminiferous tubule lumen, epithelium depletion and maturation arrest were also observed. However, all these changes showed recovery to varied degrees following the post-exposure period indicating that the adverse effects of RFR on mice germ cells are detrimental but reversible. To conclude, RFR exposure-induced oxidative stress causes DNA damage in germ cells, which alters cell cycle progression leading to low sperm count in mice.

Comment: adequate/positive.

5. Pandey et al., 2018.

India. Swiss mice (M). Reproductive toxicity.

The present study investigated the effect of RFR Global System for Mobile communication (GSM) type, 900 MHz and melatonin supplementation on germ cell development during spermatogenesis. Swiss albino mice were divided into four groups. One group received RFR exposure for 3 h twice/day for 35 days and the other group received the same exposure but with melatonin (N-acetyl-5-methoxytryptamine) (MEL; 5 mg/kg bw/day). Two other groups received only MEL or remain unexposed. Sperm head abnormality, total sperm count, biochemical assay for lipid peroxides, reduced glutathione, superoxide dismutase activity and testis histology were evaluated. Additionally, flow cytometric evaluation of germ cell subtypes and comet assay were performed in testis. Extensive DNA damage in germ cells of RFR-exposed animals along with arrest in pre-meiotic stages of spermatogenesis eventually leading to low sperm count and sperm

head abnormalities were observed. Furthermore, biochemical assays revealed excess free radical generation resulting in histological and morphological changes in testis and germ cells morphology, respectively. However, these effects were either diminished or absent in RFR-exposed animals supplemented with melatonin. Hence, it can be concluded that melatonin inhibits pre-meiotic spermatogenesis arrest in male germ cells through its anti-oxidative potential and ability to improve DNA reparative pathways, leading to normal sperm count and sperm morphology in RFR-exposed animals.

Comment*: *Adequate/positive (group treated without any supplement of melatonine).

6. Shahin et al., 2018.

India. Swiss mice. Reproductive toxicity.

The aim of present study was to investigate the underlying detailed pathway of the testicular apoptosis induced by free radical load and redox imbalance due to 2.45 GHz MW radiation exposure and the degree of severity along with the increased exposure duration. Twelve-week old male mice were exposed to 2.45 GHz MW radiation [continuous-wave (CW) with overall average Power density of 0.0248 mW/cm2 and overall average whole body SAR value of 0.0146 W/kg] for 2 hr/day over a period of 15, 30, and 60 days. Testicular histology, serum testosterone, ROS, NO, MDA level, activity of antioxidant enzymes, expression of pro-apoptotic proteins (p53 and Bax), anti-apoptotic proteins (Bcl-2 and Bcl-xL), cytochrome-c, inactive/active caspase-3, and uncleaved PARP-1 were evaluated. Findings suggest that 2.45 GHz MW radiation exposure induced testicular redox imbalance not only leads to enhanced testicular apoptosis via p53 dependent Bax-caspase-3 mediated pathway, but also increases the degree of apoptotic severity in a duration dependent manner.

Comment*: *Adequate/positive.

Female mice (Table 22, a)

7. Gul et al., 2009.

Turkey. Rats (F). Reproductive toxicity.

The aim of this study was to investigate whether there were any toxic effects of microwaves of cellular phones on ovaries in rats. In this study, 82 female pups of rats, aged 21 days (43 in the study group and 39 in the control group) were used. Pregnant rats in the study group were exposed to mobile phones that were placed beneath the polypropylene cages during the whole period of pregnancy. The cage was free from all kinds of materials, which could affect electromagnetic fields. A mobile phone in a standby position for 11 h and 45 min was turned on to speech position for 15 min every 12 h and the battery was charged continuously. On the 21st day after the delivery, the female rat pups were killed and the right ovaries were removed. The volumes of the ovaries were measured and the number of follicles in every tenth section was counted. The analysis revealed that in the study group, the number of follicles was lower than that in the control group. The decreased number of follicles in pups exposed to mobile phone microwaves suggest that intrauterine exposure has toxic effects on ovaries. We suggest that the microwaves of mobile phones might decrease the number of follicles in rats by several known and, no doubt, countless unknown mechanisms.

Comment*: *Adequate/equivocal.

8. Shahin et al., 2017.

India. Swiss mice (F). Reproductive toxicity.

The present study investigated the long-term effects of mobile phone (1800 MHz) radiation in stand-by, dialing and receiving modes on the female reproductive function (ovarian and uterine histo-architecture, andsteroidogenesis) and stress responses (oxidative and nitrosative stress). We observed that mobile phone radiation induces significant elevation in ROS, NO, lipid peroxidation, total carbonyl content and serum corticosterone coupled with significant decrease in antioxidant enzymes in hypothalamus, ovary and uterus of mice. Compared to control group, exposed mice exhibited reduced number of developing

and mature follicles as well as corpus lutea. Significantly decreased serum levels of pituitary gonadotrophins(LH, FSH), sex steroids (E2 and P4) and expression of SF-1, StAR, P-450scc, 3beta-HSD, 17beta-HSD, cytochromeP-450 aromatase, ER-alfa and ER-beta were observed in all the exposed groups of mice, compared to control.These findings suggest that mobile phone radiation induces oxidative and nitrosative stress, which affects the reproductive performance of female mice.

Comment*: *Adequate/positive.

Male Rats (Tables 23, a-c)

9. Ozguner et al., 2005.

China. Sprague-Dawley rats (M). Reproductive toxicity.

The aim of this experimental study was to determine the biological and morphological effects of 900 MHz radiofrequency (RF) EMF on rat testes. The study was performed in the Physiology and Histology Research Laboratories of Süleyman Demirel University, Faculty of Medicine, Isparta, Turkey in May 2004. Twenty adult male Sprague-Dawley rats weighing 270 - 320 gm were randomized into 2 groups of 10 animals: Group I (control group) was not exposed to EMF and Group II (EMF group) was exposed to 30 minutes per day, 5 days a week for 4 weeks to 900 MHz EMF. Testes tissues were submitted for histologic and morphologic examination. Testicular biopsy score count and the percentage of interstitial tissue to the entire testicular tissue were registered. Serum testosterone, plasma luteinising hormone (LH) and follicle stimulating hormone (FSH) levels were assayed biochemically. Results: The weight of testes, testicular biopsy score count and the percentage of interstitial tissue to the entire testicular tissue were not significantly different in EMF group compared to the control group. However, the diameter of the seminiferous tubules and the mean height of the germinal epithelium were significantly decreased in EMF group ($p<0.05$). There was a significant decrease in serum total testosterone level in EMF group ($p<0.05$). Therefore, there was an insignificant decrease in plasma LH and FSH levels in EMF group compared to the control group ($p>0.05$). The biological and morphological effects resulting from 900 MHz RF EMF exposure lends no support to suggestions of adverse effect on spermatogenesis, and on germinal epithelium. Therefore, testicular morphologic alterations may possibly be due to hormonal changes.

Comment*: *Adequate/positive.

10. Lee et al., 2010.

Korea. Sprague Dawley rats (M). Reproductive toxicity.

We examined the histological changes by radiofrequency (RF) fields on rat testis, specifically with respect to sensitive processes such as spermatogenesis. Male rats (20 x group) were exposed to 848.5 MHz RF for 12 weeks. The RF exposure schedule consisted of two 45-min RF exposure periods, separated by a 15-min interval. The whole-body average specific absorption rate (SAR) of RF was 2.0 W/kg. We then investigated correlates of testicular function such as sperm counts in the cauda epididymis, malondialdehyde concentrations in the testes and epididymis, frequency of spermatogenesis stages, germ cell counts, and appearance of apoptotic cells in the testes. We also performed p53, bcl-2, caspase 3, p21, and PARP immunoblotting of the testes in sham- and RF-exposed animals. Based on these results, we concluded that subchronic exposure to 848.5 MHz with 2.0 W/kg SAR RF did not have any observable adverse effects on rat spermatogenesis.

Comment*: *Adequate/negative.

11. Imai et al., 2011.

Japan. Sprague-Dawley rats (M). Reproductive toxicity.

In recent years concern has arisen whether carrying a cellular phone near the reproductive organs such as the testes may cause dysfunction and particularly decrease in sperm development and production, and thus fertility in men. The present study was performed to investigate the effects of a 1.95 GHz electromagnetic field on testicular function in male Sprague-Dawley rats. Five week old animals were

divided into 3 groups of 24 each and a 1.95-GHz wide-band code division multiple access (W-CDMA) signal, which is used for the freedom of mobile multimedia access (FOMA), was employed for whole body exposure for 5 hours per day, 7 days a week for 5 weeks (the period from the age of 5 to 10 weeks, corresponding to reproductive maturation in the rat). Whole-body average specific absorption rates (SAR) for individuals were designed to be 0.4 and 0.08 W/kg respectively. The control group received sham exposure. There were no differences in body weight gain or weights of the testis, epididymis, seminal vesicles, and prostate among the groups. The number of sperm in the testis and epididymis were not decreased in the electromagnetic field (EMF) exposed groups, and, in fact, the testicular sperm count was significantly increased with the 0.4 SAR. Abnormalities of sperm motility or morphology and the histological appearance of seminiferous tubules, including the stage of the spermatogenic cycle, were not observed. Thus, under the present exposure conditions, no testicular toxicity was evident.

Comment*: *Adequate/negative.

12. Meo et al., 2011.
Saudi Arabia. Wistar rats. Reproductive toxicity.

Forty male Wistar albino rats were divided in three groups. First group of eight served as the control. The second group [group B, n=16] was exposed to mobile phone radiation for 30 minutes/day and the third group [group C, n=16] was exposed to mobile phone radiation for 60 minutes/day for a total period of 3 months. Morphological changes in the testes induced by mobile phone radiations were observed under a light microscope. Exposure to mobile phone radiation for 60 minutes/day caused 18.75% hypospermatogenesis and 18.75% maturation arrest in the testis of albino rats compared to matched controls. However, no abnormal findings were observed in albino rats that were exposed to mobile phone radiation for 30 minutes/day for a total period of 3 months. Long-term exposure to mobile phone radiation can cause hypospermatogenesis and maturation arrest in the spermatozoa in the testis of Wistar albino rats.

Comment*: *Adequate (smaller no. of animals as controls)/equivocal.

13. Al-Damegh, 2012.
Saudi Arabia. Wistar rats (M). Reproductive toxicity.

The aim of this study was to investigate the possible effects of electromagnetic radiation from conventional cellular phone use on the oxidant and antioxidant status in rat blood and testicular tissue and determine the possible protective role of vitamins C and E in preventing the detrimental effects of electromagnetic radiation on the testes. The study population comprised 120 male Wistar albino rats, distributed at least 10xgroup. The treatment groups were exposed to an electromagnetic field, electromagnetic field plus vitamin C (40 mg/kg/day) or electromagnetic field plus vitamin E (2.7 mg/kg/day). All groups were exposed to the same electromagnetic frequency for 15, 30, and 60 min daily for two weeks. There was a significant increase in the diameter of the seminiferous tubules with a disorganized seminiferous tubule sperm cycle interruption in the electromagnetism-exposed group. The serum and testicular tissue conjugated diene, lipid hydroperoxide, and catalase activities increased 3-fold, whereas the total serum and testicular tissue glutathione and glutathione peroxidase levels decreased 3-5 fold in the electromagnetism-exposed animals. Results indicate that the adverse effect of the generated electromagnetic frequency had a negative impact on testicular architecture and enzymatic activity. This finding also indicated the possible role of vitamins C and E in mitigating the oxidative stress imposed on the testes and restoring normality to the testes.

Comment*: *Adequate/positive.

14. Celik et al., 2012.
Turkey. Wistar rats (M). Reproductive toxicity.

Wistar-Kyoto male rats were placed into either a control group or a group that was exposed to an electromagnetic field (EMF). Two cell phones with Specific Absorbation Rate values of 1.58 were placed

and left off in cages that housed 15 rats included in the control group, and four cell phones were placed and left on in cages that housed 30 rats included in the experimental group. After 3 months, weights, seminiferous tubule diameters, and spermatogenic cell conditions of all testes of the rats were evaluated. One half of each testis was examined also under an electron microscope. No significant differences were observed between the testis weights, seminiferous tubule diameters, and histopathological evaluations between rats that had and had not been exposed to EMF. Electron microscope analysis revealed that the membrana propria thickness and the collagen fiber contents were increased and the capillary veins extended in the experimental group. Common vacuolisation in the cytoplasm of the Sertoli cells, growth of electron-dense structures, and existence of large lipid droplets were noted as the remarkable findings of this study. Although the cells that had been exposed to long-term, low-dose EMF did not present any findings that were contrary to the control conditions, the changes observed during ultrastructural examination gave the impression that significant changes may occur if the study period were to be extended. Longer studies are needed to better understand the effects of EMFs on testis tissue.

Comment: Adequate/negative.

15. Lee et al., 2012.
Korea. Sprague Dawley rats (M). Reproductive toxicity.

The effects of combined exposure to radiofrequency electromagnetic fields (RF-EMF) on rat testicular function, specifically with respect to sensitive processes such as spermatogenesis were examined. Male rats (20 x group) were exposed to single code division multiple access (CDMA) and wideband code division multiple access (WCDMA) RF signals for 12 weeks. The RF exposure schedule comprised 45 min/day, 5 days/week for a total of 12 weeks. The whole-body average specific absorption rate (SAR) of CDMA and WCDMA was 2.0 W/kg each or 4.0 W/kg in total. The correlates of testicular function such as sperm count in the cauda epididymis, testosterone concentration in the blood serum, malondialdehyde concentrations in the testes and epididymis, frequency of spermatogenesis stages, and appearance of apoptotic cells in the testes were investigated. Immunoblot for p53, bcl2, GADD45, cyclin G, and HSP70 in the testes of sham- and combined RF-exposed animals were performed. Based on the results, we concluded that simultaneous exposure to CDMA and WCDMA RF-EMFs at 4.0 W/kg SAR did not have any observable adverse effects on rat spermatogenesis.

Comment*: *Adequate/negative.

16. Ozlem-Nisbet et al., 2012.
Turkey. Wistar rats (M). Reproductive toxicity.

Male albino Wistar rats (2 days old) were exposed toexposure on reproduction in growing male rats. Male albino Wistar rats (2 days old) were exposed to EMF 1800 and 900 MHz for 2 h continuously per day for 90 days. Sham control was kept under similar conditions except that the field was not applied for the same period. After blood samples were collected, the animals were sacrificed 24 h after the last exposure and the tissues of interest were harvested. The mean plasma total testosterone showed similarity among the two study groups and was significantly higher than the sham control rats. The percentage of epididymal sperm motility was significantly higher in the 1800 MHz group ($P < 0.05$). The morphologically normal spermatozoa rates were higher and the tail abnormality and total percentage abnormalities were lower in the 900 MHz group ($P < 0.05$). Histopathologic parameters in the 1800 MHz group were significantly higher ($P < 0.05$). In conclusion, the present study indicated that exposure to electromagnetic wave caused an increase in testosterone level, epididymal sperm motility (forward), and normal sperm morphology of rats. As a consequences, 1800 and 900 MHz EMF could be considered to be a cause of precocious puberty in growing rats.

