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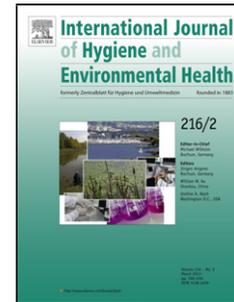
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Towards 5G communication systems: are there health implications?**Author:**

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Highlights RF-EMF exposure is rising and health effects of are still under investigation

- Both oncologic and non-cancerous chronic effects have been suggested
- 5G networks could have health effects and will use MMW, still scarcely explored
- Adequate knowledge of RF-EMF biological effects is also needed in clinical practice
- Underrating the problem could lead to a further rise in noncommunicable diseases

Abstract

The spread of radiofrequency electromagnetic fields (RF-EMF) is rising and health effects are still under investigation. RF-EMF promote oxidative stress, a condition involved in cancer onset, in several acute and chronic diseases and in vascular homeostasis. Although some evidences are still controversial, the WHO IARC classified RF-EMF as “possible carcinogenic to humans”, and more recent studies suggested reproductive, metabolic and neurologic effects of RF-EMF, which are also able to alter bacterial antibiotic resistance. In this evolving scenario, although the biological effects of 5G communication systems are very scarcely investigated, an international action plan for the development of 5G networks has started, with a forthcoming increment in devices and density of small cells, and with the future use of millimeter waves (MMW). Preliminary observations showed that MMW increase skin temperature, alter gene expression, promote cellular proliferation and synthesis of proteins linked with oxidative stress, inflammatory and metabolic processes, could generate ocular damages, affect neuro-muscular dynamics. Further studies are needed to better and independently explore the health effects of RF-EMF in general and of MMW in particular. However, available findings seem sufficient to demonstrate the existence of biomedical effects, to invoke the precautionary principle, to define exposed subjects as potentially vulnerable and to revise existing limits. An adequate knowledge of pathophysiological mechanisms linking RF-EMF exposure to health risk should also be useful in the current clinical practice, in particular in consideration of evidences pointing to extrinsic factors as heavy contributors to cancer risk and to the progressive epidemiological growth of noncommunicable diseases.

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Introduction

The distribution of radiofrequency electromagnetic fields (RF-EMF) in the everyday environment is rapidly growing, with the majority of emitting devices working in the frequency range above 100 kHz up to some GHz.

Although typical RF-EMF exposure levels are usually below current regulatory limits in European countries(Sagar et al., 2017; Urbinello et al., 2014), the real health impact of the advancement and spreading in communication technology is still under investigation.

It has been documented by several studies the ability of RF-EMF to induce oxidative stress(Dasdag and Akdag, 2016; Yakymenko et al., 2016) (mainly by an increased production of reactive oxygen species)(Chauhan et al., 2017; Friedman et al., 2007; Houston et al., 2016; Kazemi et al., 2015; Kesari et al., 2011; Oyewopo et al., 2017; Sun et al., 2017), and oxidative DNA base damage (Duan et al., 2015).

These findings might have systemic relevance, since chronic oxidative stress is involved, in humans, in the onset and progression of several cancers(Kruk and Aboul-Enein, 2017), in metabolic(Newsholme et al., 2016; Tangvarasittichai, 2015), reproductive(Agarwal et al., 2012; Agarwal and Bui, 2017), neurodegenerative diseases(Cahill-Smith and Li, 2014), and in vascular homeostasis(Bachs Schmid et al., 2013).

The WHO International Agency for Research on Cancer (IARC), classified, in the year 2011, the RF-EMF as “possibly carcinogenic to humans” (Group 2B). Besides this statement, recent studies linked RF-EMF with possible non-oncologic health risks, mainly in terms of reproductive (Falzone et al., 2011; Gye and Park, 2012; Sepehrimanesh et al., 2017), neurologic (Barthelemy et al., 2016; Del Vecchio et al., 2009; Huber et al., 2005; Kim et al., 2017b; Schoeni et al., 2015; Zhang et al., 2013) and metabolic diseases (Lin et al., 2016; Meo et al., 2015; Sangun et al., 2015; Shahbazi-Gahrouei et al., 2016).