Comment*: *Adequate/positive.

17. Bin-Meferijand El-kott, 2015.

Saudi Arabia. Sprague Dawley rats (M). Reproductive toxicity.

The purpose of this study was to explore the capability of polyphenolic-rich Moringa oleifera leaf extract inprotecting rat testis against EMR-induced impairments based on evaluation of sperm count, viability, motility, sperm cell morphology, anti-oxidants (SOD and CAT), oxidative stress marker, testis tissue histopathology and PCNA immunohistochemistry. The sample consisted of sixty male Wistar rats which were divided into four equal groups. The first group (the control) received only standard diet while the second group was supplemented daily and for eight weeks with 200 mg/kg aqueous extract of Moringa leaves. The third group was exposed to 900 MHz fields for one hour a day and for (7) days a week. As for the fourth group, it was exposed to mobile phone radiation and received the Moringa extract. The results showed that the EMR treated group exhibited a significantly decrease sperm parameters. Furthermore, concurrent exposure to EMR and treated with MOE significantly enhanced the sperm parameters. However, histological results in EMR group showed irregular seminiferous tubules, few spermatogonia, giant multinucleated cells, degenerated spermatozoa and the number of Leydig cells was significantly reduced. PCNA labelling indices were significant in EMR group versus the control group. Also, EMR affects spermatogenesis and causes to apoptosis due to the heat and other stress-related EMR in testis tissue. This study concludes that chronic exposure to EMR marked testicular injury which can be prevented by Moringa oleifera leaf extract.

Comment*: *Adequate/positive.

18. Liu et al., 2015.

China. Sprague-Dawley rats (M) .Reproductive toxicity.

Twenty four rats were exposed to 900 MHz electromagnetic radiation with a special absorption rate of 0.66 ± 0.01 W/kg for 2 h/d. After 50d, the sperm count, morphology, apoptosis, reactive oxygen species (ROS), and total antioxidant capacity (TAC), representing the sum of enzymatic and nonenzymatic antioxidants, were investigated. Western blotting and reverse transcriptase PCR were used to determine the expression levels of apoptosis-related proteins and genes, including bcl-2, bax, cytochrome c, and capase-3. Results: In the present study, the percentage of apoptotic sperm cells in the exposure group was significantly increased by 91.42 % compared with the control group. Moreover, the ROS concentration in exposure group was increased by 46.21 %, while the TAC was decreased by 28.01 %. Radiation also dramatically decreased the protein and mRNA expression of bcl-2 and increased that of bax, cytochrome c, and capase-3. Conclusion: RF-EMR increases the ROS level and decreases TAC in rat sperm. Excessive oxidative stress alters the expression levels of apoptosis-related genes and triggers sperm apoptosis through bcl-2, bax, cytochrome c and caspase-3 signaling pathways.

Comment*: *Adequate/positive.

19. Saygin et al., 2015.

Turkey. Sprague Dawley rats. Reproductive toxicity.

The aim of this study was to investigate electromagnetic radiation (EMR) transmitted by wireless devices (2.45 GHz), which may cause physiopathological or ultrastructural changes, in the testes of rats. We addressed if the supplemental gallic acid (GA) may reduce these adverse effects. Six-week-old male Sprague Dawley rats were used in this study. Forty eight rats were equally divided into four groups, which were named: Sham, EMR only (EMR, 3 h day21 for 30 days), EMR1GA (30 mg/kg/daily), and GA (30 mg/kg/daily) groups. Malondialdehyde (MDA) and total oxidant status (TOS) levels increased (p50.001 for both) in EMR only group. TOS and oxidative stress index (OSI) levels decreased in GA treated group significantly (p50.001 and p50.045, respectively). Total antioxidant status (TAS) activities decreased in EMR only group and increased in GA treatment group (p50.001 and p50.029, respectively). Testosterone and vascular endothelial growth factor (VEGF) levels decreased in EMR only group, but this was not statistically significant. Testosterone and VEGF levels increased in EMR1GA group, compared with EMR only group (p50.002), and also increased in GA group compared with the control and EMR only group (p50.044 and

p50.032, respectively). Prostaglandin E2 (PGE2) and calcitonin gene releated peptide (CGRP) staining increased in tubules of the testes in EMR only group ($p<0.001$ for both) and decreased in tubules of the testes in EMR1GA group ($p<0.001$ for all parameters). In EMR only group, most of the tubules contained less spermatozoa, and the spermatozoon counts decreased in tubules of the testes. All these findings and the regenerative reaction, characterized by mitotic activity, increased in seminiferous tubules cells of the testes in EMR1GA group ($p<0.001$). Long term EMR exposure resulted in testicular physiopathology via oxidative damage and inflammation. GA may have ameliorative effects on the prepubertal rat testes physiopathology.

Comment*: *Adequate/positive.

20. Bilgici et al., 2018.

Turkey. Wistar rats (M). Reproductive toxicity.

Inflammatory effect and testicular damage on rats exposed to low level of electromagnetic fields (EMF) at 2.45GHz microwave radiation were investigated. Twenty two Wistar rats were divided into two groups. Group 1 was the control group and not exposed to EMF. Group 2 was exposed to low level EMF (average E-field 3.68 ± 0.36 V/m, whole body average SAR, 0.0233 W/kg, in 10 g tissue) at 2.45GHz for 1 hour/day for 30 consecutive days. At the end of the study, interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-32 (IL-32), C-reactive protein (CRP) were measured in rat serum and IL-6, IL-10, IL-32 were measured in rat testis tissue.Furthermore, testicular tissues were evaluated histopathologically in terms of spermatogenesis and coagulation necrosis. Serum IL-6 and CRP levels were found to be significantly different in the study group compared to the control group ($p<.05$), but no significant difference was found in serum IL-10, IL-32 levels and testis tissue IL-6, IL-10, IL-32 levels compared to the control group ($p>.05$). On the other hand, histopathological evaluation of testicular tissue revealed a significant difference in necrosis and spermatogenesis when compared with the control group ($p<.05$). It may be concluded that low level EMF at 2.45GHz increases inflammation and testicular damage and negative impact on male reproductive system function.

Comment*: *Adequate/positive.

21. Guo et al., 2019.

China.Sprague-Dawlwy rats. Reproductive toxicity.

Under some occupational conditions, workers are inevitably exposed to high-intensityradiofrequency (RF) fields. In this study, we investigated the effects of one-month exposure to a220 MHz pulsed modulated RF field at the power density of 50 W/m2on the sperm quality in maleadult rats. The sperm quality was evaluated by measuring the number, abnormality and survivalrate of sperm cells. The morphology of testis was examined by hematoxylin–eosin (HE) staining. Thelevels of secreting factors by Sertoli cells (SCs) and Leydig cells (LCs) were determined by enzymelinked immunosorbent assay (ELISA). The level of cleaved caspase 3 in the testis was detected byimmunofluorescence staining. Finally, the expression levels of the apoptosis-related protein (caspase 3,BAX and BCL2) in the testis were assessed by Western blotting. Compared with the sham group, thesperm quality in the RF group decreased significantly. The levels of secreting factors of SCs and themorphology of the testis showed an obvious change after RF exposure. The level of the secretingfactor of LCs decreased significantly after RF exposure. The levels of cleaved caspase 3, caspase 3,and the BAX/BCL2 ratio in the testis increased markedly after RF exposure. These data collectivelysuggested that under the present experimental conditions, 220 MHz pulsed modulated RF exposure could impair sperm quality in rats, and the disruption of the secreting function of LCs and increased apoptosis of testis cells induced by the RF field might be accounted for by this damaging effect.

Comment*: *Adequate/positive.

22. Yu et al., 2020.

China. Sprague Dawley rats. Reproductive toxicity (exp.1 and 2).

The correlation between long-term exposure to SRF-EMR and the decline in male fertility is gradually receiving increasing attention fromthe medical society.While male reproductive organs are often exposed to SRF-EMR, little is currently known about the direct effects of long-termSRF-EMR exposure on the testes and its involvement in the suppression of male reproductive potential. The present study was designed to investigate this issue by using 4G SRF-EMR in rats. A unique exposure model using a 4G smartphone achieved localized exposure to the scrotum of the rats for 6 h each day (the smartphone was kept on active talk mode and received an external call for 1 min over 10min intervals). Results showed that SRF-EMR exposure for 150 days decreased spermquality and pupweight, accompanied by testicular injury. However, these adverse effectswere not evident in rats exposed to SRF-EMR for 50 days or 100 days. Sequencing analysis and western blotting suggested Spock3 overexpression in the testes of rats exposed to SRF-EMR for 150 days. Inhibition of Spock3 overexpression improved sperm quality decline and alleviated testicular injury and BTB disorder in the exposed rats. Additionally, SRF-EMR exposure suppressed MMP2 activity, while increasing the activity of the MMP14–Spock3 complexes and decreasing MMP14–MMP2 complexes; these results were reversed by Spock3 inhibition. Thus, long-term exposure to 4G SRF-EMR diminished male fertility by directly disrupting the Spock3–MMP2–BTB axis in the testes of adult rats. To our knowledge, this is the first study to show direct toxicity of SRF-EMR on the testes emerging after long-term exposure.

***Comment*: *Adequate/positive*.**

DEVELOPMENTAL TOXICITY

Hamsters (Table 24, a)

23. Lerchl 2008a, 2008b, 2008c.

Germany. Djiungarian Hamsters. Developmental toxicity.

In three experiments, adult male Djungarian hamsters (Phodopus sungorus) were exposed 24 hr/day for 60 days to radio frequency electromagnetic fields (RF-EMF) at 383, 900, and 1800 MHz, modulated according to the TETRA (383 MHz) and GSM standards (900 and 1800 MHz), respectively. A radial waveguide system ensured a well defined and uniform exposure at whole-body averaged specific absorption rates of 80 -mW/kg, which is equal to the upper limit of whole-body exposure of the general population in Germany and other countries. For each experiment, using two identical waveguides, hamsters were exposed (n = 120) and sham-exposed (n = 120) in a blind fashion. In all experiments, pineal and serum melatonin levels as well as the weights of testes, brain, kidneys, and liver were not affected. At 383 MHz, exposure resulted in a significant transient increase in body weight up to 4%, while at 900 MHz this body weight increase was more pronounced (up to 6%) and not transient. At 1800 MHz, no effect on body weight was seen. The results corroborate earlier findings which have shown no effects of RF EMF on melatonin levels in vivo and in vitro. The data are in accordance with the hypothesis that absorbed RF energy may result in metabolic changes which eventually cause body weight increases in exposed animals. The data support the notion that metabolic effects of RF-EMFs need to be investigated in more detail in future studies.

Comment: Adequate/negative.

Mice (Table 25, a-c)

24. Finnie et al. a, b (2006, 2009)

BALB/c mice. Developmental toxicity.

To determine whether whole of gestation exposure of fetal mouse brain to mobile telephone radiofrequency fields produces a stress response detectable by induction of heat shock proteins (HSPs). Using a purpose-designed exposure system at 900 MHz, pregnant mice were given a single, far-field, whole body exposure at a specific absorption rate of 4 W/kg for 60 min/day from day 1 to day 19 of gestation. Control mice were sham-exposed or freely mobile in a cage to control for any stress caused by restraint in the exposure module. Immediately prior to parturition on day 19, fetal brains were collected, fixed in 4% paraformaldehyde and paraffin-embedded. Three coronal sections encompassing a wide range of anatomical regions were cut from each brain and any stress response detected by immunostaining for HSP25, 32 and 70. Results There was no induction of HSP32 or 70 in any brains, while HSP25 expression was limited to two brainstem nuclei and occurred consistently in exposed and non-exposed brains.

Comment*: *Adequate/negative.

25. Lee et al., 2009.

Korea. ICR mice. Developmental toxicity (teratogenesis).

The murine fetus is a very sensitiveindicator of the effects of stress or stimuli in the environment.Therefore, we investigated the teratogenic effects of multi-signal radiofrequency electromagnetic fields (RF EMFs) on mouse fetuses. Pregnant mice were simultaneously exposed to two types of RF signals, single code division multiple access (CDMA) and wideband code division multiple access (WCDMA). Mice received two 45-min RF-field exposures, separated by a 15-min interval, daily throughout the entire gestation period. The whole-body average specific absorption rate (SAR) of CDMA or WCDMA was 2.0 W/kg. The animals were killed humanely on the 18th day of gestation and fetuses were examined for mortality, growth retardation, changes in head size and other morphological abnormalities. From the results, we report for the first time that simultaneous experimental exposure to CDMA and WCDMA RF EMFs did not cause any observable adverse effects on mouse fetuses.

Comment*: *Adequate (short daily exposure)/negative.

26. Fragopoulou et al., 2010.

Greece. Balb/c mice. Developmental toxicity.

This study focuses on foetal development following mild daily exposure of pregnant mice to near field electromagnetic radiation emitted by a mobile phone.The investigation was motivated by the fact that the potentially hazardous electromagnetic radiation emitted by mobile phones is currently of tremendous public interest. Physically comparable pregnant mice were exposed to radiofrequency radiation GSM 900MHz emitted by a mobile phone.Within 5 h after birth most cubs were fixed followed by double staining in toto, and conventional paraffin histology. Other cubs remained with their mothers until teeth eruption. Structural development was assessed by examining newborns for the presence of anomalies and/or variations in soft tissues and skeletal anatomy. Electromagnetic radiofrequency exposed newborns, externally examined, displayed a normal phenotype. Histochemical and histological studies, however, revealed variations in the exposed foetuses with respect to control ones concerning the ossification of cranial bones and thoracic cage ribs, as well as displacement of Meckelian cartilage. Littermates examined after teeth eruption displayed normal phenotypes. It is concluded that mild exposure to mobile phone radiation may affect, although transiently, mouse foetal development at the ossification level. The developmental variations observed could be explained by considering the different embryonic origin and mode of ossification of the affected skeletal elements.

Comment*: *Adequate/positive.

27. Sambucci et al., 2011.

Italy. C57BL/6 newborns mice (M and F). Developmental toxicity (immunotoxicology).

The development of the immune system begins during embryogenesis, continues throughout fetal life, and completes its maturation during infancy. Exposure to immune-toxic compounds at levels producing limited/transient effects in adults, results in long-lasting or permanent immune deficits when it occurs during perinatal life. Potentially harmful radiofrequency (RF) exposure has been investigated mainly in adult animals or with cells from adult subjects, with most of the studies showing no effects. Is the developing immune system more susceptible to the effects of RF exposure? To address this question, newborn mice were exposed to WiFi signals at constant specific absorption rates (SAR) of 0.08 or 4 W/kg, 2 h/day, 5 days/week, for 5 consecutive weeks, starting the day after birth. The experiments were performed with a blind procedure using sham-exposed groups as controls. No differences in body weight and development among the groups were found in mice of both sexes. For the immunological analyses, results on female and male newborn mice exposed during early post-natal life did not show any effects on all the investigated parameters with one exception: a reduced IFN-g production in spleen cells from microwaves (MW)-exposed (SAR 4 W/kg) male (not in female) mice compared with sham-exposed mice. Altogether our findings do not support the hypothesis that early post-natal life exposure to WiFi signals induces detrimental effects on the developing immune system.

Comment*: *Adequate/negative, except for reduced IFN-g production in spleen cells from microwaves exposed (SAR 4 W/kg) male (not in female) mice compared with sham-exposed mice.

28. Zhang et al., 2015.

China. CD1 mice. Developmental toxicity (behavioral study).

The recent rapid development of electronic communication techniques is resulting in a marked increase in exposure of humans to electromagnetic fields (EMFs). This has raised public concerns about the health hazards of long-term environmental EMF exposure for fetuses and children. Some studies have suggested EMF exposure in children could induce nervous system disorders. However, gender-dependent effects of microwave radiation exposure on cognitive dysfunction have not previously been reported. Here we investigated whether in utero exposure to 9.417-GHz microwave throughout gestation (Days 3.5–18) affected behavior, using the open field test (OFT), elevated-plus maze (EPM), tail suspension test (TST), forced swimming test (FST) and Morris water maze (MWM). We found that mice showed less movement in the center of an open field (using the OFT) and in an open arm (using the EPM) after in utero exposure to 9.417-GHz radiation, which suggested that the mice had increased anxiety-related behavior. Mice demonstrated reduced immobility in TST and FST after in utero exposure to 9.417-GHz radiation, which suggested that the mice had decreased depression related behavior. From the MWM test, we observed that male offspring demonstrated decreased learning and memory, while females were not affected in learning and memory, which suggested that microwaves had gender-dependent effects. In summary, we have provided the first experimental evidence of microwaves inducing gender-dependent effects.

Comment*: *Adequate/ positive (gender dependent effects).

29. Fatehi et al., 2018.

Iran. NMRI-mice. Developmental toxicity.

Two hundred male and female NMRI-mice were used. One hundred males divided in five groups (n = 20) as control and exposed groups. Those irradiated with cell-phone RF in ''Standby-mode" 1, 5 and 10 h daily named groups II, III and IV; respectively. Group V irradiated with cell-phone on ''Active-mode" one hour daily. After 30 days irradiation, 50 males and 50 females were kept 24 h to assess their embryos. Fifty males were scarified to evaluate both in vitro and in vivo parameters, and 50 females received PMSG and HCG for both quantitative and qualitative evaluation. Comparing groups III, IV and V with control-group showed significantly decreased in the number of two-cell embryos (p = .000); however, a significant increase was found in the number of dead embryos (p = .000). Furthermore, 5 h daily irradiation significantly decreased grade-A embryos (p = .015); while, it significantly increased grade-B, C and D embryos (p-values = 0.026,

0.007, 0.006; respectively). Moreover, comparing groups IV and V to control-group, significant increase was found in pregnancy duration (p = .005, p = .009; respectively). However, in the mentioned groups a significant decrease was seen in number of newborn mice (p = .001, p = .004; respectively). In conclusion, findings showed that the cell-phone radiation can affect development of embryos as well as the number of newborn and pregnancy duration in NMRI-mouse, which might be a significant cause of reproductive failure .

Comment* : *Adequate/positive.

Rats (Table 26, a)

30. Nelson et al., 1991, 1994, 1997, 1997. USA. Sprague-Dawley rats. Developmental toxicity (synergistic effects).

Concurrent exposures to chemical and physical agents occur in the workplace; exposed workers include those involved with microelectronics industry, plastic sealers and electrosurgical units. Previous animal research indicates that hyperthermia induced by an elevation in ambient temperature can potentiate the toxicity and teratogenicity of some chemical agents. We previously demonstrated that combined exposure to radiofrequency (r.f.; 10 MHz) radiation, which also induces hyperthermia and is teratogenic to exposed animals, and the industrial solvent 2-methoxyethanol (2ME) produces enhanced teratogenicity in rats. A subsequent study replicated and extended that research by investigating the interactive dose-related teratogenicity of r.f. radiation (sham exposure or maintaining colonic temperatures at 42.0 degrees C for 0, 10, 20 or 30 min by r.f. radiation absorption) and 2ME (0, 75, 100, 125 or 150 mg/kg) on gestation days 9 or 13 of rats. The purpose of the present research is to determine the effects of r.f. radiation (sufficient to maintain colonic temperatures at 42.0 degrees C for 10 min) on a range of doses of 2ME (0, 20, 40, 60, 80, 100, 120 and 140 mg kg-1) administered on gestation day 13 of rats. Focusing on characterising the dose-response pattern of interactions, this research seeks to determine the lowest interactive effect level. Day 20 fetuses were examined for external and skeletal malformations. The results are consistent with previous observations. Dose-related developmental toxicity was observed for 2ME both in the presence and absence of r.f. radiation. However, concurrent RF radiation exposure changed the shape of the dose-effect curve of 2ME. These data indicate that combined exposure effects should be considered when developing exposure guidelines and intervention strategies.

Comment*: *Inadequate (thermal effects are considered for studying synergistic effects).

31. Nelson et al., 2001.

USA. Sprague-Dawley rats. Developmental toxicity ((synergistic effects).

The purpose of the present research is to investigate if the interactive effects noted for RF radiation and 2ME are unique to these agents, or if similar interactions might be seen with other chemicals. Because methanol is widely used as a solvent as well as fuel additive, and, at high levels, is teratogenic in animals, we selected methanol as a chemical to address generalisability. Based on the literature and our pilot studies, 0, 2, or 3 g/kg methanol (twice, at 6-hour intervals) were administered on gestation day 9 or 13 to groups of 10 Sprague-Dawley rats. Dams treated on day 9 were given methanol and exposed to RF radiation sufficient to maintain colonic temperature at 41 degrees C for 60 minutes (or sham). Those treated on day 13 were given methanol plus either 0 or 100 mg/kg 2ME. Because we observed that methanol produced hypothermia, some groups were given the initial dose of methanol concurrently with the RF or 2ME, and others were given the first dose of methanol 1.5 hours prior to RF or 2ME. Dams were sacrificed on gestation day 20, and the fetuses were examined for external malformations. The results indicate that RF radiation or methanol on day 9 increased the incidence of resorbed fetuses, but no interactive effects were observed. The resorptions were highest in groups given the experimental treatments 1.5 hours apart. The higher dose of methanol also reduced fetal weights. Administration of 2ME or methanol on day 13 increased the rate of malformations, and there was evidence of a positive

interaction between 2ME and methanol. Fetal weights were reduced by 2ME and methanol alone, but no interaction was observed. Also, separation of the dosing with the teratogens did not affect the results. These results point out that interactions in developmental toxicology, such as those of RF radiation, 2ME, and methanol that we have studied, are complex, and such interactions cannot be fully understood or predicted without more research. It is important that combined exposure effects be considered when developing both physical agent and chemical agent exposure guidelines and intervention strategies.

Comment*: *Inadequate (thermal effects are considered for studying synergistic effects).

32. Ogawa et al., 2009.

Japan. Sprague-Dawley rats (F), 10 days. Developmental toxicity.

The present study was designed to evaluate whether gestational exposure to an EMF-targeting the head region, similar to that from cellular phones, might affect embryogenesis in rats. A 1.95-GHz wideband code division multiple access (W-CDMA) signal, which is one applied for the International Mobile Telecommunication 2000 (IMT-2000) system and used for the freedom of mobile multimedia access (FOMA), was employed for exposure to the heads of four groups of pregnant CD(SD) IGS rats (20 per group) for gestational days 7–17. The exposure was performed for 90 min/day in the morning. The spatial average specific absorption rate (SAR) for individual brains was designed to be 0.67 and 2.0 W/kg with peak brain SARs of 3.1 and 7.0 W/kg for low (group 3) and high (group 4) exposures, respectively, and a whole-body average SAR less than 0.4 W/kg so as not to cause thermal effects due to temperature elevation. Control and sham exposure groups were also included. At gestational day 20, all dams were killed and fetuses were taken out by cesarean section. There were no differences in maternal body weight gain. No adverse effects of EMF exposure were observed on any reproductive and embryotoxic parameters such as number of live (243–271 fetuses), dead or resorbed embryos, placental weights, sex ratios, weights or external, visceral or skeletal abnormalities of live fetuses.

Comment*: *Adequate/negative.

33. Sommer et al., 2009.

Germany, C57BL mice (M, F). Multi-generation study. Developmental toxicity.

Male and female mice (C57BL) were chronically exposed (life-long, 24 h/day) to mobile phone communication electromagnetic fields at approximately 1966 MHz (UMTS). Their development and fertility were monitored over four generations by investigating histological, physiological, reproductive and behavioral functions. Exposure of 24 h/day, 7 days/week, using 128 M and 256 F over four generations. The mean whole-body SARs, calculated for adult animals at the time of mating, were 0 (sham), 0.08, 0.4 and 1.3 W/kg. Power densities were kept constant for each group (0, 1.35, 6.8 and 22 W/m(2)), resulting in varying SARs due to the different numbers of adults and pups over the course of the experiment. The experiment was done in a blind fashion. The results show no harmful effects of exposure on the fertility and development of the animals. The number and the development of pups were not affected by exposure. Some data, albeit without a clear dose-response relationship, indicate effects of exposure on food consumption that is in accordance with some data published previously. In summary, the results of this study do not indicate harmful effects of long-term exposure of mice to UMTS over several generations.

Comment*: *Adequate/negative.

34. Ozorak et al., 2013.

Turkey. Wistar rats. Developmental toxicity.

The present study was designed to determine the effects of both Wi-Fi (2.45 GHz)- and mobile phone (900 and 1800 MHz)-induced electromagnetic radiation (EMR) on oxidative stress and trace element levels in the kidney and testis of growing rats from pregnancy to 6 weeks of age. Thirty-two rats and their 96 newborn offspring were equally divided into four different groups, namely, control, 2.45 GHz, 900 MHz,

and 1800 MHz groups. The 2.45 GHz, 900 MHz, and 1, 800MHz groups were exposed to EMRfor 60min/day during pregnancy and growth. During the fourth, fifth, and sixth weeks of the experiment, kidney and testis samples were taken from decapitated rats. Results from the fourth week showed that the level of lipid peroxidation in the kidney and testis and the copper, zinc, reduced glutathione (GSH), glutathione peroxidase (GSH-Px), and total antioxidant status (TAS) values in the kidney decreased in the EMR groups, while iron concentrations in the kidney as well as vitamin A and vitamin E concentrations in the testis increased in the EMR groups. Results for fifth-week samples showed that iron, vitamin A, and β-carotene concentrations in the kidney increased in the EMR groups, while the GSH and TAS levels decreased. The sixth week results showed that iron concentrations in the kidney and the extent of lipid peroxidation in the kidney and testis increased in the EMR groups, while copper, TAS, and GSH concentrations decreased. There were no statistically significant differences in kidney chromium, magnesium, and manganese concentrations among the four groups. In conclusion, Wi-Fi- and mobile phone-induced EMR caused oxidative damage by increasing the extent of lipid peroxidation and the iron level, while decreasing total antioxidant status, copper, and GSH values.Wi-Fi- and mobile phone-induced EMR may cause precocious puberty and oxidative kidney and testis injury in growing rats.

Comment*: *Adequate, positive (testes injuries too).

35. Poulletier de Gannes et al., 2013.

France. Wistar rats (M, F). Developmental toxicity.

For the first time, we evaluated the effects of exposure to the 2450 MHz Wi-Fi signal (1 h/day,6 days/week) on the reproductive system of male and female Wistar rats, pre-exposed to Wi-Fi during sexual maturation. Thirty-six Wistar Han male and female rats were purchased (Janvier, France) at 6 and 7 weeks of age, respectively and exposed 1 h/day, 6 days/week, 12 animals per group Exposure lasted 3 weeks (males) or 2 weeks (females), then animals were mated and couples exposed for 3 more weeks. On the day before delivery, the fetuses were observed for lethality, abnormalities, and clinical signs. In our experiment, no deleterious effects of Wi-Fi exposure on rat male and female reproductive organs and fertility were observed for 1 h per days. No macroscopic abnormalities in fetuses were noted, even at the critical level of 4 W/kg.

Comment*: *Adequate/negative.

36. Celik et al., 2016.

Turkey. Wistar rats. Developmental toxicity (neuro).

The study investigates the effects of Wi-Fi-induced EMR on the brain and liver antioxidant redox systems in the rat during pregnancy and development. Sixteen pregnant rats and their 48 newborns were equally divided into control and EMR groups. The EMR groups were exposed to 2.45 GHz EMR (1 h/day for 5 days/week) from pregnancy to 3 weeks of age. Brain cortex and liver samples were taken from the newborns between the first and third weeks. In the EMR groups, lipid peroxidation levels in the brain and liver were increased following EMR exposure; however, the glutathione peroxidase (GSH-Px) activity, and vitamin A, vitamin E and b-carotene concentrations were decreased in the brain and liver. Glutathione (GSH) and vitamin C concentrations in the brain were also lower in the EMR groups than in the controls; however, their concentrations did not change in the liver. In conclusion, Wi-Fi-induced oxidative stress in the brain and liver of developing rats was the result of reduced GSH-Px, GSH and antioxidant vitamin concentrations. Moreover, the brain seemed to be more sensitive to oxidative injury compared to the liver in the development of newborns.

Comment*: *Adequate/positive.

37. Shirai et al., 2016.

Japan. Sprague-Dawley rats. Developmental toxicity.

To evaluate the possible adverse effects of multifrequency RF-EMFs, an experiment in which pregnant rats and their delivered offspring were simultaneously exposed to eight different communication signal EMFs (two of 800 MHz band, two of 2 GHz band, one of 2.4 GHz band, two of 2.5 GHz band and one of 5.2 GHz band) was performed. Thirty six pregnant Sprague-Dawley (SD) 10-week-old rats were divided into three groups of 12 rats: one control (sham exposure) group and two experimental (low- and high-level RF EMF exposure) groups. The whole body of the mother rats was exposed to the RF EMFs for 20 h per day from Gestational Day 7 to weaning, and F1 offspring rats (46–48 F1 pups per group) were then exposed up to 6 weeks of age also for 20 h per day. The parameters evaluated included the growth, gestational condition and organ weights of the dams; the survival rates, development, growth, physical and functional development, memory function, and reproductive ability of the F1 offspring; and the embryotoxicity and teratogenicity in the F2 rats. No abnormal findings were observed in the dams or F1 offspring exposed to the RF EMFs or to the F2 offspring for any of the parameters evaluated. Thus, under the conditions of the present experiment, simultaneous whole-body exposure to eight different communication signal EMFs at frequencies between 800 MHz and 5.2 GHz did not show any adverse effects on pregnancy or on the development of rats.