The latest opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on potential health effects from electromagnetic fields concluded (year 2015), at variance with the IARC, that “RF-EMF exposure do not show an increased risk of brain tumours” and, in general, pointed to a lack of clear adverse health effects deriving from RF-EMF exposure(Scientific Committee on Emerging Newly Identified Health, 2015). These conclusions have been criticized underlying that SCENIHR should have searched for demonstration of certain causal effects, rather than for the possibility of health risks related with RF-EMF exposure, and that “even where the report documents good quality, peer reviewed study evidence for potential risk, these data are simply dismissed”(Sage et al., 2015).

On the other hand, the “Bioinitiative Report” (<http://www.bioinitiative.org>) an extensive review on biological and health effects of EMF written by an independent international study group,

concluded in the year 2012 for the need, according to available evidences, to adopt a new precautionary action level for chronic exposure to RF-EMF (0.3-0.6nW/cm², corresponding to 0.04 V/m) which is hundreds of time lower than the international reference levels indicated by the International Commission on Non-Ionising Radiation Protection (ICNIRP, 41 V/m for 900 MHz, 58 V/m for 1800 MHz and 61 V/m for 2100 MHz)(ICNIRP, 1998), which only consider acute effects, and not chronic, low exposures, and are based on thermal, and not on biological effects of RF-EMF exposure(Hardell, 2017; Redmayne, 2016).

In this uncertain, confused and evolving scientific scenario, in September 2016 the European Commission published a document titled “5G for Europe: An Action Plan” (Commission, 2016), aimed to describe “*an action plan for timely and coordinated deployment of 5G networks in Europe through a partnership between the Commission, Member States, and Industry*”. This document was targeted to early introduce the new 5G (5th Generation) networks by 2018 and, subsequently, to a “*commercial large scale introduction by the end of 2020 at the latest*”. Following this document, several member States are currently planning, at a national level, preliminary “5G experimentations” by private phone operators, aimed at testing the network at frequencies over 6 GHz before the final introduction, on the medium-long term, of the typical 5G frequencies (over 30 GHz, millimeter waves) (AGCOM, 2017), never employed before with a large number of devices and on a large scale in urbanized contexts.

A document by the Italian Authority for Security in Communication (AGCOM, March 28, 2017)(AGCOM, 2017) stated that “*the 5G networks will serve an elevated number of devices and will connect, according to the prevalent hypothesis based on ongoing standardization developments, about 1 million devices per Km². This device density will cause an increase of the traffic and the need to install small cells in order to allow adequate connectivity performances, with subsequent increment of the density of the installed antennas*”.

A recent systematic review on 133 diseases and injuries showed that 23% of global deaths and 22% of global disabilities adjusted life years (DALYs) can be attributed to environmental risks in the year 2012, and that this burden is dominated by noncommunicable diseases (Pruss-Ustun et al., 2017). Furthermore, according to the World Health Organization, noncommunicable diseases kill 40 million people each year, equivalent to 70% of all deaths globally (WHO, 2017). These findings are paralleled by evidences documenting that intrinsic risk factors contribute only in less than 30% of cases to the development of cancer (Wu et al., 2016), and that there is a progressive rise in the incidence of childhood cancer (Steliarova-Foucher et al., 2017) (including central nervous system tumors in adolescents and young adults, in particular in European Countries (Georgakis et al., 2017)), and of a number of chronic diseases including neurodevelopmental disorders (Fombonne, 2009), psychiatric and neurodegenerative diseases (i.e. dementia (Prince et al., 2015), Parkinson (Savica et al., 2016) and Alzheimer’s disease (Brookmeyer et al., 2007)),

metabolic disorders as obesity (Flegal et al., 2016; Stevens et al., 2012), type 2 (Jaacks et al., 2016; Shaw et al., 2010) and type 1 diabetes (Patterson et al., 2012; Tuomilehto, 2013). From this point of view, the correct assessment of the relationships between environmental exposures and both cancer and non-oncologic noncommunicable diseases could strongly contribute in reducing the global burden of these health hazards, mainly in terms of primary prevention. The potential health consequences of the continuing spread of RF-EMF exposure, if confirmed, could be of interest mainly due to these implications and to the central role of public policies in the management and prevention of these pathologic conditions.

Thus, aim of the present review is to explore the more recent (i.e. following the IARC statement in the year 2011) peer-reviewed studies on biological and health effects of RF-EMF, and to check the available evidences on the effects of millimeter waves, which will be employed worldwide, in the medium-long term, in 5G communication systems.