Comment*: *Adequate/negative.

38. Stasinopouloua et al., 2016.

Greece. Wistar rats. Developmental toxicity (neuro).

In the present study, to evaluate the effects of wireless 1880–1900 MHz Digital Enhanced CommunicationTelephony (DECT) base radiation on fetal and postnatal development, Wistar rats (80 dams in 4 groups) were exposed at an average electric field intensity of 3.7 V/m, 12 h/day, during pregnancy. After parturition, a group of dams and offspring were similarly exposed for another 22 days. Controls were sham-exposed. The data showedthat DECT base radiation exposure caused heart rate increase in the embryos on the 17th day of pregnancy.Moreover, significant changes on the newborns' somatometric characteristics were noticed. Pyramidalcell loss and glia fibrilliary acidic protein (GFAP) over-expression were detected in the CA4 region of thehippocampus of the 22-day old pups that were irradiated either during prenatal life or both pre- and postnatally. Changes in the integrity of the brain in the 22-day old pups could potentially be related to developmental behavioral changes during the fetal period.

Comment*: *Adequate/positive.

39. Othman et al., 2017.

Tunisia. Wistar rats. Developmental toxicity (neuro).

The present work investigated the effects of prenatal exposure to radiofrequency waves of conventional WiFi devices on postnatal development and behavior of rat offspring. Ten Wistar albino pregnant rats were randomly assigned to two groups (n =5). The experimental group was exposed to a 2.45 GHz WiFi signal for 2 h a day throughout gestation period. Control females were subjected to the same conditions as treated group without applying WiFi radiations. After delivery, the offspring was tested for physical and neurodevelopment during its 17 postnatal days (PND), then for anxiety (PND 28) and motricity (PND 40-43), as well as for cerebral oxidative stress response and cholinesterase activity in brain and serum (PND 28 and 43). Our main results showed that the in-utero WiFi exposure impaired offspring neurodevelopment during the first seventeen postnatal days without altering emotional and motor behavior at adult age. Besides, prenatal WiFi exposure induced cerebral oxidative stress imbalance (increase in malondialdehyde level (MDA) and hydrogen peroxide (H2O2) levels and decrease in catalase (CAT) and superoxide dismutase (SOD) activities) at 28 but not 43 days old, also the exposure affected acethylcolinesterase activity at both cerebral and seric levels. Thus, the current study revealed that maternal exposure to WiFi radiofrequencies led to various adverse neurological effects in the offspring by affecting neurodevelopment, cerebral stress equilibrium and cholinesterase activity.

Comment*: *Adequate/positive.

Table 21 – Reproductive/developmental effects in experimental animals: reproductive toxicity in male mice (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
1. Mugunthan et al., 2012, Swiss albino mice (M), 30 to 180 days	2G ultra-high frequency radiation (900 - 1900 MHz); the highest SAR value for this standard handset was 1.69W/Kg	48 minutes/day; 18 mice/group	Exposed animal weight was lower at first, second and fourth month ($p<0.05$). The mean testis weight of exposed mice was significantly reduced in all months except fourth month ($p<0.05$) and the mean testis volume was significantly reduced in the first three months ($p < 0.05$). Mean seminiferous tubule density per unit area was significantly lower in exposed testis ($p< 0.01$). The mean seminiferous tubule diameter was significantly reduced in exposed testis ($p < 0.01$) except the second month. The mean number of Sertoli cells and Leydig cells were significantly reduced in exposed mice ($p < 0.01$). Mean serum testosterone level of exposed mice were significantly lower ($p < 0.01$). The following microscopic changes were found in the testis of RFR exposed mice. 1. The interstitium appeared wide 2. Sertoli cells and spermatogonia were detached from the basal lamina. 3. Vacuolar degeneration and desquamation of seminiferous epithelium. Most of the peripheral tubules showed maturation arrest in the spermatogenesis. Seminiferous tubules scored between 8 and 9 using Johnson testicular biopsy score count.	**Adequate/positive**
2.Shahin et al., 2014, Swiss mice (M), 30 days	2.45-GHz; SAR: 0.018 W/Kg	2 h/day; 20 mice group, 40 in total	RFR induced a significant decrease in sperm count and sperm viability along with the decrease in seminiferous tubule diameter and degeneration of seminiferous tubules. Reduction in testicular 3ß HSD activity and plasma testosterone levels was also observed in the exposed group of mice. Increased expression of testicular i-NOS was observed in the MW-irradiated group of mice ($p < 0.01$)	**Adequate/positive**
3. Zhu et al., 2015, ICR mice (SPF) (M adult), [12 virgin females per each male were used for mating], 15 days	900 MHz; 1.6 mW/cm2, whole body average SAR 0.731 W/kg; acute 2 Gy irradiation from Co60 source, at a dose rate of 1 Gy per minute, as positive control	4 h/day; 10 male mices per exposure group. After exposures, each male mouse was kept in a separate cage with 3 virgin females for mating. After 7 days, each male was separated from the females and transferred to a fresh cage with a new batch of 3 virgin females for mating in the second, third and fourth weeks (in total: 12 females per each male).	Not any statistically significant effect on average body weight, testes weight in male mice exposed to RFR. Comparison between the females mated to RF- and sham-exposed mice: non-significant differences in percentages of pregnancies, live and dead implants. There were no significant differences in calculated total implants, live and dead implants per pregnant female ($p > 0.05$).	**Adequate/negative**

Table 21 – Reproductive/developmental effects in experimental animals: reproductive toxicity in male mice (450-6000 MHz) (continue b)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
4. Pandey et al., 2017, Swiss albino mice (M), 35 days	900 MHz (GSM), 0.0054 - 0.0516 W/kg	4 or 8 h/day, 7 days/week, 15/group	Increased damage index in germ cells, sperm head defects, decreased sperm count, arrest in pre-meiotic stage of spermatogenesis, loss of immature germ cells into the seminiferous tubule lumen, epithelium depletion and maturation arrest ($p<0.05$)	**Adequate/positive**
5.Pandey et al., 2018, Swiss albino mice (M), 35 days	900 MHz (GSM), (Melatonin 5 mg/kg bw/day), 0.0054 - 0.0516 W/kg	6 h/day, 7 days/week, 15/group	Decreased sperm count, sperm head abnormalities, extensive DNA damage in germ cells, arrest in pre-meiotic stages of spermatogenesis, excess free radical generation resulting in histological and morphological changes in testis and germ cells morphology ($p<0.05$)	**Adequate/positive (group treated without any supplement of melatonine)**
6. Shahin et al., 2018, Swiss albino mice (M), 15, 30, and 60 days	2.45 GHz MW, whole body SAR 0.0146 W/kg	2 h/day; 10 mice/group	Exposure to 2.45 GHz MW leads to altered testicular histoarchitecture, decreased seminiferous tubule diameter, sperm count, sperm viability, and serum testosterone level. Duration dependent increment in total ROS, NO, and MDA level was observed in the testes of exposed animals. Exposure to RFR leads to altered expression of p53, Bax, Bcl-xL, Bcl-2, pro-caspase-3, active-caspase-3, and PARP-1. The expression of cytochrome c was found to be increased significantly in duration dependent manner in the testes of all RFR exposed mice as compared with controls. ($p < 0.05$)	**Adequate/positive**

Table 22 – Reproductive/developmental effects in experimental animals: reproductive toxicity in female mice (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
7. Gul et al., 2009, Swiss mice (F), 21 days	NR (mobile phone in standby position for 11 h and 45 min, and in call position for 15 min), NR	12 h/day, 7 days/week, 30/group	Decreased number of follicles in mice ovaries, decreased ovarian volume ($p<0.01$)	**Adequate/equivocal**
8.Shahin et al., 2017, Swiss albino mice (F), 4 months (120 days)	1800 MHz, Nokia 100 (2G, GSM) dual-band mobile phones, in different operative modes (dialing, receiving, stand-by and switched-off)	3 h/day; 24 mice/group, 2 experiments of 12mice/group, 48 female mice in total each.	Exposure caused significant elevation in ROS, NO, lipid peroxidation, total carbonyl content and serum corticosterone coupled with significant decrease in antioxidant enzymes in hypothalamus, ovary and uterus of mice. Compared to controls, exposed mice exhibited reduced number of developing and mature follicles as well as corpus lutea. Significantly decreased serum levels of pituitary gonadotrophins (LH, FSH), sex steroids (E2 and P4) and expression of SF-1, StAR, P-450scc, 3ß-HSD, 17ß-HSD, cytochrome P-450 aromatase, ER-α and ER-α were observed in all the exposed groups of mice, compared to control ($p < 0.01$)	**Adequate/positive**

Table 23 – Reproductive/developmental effects in experimental animals: reproductive toxicity in male rats (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
9. Ozguner et al., 2015, Sprague-Dawley rats (M), 4 weeks	900 MHz, 2 watts peak power, average power density 1 ± 04 mW/cm^2	30 minutes/day, 5 days/week; 10 rats/group, 20 in total	The weight of testes, testicular biopsy score count and the percentage of interstitial tissue to the entire testicular tissue were not significantly different in RFF group compared to the controls. The diameter of the seminiferous tubules and the mean height of the germinal epithelium were significantly decreased in RFF group ($p<0.05$). There was a significant decrease in serum total testosterone level in RFR group ($p<0.05$). Therefore, there was an insignificant decrease in plasma LH and FSH levels in RFF group compared to the control group ($p>0.05$).	**Adequate/positive**
10.Lee et al., 2010, Sprague-Dawley rats, 12 weeks	848.5 MHz, 2.0 W/kg (CDMA)	90 min/day, 5 days/week, 20/group	Not any statistically significant alteration (NS) for testicular function and spermatogenesis ($p>0.05$)	**Adequate/ negative**
11. Imai et al., 2011, Sprague-Dawley rats, 5 weeks	1950 MHz (CDMA), 0.4 W/kg, 0.08 W/kg	5 h/day, 7 days/week, 24/group	Not any statistically significant alteration (NS) for testicular function ($p>0.05$).	**Adequate/negative**
12. Meo et al., 2011, Wistar rats, 12 weeks	900, 1800 GHz (GSM). Intensities: NR	30 minutes/day, 60 minutes/day, 7 days/week 16/group (control group: 8)	Hypospermatogenesis and maturation arrest in the testis (Significance: NR)	**Adequate/equivocal**
13. Al-Damegh, 2012, Wister albino rats (M), 14 consecutive days	900/1800/1900 MHz (GSM), 0.9 W/kg, vitamin C (40 mg/kg/day) or vitamin E (2.7 mg/kg/day)	15, 30, and 60 min/day; 30/group of exposed rats; 10/group of control rats	There was a significant increase in the diameter of the seminiferous tubules with a disorganized seminiferous tubule sperm cycle interruption in RFR-exposed group. The serum and testicular tissue conjugated diene, lipid hydroperoxide, and catalase activities increased 3-fold, whereas the total serum and testicular tissue glutathione and glutathione peroxidase levels decreased 3-5 fold in RFR-exposed animals ($p<0.05$)	**Adequate/positive**
14. Celik et al., 2012, Wistar-Kyoto rats (M), 3 months	NR, cell phone radiations, SAR 1.58 W/kg	24 h/day (30 M exposed, 15 M controls)	No significant differences in testis weights, seminiferous tubule diameters, and histopathological evaluations ($p>0.05$). Electron microscope analysis: membrana propria thickness and collagen fiber contents were increased, and the capillary veins extended in exposed animals. Common vacuolisation in the cytoplasm of the Sertoli cells, growth of electron-dense structures, and existence of large lipid droplets are the remarkable findings of this study.	**Inadequate**
15.Lee et al., 2012, Sprague-Dawley rats, 12 weeks	848.5 MHz (CDMA), 1950 MHz (WCDMA), 4.0 W/kg	45 min/day, 5 days/week, 20/group (cage control group: 5)	Not any statistically significant alteration (NS) for testicular function and spermatogenesis ($p>0.05$)	**Adequate/negative**
16.Ozlem-Nisbet et al., 2012, Albino Wistar rats (M), 90 days	1800 and 900 MHz, SAR: 3.00, 2.7, 2.2, 1.2 mW/kg for 900 MHz for 10, 20, 50, 70 days old rats; 0.053, 0.046, 0.011, 0.011 mW/kg for 1800 MHz for 10, 20, 50, 70 days old rats	2 h/day; 11 rats/group	The mean plasma total testosterone showed similarity among the two study groups and was significantly higher than the sham control rats. The percentage of epididymal sperm motility was significantly higher in the 1800 MHz group ($P < 0.05$). The morphologically normal spermatozoa rates were higher and the tail abnormality and total percentage abnormalities were lower in the 900 MHz group ($P < 0.05$). Histopathologic parameters in the 1800 MHz group were significantly higher ($P < 0.05$).	**Adequate/positive**