Materials and Methods

Articles have been selected by using the PubMed (www.ncbi.nlm.nih.gov/pubmed) bibliographic database with keywords including the terms “electromagnetic fields”, “cellular phone”, “mobile phone”, “base station”, “RF-EMF”, “radiofrequency”, “millimeter waves”, “wi-fi”, “MMW”, “5G”, “cellular networks”. Peer reviewed original articles published in the English language until January 2018 (health/biological effects of exposure to millimeter waves) or in the period 2011- January 2018 (general effects of RF-EMF exposure) were considered.

Results

General effects of RF-EMF exposure: evidences following the IARC statement

Cancer

In the year 2011 the WHO IARC classified RF-EMF as “possibly carcinogenic to humans” (Group 2B)(IARC, 2013) based on evidences documenting an increased risk for glioma associated with wireless phone use. The IARC monograph comprehensively discussed the literature on the relationships between RF-EMF and cancer available before the publication of the final report.

After the IARC statement, a case-control study has documented an increased risk of brain tumor in mobile phone users or after cordless phone use (latency >15-20 years)(Hardell et al., 2013). Additionally, a large study on 1678 patients with glioma demonstrated a decreased survival per year of latency for mobile phone use (Carlberg and Hardell, 2014).

Conversely, a prospective study in a cohort of UK women did not demonstrate a significant association between mobile phone use and increased incidence of glioma, meningioma or non-central nervous system (CNS) cancers, although an increased risk for acoustic neuroma was shown in long term users vs never users, with the risk increasing with duration of use (Benson et

al., 2013). Furthermore, a Korean study on 285 patients with glioma and 285 matched controls did not show significant relationships between gliomas and use of mobile phones. However, the existence of a non-significant increased risk among ipsilateral users and some methodological limitation (i.e. possible recall and selection bias), lead the Authors to suggest the need for further evaluation, in particular in longer time users (Yoon et al., 2015).

Results from the French CERENAT multicenter, case-control study did not show associations between mobile phone use and brain tumors when comparing users vs non-users, although a significant positive association (glioma, meningioma) was evident in the heaviest users when considering life-long cumulative duration and number of calls (glioma)(Coureau et al., 2014).

A Swiss census-based cohort study did not suggest relationships between modeled exposure from broadcast transmitters and childhood cancer (i.e. all cancers, leukemia, CNS) in terms of hazards ratios (exposed to a predicted RF-EMF below 0.05 V/m, vs the highest exposure category, ≥ 0.2 V/m), although the linear exposure-response analysis with CNS cancers reached statistical significance (positive correlation) for all types of transmitters. The elevated risk of CNS tumors in the time-to-event analysis, however, was not confirmed in the incidence density analysis (Hauri et al., 2014).

A meta-analysis exploring papers published until the end of March 2014 (24 studies, 26,846 cases, 50,013 controls) reported a higher risk of intracranial tumor (mobile phone use over 10 years) and for the ipsilateral location, although Authors indicated the need for further studies to confirm this epidemiological association (Bortkiewicz et al., 2017).

Of note, a recent re-analysis (correcting for possible biases) of Canadian data from the multinational INTERPHONE study demonstrated an odds ratio of 2.2 for glioma (95% confidence interval 1.3-4.1, highest quartile of phone users vs non regular users), and an increased risk of meningioma, acoustic neurinoma and parotid gland tumors in relation to mobile phone use(Momoli et al., 2017). The finding of an increased risk of parotid gland tumors did not confirm conclusions from a previous study showing no significant relationships between these tumors and light to moderate exposure to wireless phones during less than 10 years (Soderqvist et al., 2012).

As far as animal studies were concerned, exposure of AKR/J mice (used as lymphoma model) to RF-EMF for 45 min/day, 5 days/week, for a total of 42 weeks (SAR 4.0 W/kg) did not generate differences in lymphoma and splenomegaly incidence between sham- and exposed animals (Lee et al., 2011). This finding confirmed a previous evidence showing, in AKR/J mice, the lack of effects from exposure to UMTS test signals (24 h per day, 7 days per week, 0.4 W/kg SAR) (Sommer et al., 2007).

On the other hand, a recent experimental study documented cancer-promoting effects of RF-EMF on mice (tumors of the lung, liver, lymphomas) at low to moderate exposure levels (0.04 and 0.4

W/kg SAR), well below current exposure limits (Lerchl et al., 2015).

Finally, a recent study in rats also suggested that RF-EMS effects could be mediated, at least in part, by epigenetic mechanisms, since a short term (4 hours) exposure to RF radiation from GSM cell phone was able to affect the methylation pattern of the estrogen receptor (ER α) gene, which plays a critical role in colorectal cancer (Mokarram et al., 2017).

Reproductive effects

A recent longitudinal cohort study on 153 men attending a fertility clinic failed to demonstrate (by nurse administered questionnaires) significant relationships between mobile phone use and semen quality (Lewis et al., 2017).

However, a recent review on the effects of RF-EMF on sperm function identified 21 out of 27 studies documenting negative effects of exposure (i.e. impaired sperm motility, increased production of reactive oxygen species, increased DNA damage, reduced levels of anti-oxidants) (Houston et al., 2016).

A number of studies with positive findings in humans (Agarwal et al., 2009; De Iuliis et al., 2009; Eroglu et al., 2006; Falzone et al., 2011; Fejes et al., 2005; Gorpichenko et al., 2014; Wdowiak et al., 2007; Zalata et al., 2015) have been paralleled by recent animal studies documenting, following RF-EMF exposure, oxidative and nitrosative stress-mediated DNA damage resulting in cell cycle arrest and apoptosis in spermatogenic cell lines (Solek et al., 2017), reduced testosterone levels (Kesari and Behari, 2012; Kumar et al., 2013; Sepahimanesh et al., 2014) with shrinkage of testicular size (Kumar et al., 2013), overproduction of reactive oxygen species (ROS) (Kesari and Behari, 2012), disrupted ovarian cycle in prepubertal rats (i.e. decreased follicle number, increased number of atretic follicles and apoptotic index levels) following prenatal exposure (Turedi et al., 2016), higher percentage of dead embryos at the 2-cell stage in EMF-exposed mice, as compared with controls, with an increased loss of cell viability in experimental blastocysts (Safian et al., 2016).

On the other hand, as far as RF-EMF exposure during pregnancy is concerned, a recent animal study showed that whole body exposure to different signals (average SARs of 0.08 and 0.4 W/kg) of pregnant rats (20 hours/day from gestational day 7 to weaning) and F1 offspring rats (up to 6 weeks of age) did not generate adverse effects on pregnancy nor on the development of animals (Shirai et al., 2017).

Metabolic effects

A large occupational study in 1073 workers in a power plant showed a significant positive

correlation between EMF exposure (combined RF-EMF and low-frequency EMF) and serum levels of LDL-cholesterol, with no effects on total cholesterol, HDL and triglycerides(Wang et al., 2016).

Preliminary observations in pediatric age also suggested a possible effect of environmental RF-EMF exposure on glucose metabolism. In a group of 159 students from elementary schools exposed to RF-EMF from mobile phone base stations, significantly higher blood levels of glycated hemoglobin were measured in children exposed to high (9.601 nW/cm² at frequency of 925 MHz), as compared to those exposed to low (1.909 nW/cm²) RF-EMF 6h daily, five days in a week(Meo et al., 2015).

In an animal model, the exposure to mobile phone radiations for more than 15 minutes/day for a total period of 3 months induced a significant increment in fasting serum levels of glucose and insulin in rats, as compared to non-exposed animals, with a significant increment in insulin resistance (HOMA-IR)(Meo and Al Rubeaan, 2013).

The effect of RF-EMF exposure on insulin release was not confirmed by a more recent study in rats exposed to RF radiation (SAR 2 W/kg) 6 hours/day for one week. The same study, however, showed in exposed animals histological damages in the liver (i.e. inflammatory changes in the portal spaces) and in the pancreas (i.e. damaged cells in the islet of Langerhans), linked with the duration of the exposure (Mortazavi et al., 2016).