Table 23 – Reproductive/developmental effects in experimental animals: reproductive toxicity in male rats (450-6000 MHz) (continued b)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
17. Bin-Meferij El-kott et al., 2015, Sprague-Dawley rats, 8 weeks	900 MHz for GSM, NR intensity, 200 mg/kg aqueous extract of Moringa oleifera leaves	1 h/day (15 M exposed to RF+MO extract; 15 M exposed to RF; 15 M exposed to MO extract; 15 M controls)	Statistically significant decrease of epididymal sperm counts in the exposed group ($P < 0.001$). Significant decrease of sperm motility. Significant ($P < 0.001$) increase in the frequency percentage of dead spermatozoa in exposed animals. Overall, hypospermatogenesis and maturation arrest in spermatozoa were observed in the testes of exposed rats compared to their matched control.	**Adequate/ positive**
18. Liu et al., 2015, Sprague-Dawley rats (M), 50 days (from 10 weeks of age)	900 MHz, SAR 0.66 W/kg	2 h/day (24 M exposed; 24 M controls)	Significant increase of the percentage of apoptotic sperm cells by 91.42% in exposed animals; Significant increase of the ROS concentration by 46.21%; Significant decrease of the TAC by 28%; Significant decrease of the protein and mRNA expression of bcl-2 and increase of bax, cytochrome c, and capase-3 ($p<0.05$)	**Adequate/ positive**
19. Saygin et al., 2015, Sprague-Dawley rats (young M), 30 days	2.45 GHz, whole body SAR 3.21 W/kg, Gallic acid (GA) ,30 mg/kg/daily	3h/day; 12 rats/ group, 48 in total	Malondialdehyde and total oxidant status (TOS) levels increased ($p<0.01$) in RFR only group. TOS and oxidative stress index levels decreased in GA treated group significantly ($p<0.05$). Total antioxidant status activities decreased in RFR only group and increased in GA treatment group ($p<0.05$). Testosterone and vascular endothelial growth factor levels decreased in RFR only group, but this was not statistically significant. Testosterone and VEGF levels increased in RFR+GA group, compared with RFR only group ($p<0.01$) and also increased in GA group compared with the control and RFR only group ($p<0.05$). Prostaglandin E2 and calcitonin gene releated peptide staining increased in tubules of the testes in RFR only group ($p<0.01$) and decreased in tubules of the testes in RFR+GA group ($p<0.01$). In RFR only group, most of the tubules contained less spermatozoa, and the spermatozoon counts decreased in tubules of the testes. All these findings and the regenerative reaction, characterized by mitotic activity, increased in seminiferous tubules cells of the testes in RFR+GA group ($p<0.01$).	**Adequate/ positive**
20. Bilgici et al., 2018, Wistar rats (M), 30 days	2.45 GHz, whole body average SAR 0.0233 W/kg	1 h/day (11 M exposed, 11 M controls)	Serum IL-6 and CRP levels were significantly different in in exposed animals ($p<0.05$). Significant difference in necrosis and spermatogenesis in exposed animals ($p<0.05$)	**Adequate/ positive**
21. Guo et al., 2019, Sprague-Dawley rats, 1 month	220 MHz (pulsed modulated), 0.030 W/kg	1h/day, 7 days/week, 20/group	Decreased sperm count and survival rate of sperm ($p<0.05$), increased sperm abnormalities (NS), increased expression in testes of cleaved caspase 3 ($p < 0.05$), caspase 3 ($p<0.01$), and the BAX/BCL2 ratio ($p<0.01$), decreased serum T level ($p<0.05$)	**Adequate/ positive**

Table 23 – Reproductive/developmental effects in experimental animals: reproductive toxicity in male rats (450-6000 MHz) (continued c)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
22. Yu et al., Experiment 1, 2020, Sprague-Dawley rats (M adults), 50, 100 0r 150 days	smartphone emitting SRF-EMR, 2575–2635 MHz (TD-LTE), 1.05 W/kg.	6 h/day (smartphone was kept on active talk mode and received an external call for 1 min over 10min intervals for 10 cycles); 135 rats (9 groups of 15 rats each).	After 150 days of SRF-EMR exposure, sperm concentration, motility, viability, and normal morphology were comparatively lower in the SRF group than in the control group. Mating experiment in rats exposed to SRF-EMR for 150 days: the pup weight was comparatively lower in the SRF group than in the controls. Testicular morphologic injury: after 150 days, increased disorder in spermatogenesis, as well as significant germ cell loss, and decreased epithelium height were observed, together with lower epithelium height, lower Johnsen score, and higher Cosentino score. Oxidative stress in testes: After 100 days of exposure, only CAT and GSH content was found to be significantly lower in the SRF group. After 150 days, also the levels of MDA, 4-HNE and LPO were comparatively higher, while GSH, SOD and CAT content were lower in the SRF group. Apoptosis in the testes: after 100 days, only cleaved-caspase 8 was significantly upregulated in the SRF group. After 150 days, only the level of Bcl-2 was lower, while the levels of Bax, cleaved-caspase-3, Fas, FasL and cleaved-caspase-8 were significantly higher in the SRF group ($p < 0.01$)	**Adequate/ positive**
Experiment 2, 2020, Sprague-Dawley rats (M adults), 150 days	smartphone emitting SRF-EMR, 2575–2635 MHz (TD-LTE), 1.05 W/kg.	6 h/day (smartphone was kept on active talk mode and received an external call for 1 min over 10min intervals, for 10 cycles); 10 to 15 rats/ group, 91 rats in total (7 groups)	Transcriptional profile changes: 1663 differentially expressed genes including 1446 up-regulated and 217 down-regulated. Spock3 level was higher in rats exposed to SRF-EMR for 150 days. Inhibition of Spock3 overexpression improved sperm quality decline and alleviated testicular injury and BTB disorder in the exposed rats. SRF-EMR exposure suppressed MMP2 activity, while increasing the activity of the MMP14–Spock3 complexes and decreasing MMP14–MMP2 complexes; these results were reversed by Spock3 inhibition ($p < 0.01$).	**Adequate/ positive**

Table 24 – Reproductive/developmental effects in experimental animals: : developmental toxicity in hamster in male rats (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
23. Lerchl et al., 2008 a, b, c, Djungarian hamsters (M), 60 days	a: 383 MHz (TETRA), b: 900 and c: 1800 MHz (GSM), SAR 0.08 W/kg	24 h/day (120 M exposed; 120 M sham)	a: Pineal and serum melatonin levels as well as the weights of testes, brain, kidneys, and liver were not affected; Significant transient increase in body weight up to 4%; b: Pineal and serum melatonin levels as well as the weights of testes, brain, kidneys, and liver were not affected; Significant non transient increase in body weight up to 6%; c: Pineal and serum melatonin levels as well as the weights of testes, brain, kidneys, and liver were not affected; no effect on body weight;	**Adequate/negative**

Table 25 – Reproductive/developmental effects in experimental animals: developmental toxicity in mice (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
24. Finnie et al. a, b (2006), c (2009), BALB/c mice (F)	900 MHz, 4 W/kg	1h/day, 7 days/week, 10/group	Not any statistically significant alteration (NS) in: (a): blood-brain barrier permeability in the immature brain of fetal heads, (b): immediate early gene c-fos expression as a marker of neural stress (c): stress response by induction of heat shock proteins	**Adequate/negative**
25. Lee et al., 2009, ICR mice (F breeders; F and M fetuses), Day 1-17 of gestation	CDMA (849 MHz) and WCDMA (1.95 GHz), SAR 2.0 W/kg for 2 exposure periods (total 4 W/kg)	2 exposures 45-min/day, separated by a 15-min interval (14 F sham; 17 F CDMA-exposed; 20 F sham CDMA+WCDMA controls; 20 F CDMA+WCDMA exposed). Short daily exposure	Simultaneous experimental exposure to CDMA and WCDMA RF EMFs did not cause any observable adverse effects (mortality, growth retardation, changes in head size and other morphological abnormalities) on mouse fetuses.	**Adequate/ negative**
26. Fragopoulou et al., 2010, Balb/c Mus musculus (F breeders; M and F offspring), 5 days before pregnancy; days 1-21 of gestation	GSM 900MHz, SAR 0.6–0.94 W/kg	0 (5 F control breeders, 7 M and F offspring) ; 6 min/day (7 F exposed, 20 M and F offspring); 30 min/day (7 F exposed, 20 M and F offspring)	Statistically significant variations in the ossification of cranial bones and thoracic cage ribs, and displacement of Meckelian cartilage, in exposed animals (both groups). Littermates examined after teeth eruption displayed normal phenotypes.	**Adequate/ positive**

Table 25 – Reproductive/developmental effects in experimental animals: developmental toxicity in mice (450-6000 MHz) (continued b)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
27. Sambucci et al., 2011, C57BL/6 newborns mice (M and F), 5 consecutive weeks, starting the day after birth	Wi-Fi at 2.45 GHz, 0.08 or 4 W/kg SAR	2 h/day, 5 days/week; 16 newborns/group, each with 4 adoptive mothers assigned (48 pups in total)	No differences in body weight and development among the groups were found in mice of both sexes. For the immunological analyses, results on female and male newborn mice exposed during early post-natal life did not show any effects on all the investigated parameters ($p>0.05$), with one exception: a reduced IFN-γ production in spleen cells from microwaves (MW)-exposed (SAR 4 W/kg) male (not in female) mice compared with sham-exposed mice ($p<0.05$).	**Adequate/negative**
28. Zhang et al., 2015, CD1 mice (M and F), in utero exposure, throughout gestation (Days 3.5–18)	9.417 GHz, SAR: 2.0 W/kg	12 h/day; 4 pregnant female mice per group. Previously, to obtain pregnancies: 12 breeding cages were set up, each containing one CD1 female mouse and two CD1 male mice, all aged 6 weeks.	Mice did not differ in motor ability by open field test (OFT); however, frequency of entries into and duration of time spent in the center zone for the treated group were lower compared to controls. Exposed mice had increased anxiety-related behavioral elevated-plus maze test (EPM). Tail suspension test (TST) and forced swimming test (FST) showed that RFR exposure significantly decreased immobility time, demonstrating that the offspring of exposed mice had decreased depression-related behavior. By Morris water maze (MWM), treated mice showed a progressive decline in escape latency. On the fourth and fifth days of MWM, only male mice in Radiation group spent more time trying to find the platform, indicating reduced spatial learning ability ($p < 0.01$).	**Adequate/ positive**
29. Fatehi et al., 2018, NMRI mice (M and F offspring), 30 days	900 MHz, intensity NR	Cell phone in "Standby-mode": 1, 5 and 10 h/day (group 2,3,4); cell-phone on "Active-mode": 1 h/day (group 5); 20 mice/group	Irradiated mice (at any exposure duration) had significant increases in pregnancy duration. Furthermore, when the cellphone changed from off mode to active mode, a significant delay was seen in pregnancy duration. RFR exposure leads to a significant decrease in the number of newborn mice compared to the control group. The results also demonstrated that the increase of the exposure time from 1 h per day (group 2) to 10 h per day (group 4) in the Standby mode caused a significant difference in the number of the newborns ($p < 0.05$).	**Adequate/positive**

Table 25 – Reproductive/developmental effects in experimental animals: developmental toxicity in mice (450-6000 MHz) (continued c)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
30. Nelson et al., 1991, 1994, 1997, 1997; Sprague-Dawley rats (F); 10, 20, 30 minutes	10 MHz (2-methoxyethanol at 20, 40, 60, 75, 80, 100, 120, 125, 140 or 150 mg/kg), 0.8-6.6 W/Kg . Thermal effects (temp. 42C°)	10, 20, 30 minutes; 10-27/group	Synergism between RFR and 2ME administration in the induction of teratogenic effects: increased incidence of external malformation of fetuses ($p<0.05$)	**Inadequate**
31. Nelson et al., 2001, Sprague-Dawley rats (F), 60 minutes	10 MHz (Methanol 2, 3 g/kg); 0.8-6.6 W/Kg Thermal effects (temp. 42C°)	60 minutes; 10/group	Increased incidence of resorbed fetuses ($p<0.05$). No synergistic effects.	**Inadequate**
32. Ogawa et al., 2009, Sprague-Dawley rats (F), 10 days	1950 MHz CDMA, 0.4 W/kg	90 min/day, 7 days/week, 20/group	Not any statistically significant alteration (NS) for: landmarks of sexual maturity, viable litter size/live birth index, neonatal growth, neonatal survival indices, sex ratio in progeny, physiologic endpoints revealing unique toxicities of pregnancy and lactation ($p>0.05$).	**Adequate/negative**
33. Sommer et al., 2009, C57BL mice (M, F), Multi-generation study	1966 MHz (UMTS), 0.08, 0.4, 1.3 W/kg	24 h/day, 7 days/week, 128 M and 256 F over four generations (1M and 2F per cage)	Not any statistically significant alteration (NS) for: viable litter size/live birth index, neonatal growth, neonatal survival indices, prenatal mortality, assessment of sperm quality, weight and morphology of reproductive organs, mating and fertility indices and reproductive outcome, landmarks of sexual maturity, sexual behavior ($p<0.05$)	**Adequate/negative**
34. Ozorak et al., 2013, Wistar albino rat offspring (and F pregnant adult), from pregnancy to 6 weeks of age	Wi-Fi (2.45 GHz) and mobile phone (900 and 1800 MHz) RFR, whole body SAR 0.1 W/kg	1 h/day, 5 days/week; 24 rats/group, 96 in total	Results from the fourth week showed that the level of lipid peroxidation in the kidney and testis and the copper, zinc, reduced glutathione (GSH), glutathione peroxidase, and total antioxidant status (TAS) values in the kidney decreased in the RFR groups, while iron concentrations in the kidney as well as vitamin A and vitamin E concentrations in the testis increased in the RFR groups. Results for fifth-week samples showed that iron, vitamin A, and β-carotene concentrations in the kidney increased in the RFR groups, while the GSH and TAS levels decreased. The sixth week results showed that iron concentrations in the kidney and the extent of lipid peroxidation in the kidney and testis increased in the RFR groups, while copper, TAS, and GSH concentrations decreased ($p<0.05$). There were no statistically significant differences in kidney chromium, magnesium, and manganese concentrations among the four groups ($p>0.05$).	**Adequate/positive**
35. Poulletier de Gannes et al., 2013, Wistar rats (M, F), 5 weeks F, 6 weeks M	2450 MHz (Wi-Fi signal), 0.08, 4 W/kg	1 h/day, 6 days/week, 12/group	Not any statistically significant alteration (NS) for: number of live and dead fetuses per uterine horn, number and location in each uterine horn of early and late resorption sites, distribution of implantation sites on each uterine horn (Significance: NR).	**Adequate/negative**

Table 26 – Reproductive/developmental effects in experimental animals: developmental toxicity in rats (450-6000 MHz) (a)

Reference, Strain, Species (Sex), Exposure duration	Frequency, Intensity Any other co-exposure	Exposure time, Number of animals	Observed effects	Comments
36. Celik et al., 2016, Wistar albino rats (F breeders, M offspring), from gestation to 21 days of age	2.45 GHz EMR with 217 Hz pulses, SAR 0.1 W/kg	1 h/day for 5 days/week (8 F exposed breeders, 24 M exposed offspring; 8 F control breeders, 24 M control offspring)	Oxidative stress was observed in the brain and liver of developing rats, due to reduced GSH-Px, GSH and antioxidant vitamin concentrations. Moreover, the brains were more sensitive to oxidative injury compared to the liver in the development of newborns ($p<0.05$).	**Adequate/positive**
37. Shirai et al., 2016, Sprague–Dawley rats (F adults and their offspring), Mothers: from Gestational Day 7 to weaning; F1 offspring rats from birth up to 6 weeks of age	Eight different communication signal RFR (two of 800 MHz band, two of 2 GHz band, one of 2.4 GHz band, two of 2.5 GHz band and one of 5.2 GHz band), 0.4 W/kg, each frequency contributing for 0.05 W/kg	20 h/day; mothers: 12 rats/group; 46–48 F1 pups per group.	No abnormal findings were observed in the dams or F1 offspring exposed to the RFR or to the F2 offspring for any of the parameters evaluated ($p>0.05$).	**Adequate/negative**
38. Stasinopoulou et al., 2016, Wistar rats (F adults and their offspring), Pregnant rats throughout the pregnancy, and a group of dams and their offspring for further 22 days	1880–1900 MHz, whole body SAR ranging from 0.016 to 0.020 W/kg	12 h/day; 40 rats/group	RFR exposure caused heart rate increase in the embryos on the 17th day of pregnancy. Significant changes on the newborns' somatometric characteristics were noticed. Pyramidal cell loss and glia fibrilliary acidic protein over-expression were detected in the CA4 region of the hippocampus of the 22-day old pups that were irradiated either during prenatal life or both pre- and postnatally ($p>0.05$).	**Adequate/positive**
39. Othman et al., 2017, Albino Wistar rats, Gestation period (19–20 days)	2.45 GHz from Wi-Fi, Intensity NR (Wi-Fi: Exposed group was placed at distance of 25 cm from the Antennas. D-Link DWL-3200 AP with 802.11 g mode and WPA2 net-work protection)	2 h/day; 63 control offsprings and 37 treated offspring, 5 adult pregnant exposed rats/group	In-utero WiFi exposure impaired offspring neurodevelopment during the first 17 postnatal days without altering emotional and motor behavior at adult age. Besides, prenatal WiFi exposure induced cerebral oxidative stress imbalance (increase in malondialdehyde level and hydrogen peroxide levels and decrease in catalase and superoxide dismutase activities) at 28 but not 43 days old, also the exposure affected acethylcolinesterase activity at both cerebral and seric levels ($p<0.05$)	**Adequate/positive**

Table 27 (summary tables 21-26) (a, b) – Collected data for experimental studies on reproductive/developmental effects (FR1: 450-6000 MHz)

Total studies	39								
Adequate studies	37								
Type of study	Mouse					Rat			
	Observed effects	**Total adequate studies***	**Positive results**	**Equivocal results**	**Negative results**	**Total adequate studies***	**Positive results**	**Equivocal results**	**Negative results**
Reproductive-male fertility	Semen quality Histopathological alterations Fertility	9	6		3	14	10	1	3
Reproductive-female fertility	Fertility Gestation period Number of pups Weight of litters	2	1	1					
Development-Female-litters	Neuro/behavioural effects Foetal growth Litter haematochemical characteristics	10	4		6	4	3		1

*Some of the studies include more than one outcome. One study (Ref. 23) was performed on Djungarian hamster, and was considered adequate/negative.

SUMMARY OF THE RESULTS OF REPRODUCTIVE/DEVELOPMENTAL EFFECTS IN EXPERIMENTAL ANIMALS STUDIES (FR1: 450 to 6000 MHZ)(Table 27)

From the present review, 39 studies on reproductive/developmental effects in experimental animals were selected. 20 studies were performed on mice, 18 were performed on rats, 1 on hamsters. Various end points were studied in both mice and rats in adequate studies. Summaries of the results are presented in Table 27.

Out of the 37 adequate studies, the results were:

Reproduction, male fertility (Semen quality, Histopathological alterations, Fertility).

Twentythree adequate studies were performed to investigate possible non-thermal adverse effects on reproduction in male rats and mice. In mice, 6 of 6 adequate studies, showed a positive association between exposure and adverse effects (Ref: 1, 2, 4, 5, 6, 8) and 1 was negative (Ref: 3). In rats, out of 14 studies,10 were positive (Ref: 9, 13, 16, 17, 18, 19, 20, 21, 22, 23), 1 showed equivocal outcomes (Ref: 12), 3 were negative (Ref: 10, 11, 15).

The most convincing evidence regards the statistically significant decline of sperm quality, in both rats and mice. For this outcome there is *sufficient* evidence of association between RF-EMF exposure and the decline of sperm quality.

Reproduction, female fertility (Fertility, gestation period, number of pups, weight of litters).

Only 2 studies on mice were considered adequate for the present review. One of them (Ref. 8) showed positive evidence for the association of adverse effects with RF-EMF exposure, one was equivocal (Ref: 7). Female fertility was not enough investigated, so, although statistically significant effects were found, evidence is *limited* to allow for any conclusive evaluation.

Development - Dams and litters (litter hematochemical characteristics, neuro/behavioural effects, foetal growth, etc)

Fourteen adequate studies were analysed for developmental outcomes. Out of 14, 10 were performed on mice, 4 on rats. In mice, 4 showed a positive association with exposure (Ref: 26, 28, 29, 34) and 6 were negative (Ref: 24, 25, 27, 32, 33, 35). In rats, out of 4 adequate studies, 3 were positive (Ref: 36, 38, 39) and 1 negative.

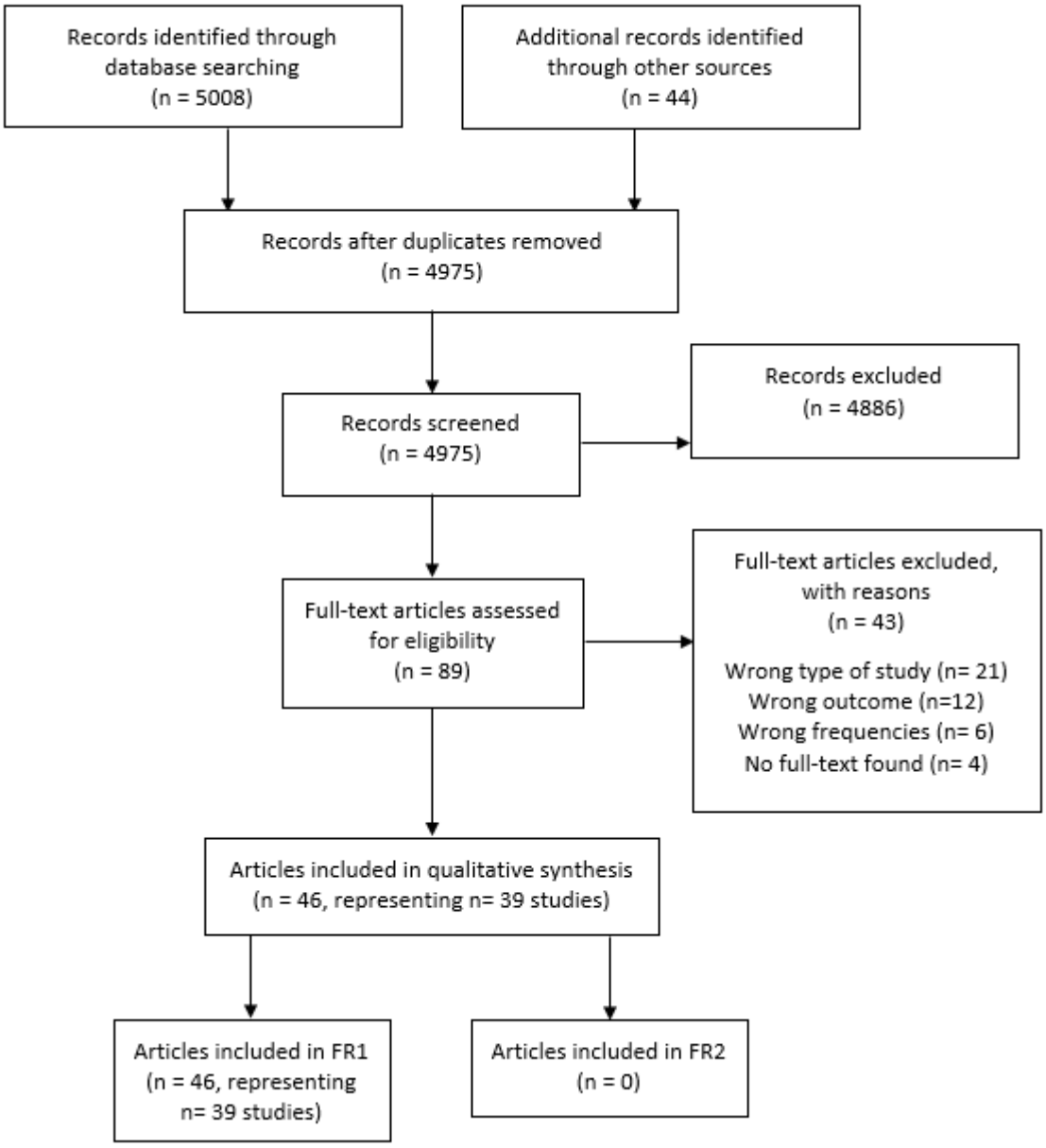
The results on this end point are mixed (conflicting) and the evidence of a possible association of developmental adverse effects with the exposure to RF-EMF is *limited*.

4.2.4 Reproductive/developmental effects in experimental animals: Studies evaluating health effects due to RF at a higher frequency range (FR2: 24 to 100 GHz, MMW) .

The articles identified through database searching and other sources were 5052. After removing duplicates (77) and excluding non-pertinent articles (4886) based on title and abstracts, 89 articles remained. Based on full-text screening, 43 papers were further excluded, so that the published articles with frequencies appropriate for inclusion in this qualitative synthesis were 46, corresponding to 39 studies. In three cases, more than one article was published reporting information on the same study for different reproductive/developmental end points (Fig. 16).

At this stage, a selection based on frequency range was also performed: out of 46 papers/39 studies, all reported exposures to the FR1 range, and none to FR2.

Figure 16 – Flow diagram. Reproductive/developmental effects in experimental animals (FR2)



5. Discussion

In its latest publication ICNIRP states that: "(…) reported adverse effects of RF-EMFs *on health need to be independently verified, be of sufficient scientific quality and consistent with current scientific understanding, in order to be taken as "evidence" and used for setting exposure restrictions. Within the guidelines, "evidence" will be used within this context, and "substantiated effect" used to describe reported effects that satisfy this definition of evidence. The reliance on such evidence in determining adverse health effects is to ensure that the exposure restrictions are based on genuine effects, rather than unsupported claims* (…)*"* (ICNIRP, 2020a).

Both in humans and in animal models, effects that ICNIRP defines as "*unsupported claims*" have been observed; and, some of them represent "*substantiated effects*", i.e. objective and relevant observations from epidemiological and experimental studies, including those on cancer and adverse effects on reproduction and development.

Epidemiological studies, when conducted with adequate information on the exposure scenarios and correct methodology, can provide strong evidence of "substantiated effects" of an agent, factor or situation. However, epidemiological studies can often have several limitations in small sample size, low statistical power, and confounding factors. These limitations include: i) Small exposed or follow up populations which may be insufficient to provide adequate statistical power; ii) The nature, amount and timing of exposures to the hazardous agent may lead to exposure misclassifications and false negative results; iii) Clear results due to confounding factors may be difficult to derive; iv) Methodological factors, such as recall bias, or publication bias, may also prevent clear results; v) The inherent delay in establishing robust epidemiological results due to the long period of tumour latency in humans (ie from first exposure to tumour indentification) on average can be 10-40 years; iv) Wide spread and diffuse exposure to other hazardous agents which may have synergistic or protective effects in combination with the agent being studied; vii) Widespread exposures to EMF creates difficulties in finding a large enough unexposed control group: which then may require the use of lowest exposure groups for comparison as the controls, which can be less robust.

The main direction of bias from many of these methodological and other limitations of human studies tends to produce "false negatives", i.e. results that exonerate the agent from being harmful but which later turn out to be wrong (Grandjean, 2013).

While sufficient evidence of carcinogenicity from RF-EMF was observed in studies on experimental animals, the following reasons suggest that the findings are important/relevant for risk assessment in humans. Animal studies (bioassays) have few limitations, and when adequately conducted to the high standards recommended (OECD, 2018b) can therefore, by comparison to human studies, provide relatively rapid and robust evidence of the association of exposure with the specific outcome.

Since the period of latency is proportional to the average lifespan of an organism, latency is proportionally shorter in the rodents that are commonly used in the laboratories. A latency time of one year in rats is equivalent to slightly more than 30 years of latency in humans, so animal bioassays, even over the rats full life time of approximately 2.5 years, allow cancer identification within a relatively short time compared to human studies.

Animal bioassays can therefore provide important information on the human risk of cancer from exposure to different agents. These data can enhance our confidence in the evidence on human cancer risks from epidemiological data.

Many human carcinogens have first been reliably identified in adequately tested laboratory animals, often many years before the human evidence was established (Huff, 1999; Huff, 2013; Maronpot et al., 2004).

There can also be consistent evidence between well conducted (OECD, 2016) animal and human studies on reproductive and developmental adverse effects.

The importance of experimental bioassays for safeguarding human health also emerges from risk assessments for chemicals as based on well conducted animal studies. Thus, animal studies are used to find the Lowest-Observed-Adverse-Effect Level (LOAEL i.e the lowest concentration of the chemical agent; or sometimes the No-Observed-Adverse-Effect Level- NOAEL) causing adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism distinguishable from unexposed animals/organisms of the same species and strain under the same exposure conditions (Gaylor, 1999).

With RF-EMF, the epidemiological study results have so far only provided "*limited evidence*" of an association with cancer, largely because of the above limitations of epidemiological studies, and the absence of sufficient independent funding of such research.

In studies on laboratory animals, however, where confounding factors and other limitations are minimal, the evidence for RF-EMF having a carcinogenic effect , particularly on peripheral and central nervous system cells, is more robust than in 2011, following publications by the US- NTP and the Ramazzini Institute in 2018/19, and now attains "*sufficiency*" of animal evidence as per IARC evidence evaluation (IARC, 2019).

5.1 Cancer and lower telecommunication frequencies (FR1: 450 to 6000 MHz)

In 2011, in view of the limited evidence in humans and in experimental animals, the Working Group of IARC classified RF-EMF as "possibly carcinogenic to humans" (Group 2B). This evaluation was supported by a large majority of Working Group members. The overall evaluation was: *Radiofrequency electromagnetic fields are possibly carcinogenic to humans* (Group 2B).

Almost 10 years later many new studies have been published and an update is necessary. An Advisory Group of 29 scientists from 18 countries met at the International Agency for Research on Cancer (IARC) in March 2019 to recommend priorities for the IARC Monographs programme during 2020–2024, and among them there are RF-EMF (IARC, 2019).

5.1.1 RF-EMF (FR 1: 450 to 6000 MHz) and cancer in humans

Our review of the literature up to 2020 has found that several new epidemiological studies have been published on the association between RF-EMF and cancer since the publication of IARC Monograph 102 (IARC, 2013), yet the evidence remains mixed (conflicting results). In the Million Women Study cohort, there was no evidence of increased risk of glioma or meningioma. There was an increased risk of vestibular Schwannoma (neurinoma of the acoustic nerve) with long-term use and a significant dose–response relationship (Benson et al., 2013).

Updated follow-up in the Danish nationwide subscribers study did not find increased risks of glioma, meningioma, or vestibular schwannoma, even among those with subscriptions of 10 years or longer (Frei et al., 2011; Schüz et al., 2011).