An animal study on rabbits exposed (whole body) in the short term to 1800 MHz GSM-like radiofrequency radiation (15 min/day for seven days) showed no effects on markers of oxidative stress and on serum levels of glucose, uric acid and aminotransferase, although cholesterol levels were significantly higher in exposed pregnant animals than in non-exposed groups. Short term RF exposure alone, however, was not able to induce the same effect on serum cholesterol in non-pregnant animals (Kismali et al., 2012)

In vitro, RF-EMF at 2GHz has been able to up-regulate the expression of genes involved in glucose transportation and the tricarboxyl acid cycle, modulating cell response (in terms of energy metabolism) to this form of environmental exposure (Lin et al., 2016).

Finally, as shown by an *in vitro* model, RF-EMF generated by a GSM mobile phone was able to reduce cell viability and proliferation rates of human mesenchymal stem cells derived from adipose tissue, with effects depending on the duration of the exposure (Shahbazi-Gahrouei et al., 2016).

Neurologic effects

In an animal model, brain exposure of adolescent rats to RF-EMF (45 minutes, SAR 0, 1.5 or 6 W/Kg, 5 days/week from postnatal day 32 to 62) did not generate any neurobiological impairment compared to sham-exposed controls(Stasinopoulou et al., 2016). Absence of harmful effects of long-term RF-EMF exposure (2 h per day, 5 days per week, from an age of 14 days to 19 months,

GSM-modulated 900 MHz RF-EMF, brain SAR 0, 0.7, 2.5 and 10 W/kg) on neuro-development, learning skills and behavior was also showed in exposed female Wistar rats(Klose et al., 2014).

On the other hand, however, a number of *in vitro* effects of RF-EMF exposure have been detected on neurons, in particular during brain development (early exposure).

Pre- and postnatal exposure to an electric field intensity of 3.7V/m for 12h/day during pregnancy and for 22 days after parturition was linked to the detection, in 22-day old pups, of pyramidal cell loss and glia fibrillary acidic protein over-expression in the CA4 region of the hippocampus (Stasinopoulou et al., 2016).

In a murine model of neural stem cells, increasing exposure duration to GSM 900-MHz RF-EMF markedly decreased the stem cell proliferation and cell differentiation into neurons, with “devastating” effects (as defined by Authors) on neurogenesis (Eghlidospour et al., 2017). Similar results were shown in another model exploring murine embryonic neural stem cells, in which exposure to 1800 MHz RF-EMF at specific absorption rate (SAR) values of 4 W/kg for 3 days inhibited the neurite outgrowth of differentiated neurons, with reduced expression of the proneural genes Ngn1 and NeuroD(Chen et al., 2014).

Besides neurodevelopmental effects, functional alterations of neurons have been described.

Exposure to 835MHz RF-EMF (4.0 W/kg SAR, for 5 h daily) significantly decreased, in mice, the density of synaptic vesicles in the presynaptic boutons of cortical neurons, with a marked reduction in the expression of synapsins I/II genes and proteins(Kim et al., 2017a).

The exposure of Sprague Dawley male rats for 15 min at a SAR of 0, 1.5, or 6 W/kg lead to an increment in total glial fibrillary acidic protein in the striatum at 1.5W/Kg, in the hippocampus and in the olfactory bulb at 6 W/Kg. Animals showed reduced long-term memory as a consequence of the RF-EMF-induced astrogliosis(Barthelemy et al., 2016).

The involvement of epigenetic mechanisms affecting gene expression could also be supposed based on results from a study showing, in Sprague-Dawley rats exposed to RF-EMF (900 MHz, 1 mW/cm² for 14 or 28 days, 3hours/day, SAR varying between 0.016 [whole body exposure] and 2 W/kg [head]), impaired spatial memory and a damage in the permeability of the blood-brain barrier secondary to the activation of the mcp-1/ERK pathway (i.e. mcp-1 expression resulting in ERK phosphorylation), as compared to unexposed animals (Tang et al., 2015).

Mice exposed to 835 MHz RF-EMF at a SAR of 4.0 W/kg for 5 hours/day during 12 weeks showed an increased induction of autophagy genes, with accumulation of autolysosome in neural cells. These alterations were paralleled by myelin sheath damage, with exposed animals showing hyperactivity-like behavior (Kim et al., 2017b).

Interestingly, the possibility of behavioral effects secondary to RF-EMF exposure has also been

suggested in humans. In fact, in a large cohort of Bavarian children and adolescents exposed to RF-EMF far below the reference level (assesses by personal dosimeter), a relationship was documented between the measured exposure to RF fields in the highest quartile and the occurrence of behavioral problems (Thomas et al., 2010).

A study based on the Danish National Birth Cohort (phone interviews) failed to demonstrate associations between prenatal cell phone use and neurodevelopmental delays among infants aged 6 and 18 months (Divan et al., 2011). More recent results from the same group, however, demonstrated that cell phone use was linked with behavioral problems in children aged 7 years (Divan et al., 2012). These results confirmed previous observations documenting that prenatal (and, although to a lesser extent, postnatal) exposure to cell phones was associated with behavioral alterations at the age of school entry (Divan et al., 2008).

A Dutch cohort study (based on retrospective questionnaires) including a total of 2618 subjects failed to demonstrate positive relationships between maternal cell/cordless phone use during pregnancy and behavioral problems in 7 years old children (Guxens et al., 2013). These negative results have not been confirmed by a more recent and large study in five birth cohorts (83,884 mother-child pairs), demonstrating an increased risk of behavioral problems (i.e. hyperactivity, inattention) in offspring from mothers who were cell phone users during pregnancy, as compared to no cell phone use. Residual concerns, however, derives from some uncontrolled confounding factors (Birks et al., 2017).

A large population-based cohort study has recently shown that perceived exposure to mobile-phone base stations was linked with the increase in modeled exposure and with the occurrence of nonspecific symptoms and sleep disturbances (Martens et al., 2017).

Recently, a cross-sectional survey on 2150 students retrospectively demonstrated an increased occurrence of headache, fatigue and sleep disturbances in mobile phone users, with a dose-response relationship. The same study showed limited associations with vicinity to base stations and lack of relationships with measured school EMF levels (Durusoy et al., 2017).

The long-term effects of RF-EMF exposure on the progression of Alzheimer disease has been studied in an animal model (5xFAD mice), showing that 1950 MHz RF-EMF at a SAR of 5.0 W/kg for 2 hours/day and 5 days/week for 8 months improved the cognitive deficits in the exposed animals, and that this finding was paralleled by an increased glucose metabolism in the hippocampus and amygdala regions of the brains, as compared to sham-exposed mice (Son et al., 2017). The finding of positive effects of RF-EMF exposure on animal models of Alzheimer disease confirms previous observations (Banaceur et al., 2013; Jeong et al., 2015).

In humans, a Danish retrospective cohort study reported a 30-40% decrement in the risk of hospitalization for Alzheimer disease in men who had a mobile phone subscription since 10 years

or more (Schuz et al., 2009), and another prospective survey described, in a group of older participants with elderly-related cognitive decline, better cognitive performances (including memory and attention) in those who were frequent mobile phone users (Ng et al., 2012). However, the epidemiological findings linking a better cognitive profile with mobile phone use could be expression of either causal or consequential association, and a meta-analysis exploring the effects of a short-term exposure to RF-EMF on human cognitive performance excluded the presence of significant positive impacts (Barth et al., 2012). A more recent meta-analysis on the consequences of electromagnetic fields emitted by GSM phones on working memory in humans found no difference between RF-EMF and sham exposed subjects, pointing to the need of further studies (Zubko et al., 2017)

Microbiological effects

In isolated colonies from human skin microbiota (genus *Staphylococcus*) the microbial growth pattern after exposure was increased or suppressed, demonstrating a possible disrupting effect of RF-EMF. Results from this preliminary study also point to a possible role on the recorded responses played by individual historic exposure to RF-EMF and life style (Crabtree et al., 2017).

As shown by a recent study on cultures of *Listeria monocytogenes* and *Escherichia coli* exposed to a GSM 900 MHz mobile phone simulator or to a 2.4 GHz Wi-Fi router, RF-EMF is able to induce antibiotic resistance in these microorganisms (Taheri et al., 2017).

This study expands previous observations on antibiotic susceptibility of *Klebsiella pneumoniae* exposed to a common wi-fi router, which showed a fall in the microbial sensitivity to all tested antibiotics after 8 hours of exposure, following a transient initial rise in sensitivity after 4.5 hours (Taheri et al., 2015).

Furthermore, it has been demonstrated a multidrug resistance in bacteria like *Bacillus* and *Clostridium* spp. surviving near telecommunication-based stations (Adebayo et al., 2014).