New reports from case–control studies that assessed long-term use also found mixed results; for example, increased risks of glioma and acoustic neuroma were reported by Hardell and Carlberg, (2015) and Hardell et al., (2013 a, b), but no evidence of increased risks for these tumours was reported by Yoon et al., (2015) and Pettersson et al., (2014).

Several large-scale studies are still in progress and should yield results within the next few years. Mobi-Kids is a multicentre case–control study of brain tumours in those aged 10–24 years. Cohort Study of Mobile Phone Use and Health (COSMOS) is a new European cohort of adult cell phone users. There will also be updated results from the Million Women Study (IARC, 2019).

Some authors state that the elevated risk of brain cancer and neurinoma evidenced by various epidemiological studies do not mirror the observed incidence time trends, which are considered informative on this specific topic. This is not what we found in the recent available literature.

Concerning malignant tumours of the central nervous system (CNS), in 2019 the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2016 (GBD 2016, published on Lancet Neurol, 2019) reports a 4.63 per 100 000 person-years global incidence of malignant CNS tumours, which represents a 17.3% increase from 1990 to 2016. The top three countries with the highest number of incident cases were China, the USA, and India.

An increase in the incidence of glioblastoma multiforme in the frontal and temporal lobes and cerebellum was also reported in USA (Little et al., 2012; Zada et al., 2012).

A register based study in Sweden (Hardell and Carlberg, 2017) showed increasing rates of tumours of unknown type in the brain with higher rate during 2007–2015, in both sexes (Fig. 17 and 18).

Figure 17 – The Swedish National Inpatients Registry (source: Hardell and Carlberg, 2017): men

Joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish National Inpatient Register for men, all ages during 1998–2015 diagnosed with D43 = tumour of unknown type in the brain or CNS (http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard).

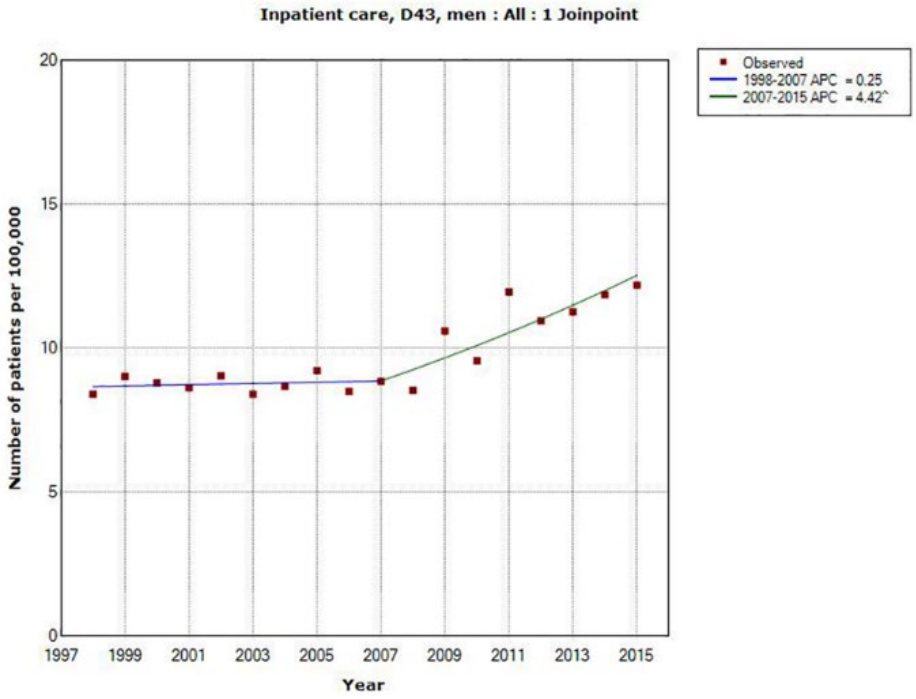
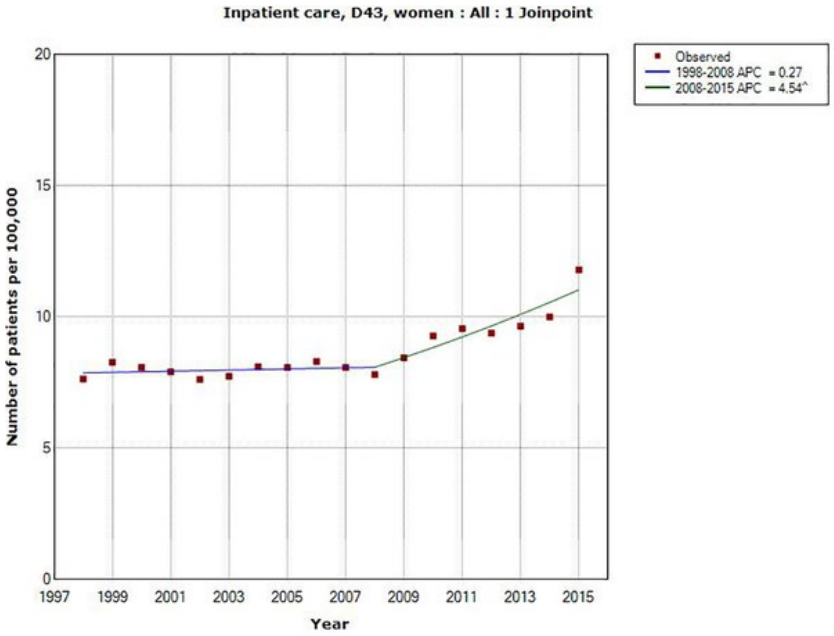


Figure 18 – The Swedish Nnl. Inpatients Registry (source: Hardell and Carlberg, 2017): women

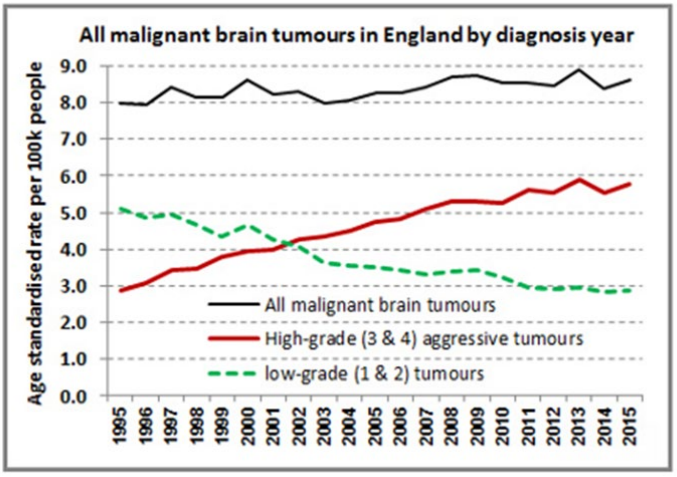
Joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish National Inpatient Register for women, all ages during 1998–2015 diagnosed with D43 = tumour of unknown type in the brain or CNS. (http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard).



Furthermore, ANSES (2019), in the volume "Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018" reports the trend of the incidence (new cases by year) of glioblastomas (malignant tumours of the brain), histologically confirmed. Between 1990 and 2018 the number of new cases by year, both in men and women, increased: this is essentially attributable to the (environmental, occupational) increase in risks related to this type of cancer (ANSES, 2019)

In a UK study of national incidence data on malignant brain tumours, there was a rise in the rates of the more aggressive type identified in the epidemiological case control studies (Fig. 19). The authors looked at the incidence of brain tumours in three "major cancer registries" over a 15-year period (1992-2006). The study showed "decreased rates of primary brain tumours in all sites with the notable exception of increased incidence of glioblastoma multiforme (GBM) in the frontal lobes, temporal lobes and cerebellum. The increase in GBMs in the temporal lobe (the region of the brain closest to the ear and potentially to a phone) was seen in all three registries, ranging from approximately 1.3% to 2.3% per year, a finding that is statistically significant (Philips et al., 2018).

Figure 19 – Trends in the incidence of of all malignant brain tumours in England
(Philips et al., 2018)



http://www.saferemr.com/2018/03/brain-tumor-incidence-trends.html

In conclusion, referred to our research on FR1, positive *limited* associations have been observed in the literature between exposure to RF-EMF from wireless phones and glioma, and acoustic neuroma in humans.

5.1.2 RF-EMF (FR1: 450 to 6000 MHz) and cancer in experimental animals

New data in experimental animals for exposure to RF-EMF (FR1) have been published since the previous IARC Monographs evaluation in 2011 (IARC, 2013).

The large study by the United States National Toxicology Program (NTP) found an increased risk of malignant schwannomas of the heart in male rats with high exposure to radiofrequency radiation at frequencies used by cell phones, as well as possible increased risks of certain types of tumour in the brain and adrenal glands, and equivocal increased risks in mice or female rats (NTP, 2018a, b).

The Ramazzini Institute (RI) study also found a statistically significant increase in schwannomas of the heart in highly exposed (50 V/m) male rats and an increase in gliomas in female rats (Falcioni et al., 2018). In the Lee et al. study (2011) on Eμ-piml transgenic mice, prone to getting lymphomas, any increase of tumour incidence was observed. Lerchl et al. (2015), in a promotion study found that tumours of the lung and liver in exposed animals were significantly higher than in sham-exposed controls. In addition, lymphomas were also found to be significantly elevated by exposure, suggesting a promotion effect of RF-EMF.

The $30 million NTP study includes both mice and rats. It took more than 10 years to complete and is one of the most comprehensive assessments to date of health effects in animals exposed to RF-EMF, mice and rats. The FDA called for this research in 1999.

In this study, in the far GSM-exposed mice, the NTP found skin tumours and lung tumours in males, and malignant lymphomas in females. Far CDMA-exposed mice showed an increase of liver hepatoblastomas in males and malignant lymphomas in females. The results were labelled as equivocal (a marginal increase of neoplasms that may be test agent related even if the increased incidence of the tumours were statistically significant).

The long term study on rats (NTP, 2018a) found that exposure to high levels of RF-EMF, like that used in 2G and 3G cell phones, was associated with:

- Clear evidence of tumours in the hearts of male rats (malignant schwannomas).

- Some evidence of tumours in the brains of male rats (malignant gliomas).

- Some evidence of tumours in the adrenal glands of male rats (pheochromocytomas).

An expert peer-review panel concluded that the NTP studies were well designed, and that the results demonstrated that both GSM- and CDMA-modulated RFR were carcinogenic to the heart (schwannomas) and brain (gliomas) of male rats (Final evaluation: *Clear evidence of carcinogenicity*) (NTP, 2018c).

The RI in Italy performed a life-span carcinogenicity study on Sprague-Dawley rats to evaluate the carcinogenic effects of RF-EMF in the far field situation, reproducing the environmental exposure to RF-EMF generated by 1.8 GHz GSM antennae at radio-base stations for mobile phones. This is the largest long-term study ever performed in rats on the health effects of RF-EMF, including 2,448 animals. The authors reported the final results regarding brain and heart tumours, confirming and strengthening the same observation as NTP on rats: a statistically significant increase in Schwannomas of the heart in males and an increase in glial malignant tumour in females.

The recent NTP and RI RF-EMF studies presented similar findings in heart schwannomas and brain gliomas, strengthening the reciprocal results. Both NTP and RI studies were well performed, no bias affecting the results. Blinding was applied in both NTP and RI experiments, following their respective Standard Operating Procedures (SOPs) or specifications. It is quite common to have a different response in carcinogenesis for mice and rats, and gender differences in the response to carcinogens are common in both experimental animals and humans. Schwannomas are tumours arising from the Schwann cells, which are peripheral glial cells that cover and protect the surface of all nerves diffused throughout the body; so vestibular (acoustic nerve) and heart schwannomas have the same tissue of origin. In rats, increases in malignant heart schwannomas, malignant glial tumours of the brain and Schwann cell hyperplasia (a pre-malignant lesion) are rare. However, these lesions were observed in exposed animals in two independent laboratories, in a wide range of RF-EMF exposures studied. As a consequence, the findings of the two laboratories could not be interpreted as occurring "by chance". The NTP and the RI studies show that the assumption that RF radiation is incapable of causing adverse health effects other than by tissue heating is not scientifically based.

It's noteworthy that both NTP and the RI in the last 40 years strongly contributed with their results to the risk assessment of various chemical and physical agents. Their results were often predictive for human health. The NTP is the world's largest toxicology program; as far as number of agents studied, the RI is second only to NTP. The NTP and RI two-year carcinogenicity studies and their publications are also considered as the "gold standard" of cancer studies due to their high quality, their utility in evaluating human health hazards, and the rigour, transparency, and independency they bring to the evaluation of the data.

In conclusion, for FR1 exposed experimental animals, positive associations, with *sufficient* evidence, have been observed between exposure to RF-EMF and glioma and neuromas (synonymous with shwannoma).

5.2 Cancer and higher telecommunication frequencies (FR2: 24 to 100 GHz)

5.2.1 RF-EMF (FR2: 24 to 100 GHz) and cancer in humans

Very few studies were performed on frequencies between 24 to 100 GHz (FR2). The largest part of them regarded occupational exposure in workers involved in radar telecommunication. The exposure was self-reported or related to job title, and based on the distance from the source of RF emissions. In conclusion, while there are weak suggestions of a possible increase in risk of brain cancers and of lymphomas and leukaemias in workers occupationally exposed, exposure

misclassification and insufficient attention to possible confounders limit the interpretation of the findings. In IARC Monograph 102 the conclusion was:

Tumours of the brain*: "exposure misclassification and insufficient attention to possible confounding limit the interpretation of findings. Thus, there is no clear indication of an association of occupational exposure to RF radiation with risk of cancer of the brain"* (IARC, 2013).

*"*Leukaemia/Lymphoma*: In summary, while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF radiation, the limited exposure assessment and possible confounding make these results difficult to interpret"* (IARC, 2013).

Other kinds of tumour emerged as potentially associated with exposure to high frequencies (uveal melanoma, cancer of the testis, breast, lung, and skin), but many of the studies showed methodological limitations and the results were inconsistent (IARC, 2013).

The present review confirms the IARC remarks, where the highest 5G frequency (FR2) is concerned, there are no adequate epidemiological studies upon which to assess the impact on health.

5.2.2 RF-EMF (FR2: 24 to 100 GHz) and cancer in experimental animals

Seventy six studies were examined for cancer in experimental animals. No available literature regarding the possible association between experimental carcinogenicity and RF radiation, at the range 24 to 100 GHz (FR2), was found.

5.3 Adverse effect on reproduction/development and lower telecommunication frequencies (FR1: 450 to 6000 MHz)

5.3.1 RF-EMF (450 to 6000 MHz) and adverse effects on reproduction /development in humans.

About 2800 studies in this review conformed to pre-set inclusion criterion. Additional records identified through reviewed articles revealed some further eligible articles. However, only a total of 40 articles were used for data extraction, and 26 epidemiological studies were reviewed as being adequate in methodology. The result of the review are presented in Table 18.