Possible specific effects of the exposure to millimeter waves and 5G networks

Millimeter waves (MMW) are characterized by a range from 30 to 300 GHz and constitute the extremely high frequency band of RF-EMF.

It is expected (although not fully demonstrated) that devices employing MMW will work with low power and, due to the small penetration depth of the radiation, the exposure should involve only superficial tissues.

However, mainly due to the low power, this technology requires a high density of small cells and a proliferation of devices is expected. This combination of factors will increase chance of human exposure to RF-EMF.

Furthermore, also hypothetically assuming that 5G networks will not increase the exposure level in the human environment when they will be fully operative, in the first stage of 5G implementation (i.e. at least some years), 5G networks will operate in parallel with current mobile systems, with an unavoidable global increase in the exposure level.

Despite MMW have been suggested for biomedical applications (Zhadobov et al., 2015) (also considering their hypoalgesic effects (Radzievsky et al., 2001; Usichenko et al., 2006; Usichenko et al., 2003; Ziskin, 2013)), specific preliminary evidences showed as the exposure to frequency over 30GHz could alter gene expression (Habauzit et al., 2014; Le Quement et al., 2012; Le Quement et al., 2014; Millenbaugh et al., 2008; Soubere Mahamoud et al., 2016), increase the temperature of the skin (Zhadobov et al., 2015), stimulate cell proliferation (Li et al., 2010; Li et al., 2014), alter the functions of cell membrane (Cosentino et al., 2013; Di Donato et al., 2012) and neuro-muscular systems (Alekseev et al., 2010; Alekseev et al., 1997; Gordon et al., 1969; Khramov et al., 1991; Pakhomov et al., 1997; Pikov et al., 2010; Shapiro et al., 2013).

Although the effects of exposure are limited to superficial tissues, systemic effects cannot be ruled out, due to irradiation of cutaneous vessels and surrounding tissues (Alekseev and Ziskin, 2009). This hypothesis seems to be confirmed, in an animal model, by the release of macrophage-activating mediators into the plasma following exposure to 35 GHz millimeter waves at 75 mW/cm² (Sypniewska et al., 2010).

In human skin cells, the exposure at MMW (60.4 GHz) with an incident power density of 20 mW/cm² (corresponding to the maximum incident power density authorized for public use) is able to alter the function of the endoplasmic reticulum (Le Quement et al., 2014) and, in keratinocytes, the expression (Habauzit et al., 2014; Soubere Mahamoud et al., 2016) of genes involved in cellular communication and endoplasmic reticulum homeostasis (Soubere Mahamoud et al., 2016).

It has been shown, in cultures of human keratinocytes, that exposure at 20 mW/cm² lead to a differential expression of 665 genes and that this effect was not completely related to the thermal effects of MMW. According to the Authors of this study, "the high number of modified genes (665) shows that the ICNIRP current limit is probably too permissive to prevent biological response" (Habauzit et al., 2014).

Some evidence suggested that MMW exposure *per se* has apparently no direct effects on gene expression (Habauzit et al., 2014; Koyama et al., 2016). However, modulation of gene expression is possible in the case of disturbed cell homeostasis, as demonstrated in human keratinocytes treated with a glycolysis inhibitor (2-deoxyglucose), in which MMW altered the expression of six genes (SOCS3, SPRY2, TRIB1, FAM46A, CSRNP1 and PPP1R15A) involved in cell signaling/transduction pathways and encoding transcription factors or inhibitors of cytokine pathways, with concerns about possible negative long-term effects of MMW exposure on metabolic

stressed cells(Soubere Mahamoud et al., 2016).

In rats exposed in vitro to 35 GHz MMW at 75 mW/cm², an increased macrophage expression of several proteins associated with inflammation, oxidative stress, and energy metabolism was recorded(Sypniewska et al., 2010), making possible systemic effects secondary to exposure.

MMW are also able to promote the synthesis of extracellular matrix and cell proliferation in chondrocytes (Li et al., 2010; Li et al., 2014), stimulating their energy metabolism and protein synthesis probably by affecting the voltage-gated K(+) channel (Li et al., 2014).