- **Man fertility**

In recent years, we have observed a general increasing percentage of male infertility. It has been attributed to an array of environmental, health and lifestyle factors.

Sperm count, motility, DNA integrity, sperm viability and morphology were the most affected parameters when men are exposed to RF-EMF.

FR1 (450 to 6000 MHz): There is sufficient evidence of the association between RF-EMF exposure and adverse effect on fertility in man.

- **Pregnant women exposure**

Miscarriage and pre-term birth among women heavily using mobile-phones during pregnancy was described as possibly associated to the exposure of the embryo/foetus during gestation; the studies are too limited in number and inadequate for exposure assessment in order to reach definitive conclusions. An association can neither be excluded nor confirmed.

FR1 (450 to 6000 MHz): There is limited evidence of the association between RF-EMF exposure and adverse effect on fertility woman.

- **Developmental effects in offspring**

In offspring, behavioural difficulties and motor/cognitive/language delay were examined by epidemiological cross-sectional and cohort studies; the results are mixed (conflicting) and not conclusive. An association can neither be excluded nor confirmed.

FR1 (450 to 6000 MHz): There is limited evidence of the association between RF-EMF exposure and adverse effect on offspring health.

5.3.2 RF-EMF (450 to 6000 MHz) and adverse effects on reproduction /development in experimental animals.

An important aspect of safety assessment of chemical and physical agents is determining their potential reproductive and developmental toxicity. A number of guidelines have outlined a series of separate reproductive and developmental toxicity studies from fertilisation through adulthood and in some cases to second generation.

The OECD Test Guideline 443 is designed to provide an evaluation of reproductive and developmental effects that may occur as a result of pre- and postnatal chemical exposure as well as an evaluation of systemic toxicity in pregnant and lactating females and young and adult offspring. This Test Guideline is designed to provide an evaluation of reproductive and developmental effects that may occur as a result of pre- and postnatal chemical exposure as well as an evaluation of systemic toxicity in pregnant and lactating females and young and adult offspring.

The Extended One-Generation Reproductive Toxicity Study (EOGRTS) is the most recent and comprehensive guideline in this series. EOGRTS determines toxicity during preconception, development of embryo/fetus and newborn, adolescence, and adults, with specific emphasis on the nervous, immunological, and endocrine systems, EOGRTS also assesses maternal and paternal toxicity.

The objective of the prenatal developmental toxicity study is to provide general information concerning the effects of prenatal exposure on the pregnant test animal and on the developing organism. More specifically, the developmental toxicity study aims to identify direct and indirect effects on embryonic and foetal development resulting from exposure to the agent; identify any maternal toxicity; establish the relationship between observed responses and dose in both dam and offspring; establish NOAELs (no observed adverse for maternal toxicity and pup development).

We selected and analysed animal studies considering their compliance with the guidelines mentioned, though our approach tended to be inclusive when the number of animals, exposure assessment and procedure were considered acceptable.

Table 27 summarises the results. Among the different adverse effects of FR1, the most evident was the impairment of sperm quality.

Structural and/or physiological analyses of the testes showed degenerative changes, reduced testosterone level, increased apoptotic cells, and increased production of reactive oxygen species (ROS).

For all other parameters results were limited and they do not allow conclusive evaluation.

➢ **Male fertility**

As regards RF-EMF exposure, sperm count, motility, DNA integrity, sperm viability and morphology were the most affected parameters when experimental animals are exposed to RF-EMF.

FR1 (450 to 6000 MHz): There is sufficient evidence of the association between RF-EMF exposure and adverse effect on fertility in male experimental animals.

➢ **Female fertility**

The studies are too limited in number in order to reach definitive conclusions. The two adequate studies examined, show adverse effects, but an association cannot be denied, nor confirmed.

FR1 (450 to 6000 MHz): There is limited evidence of the association between RF-EMF exposure and adverse effect on fertility in female experimental animals.

➢ **Developmental effects in offspring**

In offspring, gestation duration, foetal growth, litter characteristics, neurobehavioural effects were examined by experimental bioassays in rodents. Some studies were positive, but results are often conflicting for different studies and limitations were observed in exposure assessment. So, results were not conclusive. An association cannot be denied, nor confirmed.

FR1 (450 to 6000 MHz): There is limited evidence of the association between RF-EMF exposure and adverse effect on developmental parameters both in dams and offspring.

5.4 Adverse effect on reproduction/development and higher telecommunication frequencies (FR2: 24 to 100 GHz)

5.4.1 Adverse effect on reproduction/development in humans (FR2: 24 to 100 GHz)

The few available epidemiological studies we have analysed were performed on occupationally exposed men (Table 20). Adverse effects on sperm fertility were reported. However, the two available cross-sectional studies have the limit of self-reported exposure or assessment done by job title. An association cannot be denied, or confirmed. From our search, developmental adverse effects on these higher frequencies were not adequately studied in the human population.

FR2 (24 to 100 GHz): No adequate studies were performed on this band of higher frequencies.

5.4.2 Adverse effect on reproduction/development in experimental animal studies (FR2: 24 to 100 GHz)

In the few studies designed for the higher frequencies, only thermal adverse effects were adequately studied.

FR2 (24 to 100 GHz): No adequate studies were performed on this band of higher frequencies.

6. Conclusions

6.1 Telecommunication frequencies FR1 450 MHz – 6000 MHz

6.1.1 Cancer in humans

There is limited evidence in humans for the carcinogenicity of radiofrequency radiation. Starting from 2011, positive associations have again been observed between exposure to radiofrequency radiation from wireless phones and glioma and acoustic neuroma, but the evidence is not yet sufficiently strong to establish a direct relationship.

6.1.2 Cancer in experimental animals

There is sufficient evidence in experimental animals for the carcinogenicity of radiofrequency radiation.

6.1.3 Reproductive/developmental effects in humans

There is sufficient evidence of adverse effects on the fertility of men. There is *limited* evidence of adverse effects on fertility in women. There is *limited* evidence on developmental effects in offspring of mothers who were heavy users of mobile phones during pregnancy.

6.1.4 Reproductive/developmental effects in experimental animals

There is sufficient evidence of adverse effects on male rat and mouse fertility. There is *limited* evidence of adverse effects on female mouse fertility. There is *limited* evidence of adverse effects on the development in offspring of rats and mice exposed during embryo life.

6.2 Telecommunication frequencies FR2: 24 to 100 GHz

6.2.1 Cancer in humans

The few inadequate data available do not allow any evaluation.

6.2.2 Cancer in experimental animals

No available data.

6.2.3 Reproductive/developmental effects in humans

No available data.

6.2.4 Reproductive/developmental effects in experimental animals

No available data.

6.3 Overall evaluation

6.3.1 Cancer

FR1 (450 to 6000 MHz): As a synthesis of what we have managed to analyse in the available scientific literature, in both human and animal studies, we can say that RF-EMF at FR1 frequencies exposure probably cause cancer, and in particular gliomas and acoustic neuromas in humans.

FR2 (24 to 100 GHz): No adequate studies were performed on non thermal effects of the higher frequencies.

6.3.2 Reproductive developmental effects

FR1(450 to 6000 MHz): These frequencies *clearly* affect male fertility. These frequencies *possibly* affect female fertility. They *possibly* have adverse effects on the development of embryos, foetuses and newborns.

FR2 (24 to 100 GHz): *No adequate* studies were performed on non-thermal effects of the higher frequencies.

7. Policy options

The policy options resulting from the present report – applying to the 5G frequencies (700 MHz, 3600 MHz, 26 GHz) and bearing in mind that the 2G, 3G and 4G frequencies will continue to be used for many years – are reported below.

7.1 Opting for novel technology for mobile phones that enables RF exposures to be reduced

The source of RF emissions that seems at present to pose the greatest threat is the mobile phone. Though transmitting installations (radiobase masts) are perceived by some people as providing the greatest risk, actually the greatest burden of exposure in humans generally derives from their own mobile phones, and epidemiological studies have observed a statistically significant increase in brain tumours and Schwann cell tumours of the peripheral nerves, mainly among heavy cell-phone users.

We accordingly need to ensure that increasingly safer telephone devices are manufactured, emitting low energy and if possible only working when at a certain distance from the body. The cable earpiece solves much of the problem, but is inconvenient and hence puts users off; on the other hand, it is not always possible to use a speakerphone mode.

The option of lowering RF-EMF exposure as much as possible in connection with telephones still applies whatever the frequencies, from 1G to 5G. Countries such as the USA and Canada, which enforced stricter mobile phone SAR limits than Europe, were still able to build efficient 2G, 3G and 4G communications (Madjar, 2016). Since 5G aims to be more energy-efficient than the previous technologies, adopting stricter limits in the EU for mobile phone devices will be simultaneously a sustainable and a precautionary approach.

7.2 Revising the exposure limits for the public and the environment in order to reduce RF exposures from cell towers

Recently European policies (European Commission, 2019) have promoted the sustainability of a new economic and social development model which uses new technologies to constantly monitor the planet's state of health, including climate change, the energy transition, agro-ecology and the preservation of biodiversity. Using the lowest frequencies of 5G and adopting precautionary exposure limits such as those used in Italy, Switzerland, China and Russia, among others, and which are significantly lower than those recommended by ICNIRP, could help achieve these European sustainability objectives.

What epidemiological studies already showed in 2011 (IARC, 2013) has been confirmed by studies on laboratory animals, especially concerning the connection between exposure to RF-EMF and the carcinogenic effect in the nervous system. The safety level currently allowed in Europe is 61 V/m (ICNIRP, 2020a). The lowest dose at which those effects have been experimentally observed for far-field exposure is 50 V/m. In the same experimental study (Falcioni et al, 2018) any carcinogenic effect was observed at 5 V/m.

In light of this result, one policy option might be to revise residential and public exposure maxima throughout Europe. Levels could be reduced by at least 10 times, i.e. to around 6 V/m, which is an exposure level at which no cancer effects in experimental animals have been observed. 6 V/m seems also to be the precautionary limit where no adverse effects on fertility are concerned. It may sound impracticably low if we are to expand telecommunications by 5G, but it is not so.

In Italy, for example, the law sets a top limit of 20V/m, though wherever people are constantly exposed for over four hours (homes, workplaces, schools, centres of congregation, etc.) the critical value is set at 6 V/m. This limit is very close to the 5 V/m we mentioned before as being safe for experimental animals. NOAEL values ("*No Observed Adverse Effect Level*") in experimental studies are commonly used in risk assessments and research (Gaylor, 1999).

In many Italian towns, including Bologna, 5G has already been operating at a frequency of 3600 MHz. Monitoring data show that the mean exposure in the municipality of Bologna was 1.97 V/m for 2019 (peaking at 4.62 V/m in one specific instance). Statistics for 2020 are still being processed, but in no cases have the values prescribed by Italian law been exceeded. For the moment, then, it does seem possible to develop new installations whilst keeping within the legal limit.

Another example is Paris. The city has reached an agreement with France's four main mobile network operators aimed at introducing stricter network radiation norms. The RF-EMF exposure limit was lowered to 5 V/m from the previous 7 V/m for indoor spaces, representing a 30 percent reduction at the frequency reference of 900 MHz, setting a lower limit than the one adopted in Brussels (6 V/m) or Rome (6 V/m). The agreement, approved by the municipality of Paris in 2017, also includes plans for a new monitoring service to help measure EMF levels within buildings. Brussels is a third example of the adoption of a 6 V/m lower limit.

7.3 Adopting measures to incentivise the reduction of RF-EMF exposures

Much of the remarkable performance of new wireless 5G technology can also be achieved by using optic-fibre cables and by adopting engineering and technical measures to reduce exposures from 2-4G systems (Keiser, 2003; CommTech Talks, 2015; Zlatanov, 2017). This would minimise exposure, wherever connections are needed at fixed sites. For example, we could use optic fibre cables to connect schools, libraries, workplaces, houses, public buildings, all new buildings etc. Public gathering places could be 'no RF-EMF' areas (as we have for cigarette smoking) so as to avoid the passive exposure of people not using a mobile phone or long-range transmission technology, thus protecting many vulnerable elderly or immune-compromised people, children, and those who are electro-sensitive.

7.4 Promoting multidisciplinary scientific research to assess the long-term health effects of 5G and to find an adequate method of monitoring exposure to 5G

The literature contains no adequate studies by which to exclude the risk that tumours and adverse effects on reproduction and development may occur upon exposure to 5G MMW, or to exclude the possibility of some synergistic interactions between 5G and other frequencies that are already being used. This makes the introduction of 5G fraught with uncertainty concerning both health issues and forecasting/monitoring the actual exposure of the population: these gaps in knowledge are invoked to justify the call for a moratorium on 5G MMW, pending adequate research being completed.

In light of these uncertainties, one policy option is to promote multidisciplinary team research into various factors concerning exposure assessment and also into the biological effects of 5G MMW, both on humans and on the flora and fauna of the environment, non-human vertebrates, plants, fungi and invertebrates, at frequencies between 6 and 300 GHz. The results of these studies could form the basis for developing evidence-based policies regarding RF-EMF exposure of human and

non-human organisms to 5G MMW frequencies. Further studies are needed to better and independently explore the health effects of RF-EMF in general and of MMW in particular.

REACH aims to improve the protection of human health and the environment through better and earlier identification of the intrinsic properties of chemical substances. EU REACH regulates the registration, evaluation, authorisation and restriction of chemicals. It also aims to enhance innovation and competitiveness of the EU chemicals industry. EU REACH is based on the principle, "*no data no market*", placing responsibility on industry to provide safety information on substances. Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database at the European Chemicals Agency (ECHA) in Helsinki. One policy option can be to apply the same approach used for chemical agents to all types of technological innovation.

7.5 Promoting information campaigns on 5G

Unfortunately, there is a lack of information on the potential harms of RF-EMF. The information gap creates scope for deniers as well as alarmists, giving rise to social and political tension in many EU countries (OECD, 2017). Campaigns to inform the citizens should be therefore a priority.

Information campaigns should be carried out at all levels, beginning with schools. They should show the potential health risks, but also the opportunities for digital development, what infrastructural alternatives exist for 5G transmission, the safety measures (exposure limits) taken by the EU and Member States, and the correct use of the mobile phone. Only by sound and accurate information can we win back citizen trust and reach a shared agreement over a technological choice which, if properly managed, can bring great social and economic benefits.

8. References

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Recent decades have experienced an unparalleled development in wireless communication technologies (mobile telephony, Wi-Fi). The imminent introduction of 5G technology across the EU is expected to bring new opportunities for citizens and businesses, through faster internet browsing, streaming and downloading, as well as through better connectivity. However, 5G, along with 3G and 4G, with which it will operate in parallel for several years, may also pose threats to human health. This STOA report aim to take stock of our present understanding of health effects of 5G.

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