Conversely, antiproliferative effects of MMW exposure have been described in the case of cultured erythromyeloid leukemia cell line K562, with an enhancement of the glycolytic aerobic pathway and without significant cell death increment (Beneduci et al., 2007). Antiproliferative effects have been also shown in other tumoral human stable cell lines (probably through absorption of MMW by water)(Chidichimo et al., 2002), but not in RPMI 7932 human skin melanoma cells (Beneduci, 2009), normal human skin fibroblast (NB1RBG) and human glioblastoma (A172) cells (Yaekashiwa et al., 2017).

In vitro observations on human cryopreserved spermatozoa showed an increased fraction of mobile spermatozoa following MMW exposure (0.03 mW/cm²), without impairment of membrane integrity and nuclear chromatin status (Volkova et al., 2014).

In animal models, it has been shown that acute exposure to MMW (60 GHz for 6 minutes) could generate ocular damage (both eyelid and eye globes) in rabbits (Kojima et al., 2009). These findings confirm an early report on rats showing MMW-induced changes in the lens predisposing to cataract development(Prost et al., 1994). Data on ocular effects of MMW, however, are controversial. In fact, other observations showed that single (8 hours) or repeated (five separate 4-hour exposure on consecutive days) exposure to 60 GHz radiation at 10 mW/cm² did not cause ocular damage in rabbits and nonhuman primates (Kues et al., 1999), and that exposure to 60 gigahertz (GHz) radiation for 24 h at 1 mW/cm² was not able to induce genotoxicity in human eye cells (Koyama et al., 2016).

Studies in animal models suggest neurologic outcomes following MMW exposure, in terms of EEG alterations secondary to MMW-induced stress reactions (due to the increase in skin temperature)(Xie et al., 2011) and altered neuronal and neuromuscular functions (Alekseev et al., 2010; Alekseev et al., 1997; Gordon et al., 1969; Khramov et al., 1991; Pakhomov et al., 1997; Pikov et al., 2010; Shapiro et al., 2013).

Finally, the microbiological effects of MMW exposure have also been explored.

Exposure of E. Coli to 99 GHz for 1 hour did not affect bacteria viability and colony characterization. Following a19 hour exposure, the number of colonies forming units was slightly

increased (half order of magnitude higher) as compared with sham-exposed and control suspensions, in the absence of effects on bacterial metabolic activity(Cohen et al., 2010). Several other observations show altered (depressed) bacterial growth and activity following the exposure to MMW(Torgomyan and Trchounian, 2015), which could positively affect the sensitivity of microorganisms to active chemicals, including antibiotics(Bulgakova et al., 1996; Soghomonyan et al., 2016; Tadevosyan et al., 2008; Torgomian et al., 2013; Torgomyan et al., 2012; Torgomyan et al., 2011; Torgomyan and Trchounian, 2015). A recent review suggested that these effects might be independent from thermal effect of MMW, mainly acting on bacterial plasma membrane, genome and metabolic pathways(Soghomonyan et al., 2016).

Conclusions

Evidences about the biological properties of RF-EMF are progressively accumulating and, although they are in some case still preliminary or controversial, clearly point to the existence of multi-level interactions between high-frequency EMF and biological systems, and to the possibility of oncologic and non-oncologic (mainly reproductive, metabolic, neurologic, microbiologic) effects.

Biological effects have also been recorded at exposure levels below the regulatory limits, leading to growing doubts about the real safety of the currently employed ICNIRP standards(Habauzit et al., 2014; Redmayne, 2016; Starkey, 2016).

Particular concerns derive from the wide (and rapidly increasing) density of wireless devices and antennas (also in view of the forthcoming 5G networks), from the increased susceptibility to RF-EMF in children (Meo et al., 2015; Redmayne, 2016; Redmayne and Johansson, 2015; Sangun et al., 2015), and from the effects of RF-EMF at a cellular and molecular level, in particular regarding the ability to promote oxidative processes(Friedman et al., 2007; Kazemi et al., 2015; Kesari and Behari, 2012), DNA damage(Duan et al., 2015; Solek et al., 2017), alterations of gene expression(Chen et al., 2014; Habauzit et al., 2014; Kim et al., 2017a; Le Quement et al., 2012; Le Quement et al., 2014; Lin et al., 2016; Millenbaugh et al., 2008; Soubere Mahamoud et al., 2016) and to influence the development of stem cells(Chen et al., 2014; Eghlidospour et al., 2017; Shahbazi-Gahrouei et al., 2016).

Epigenetic mechanisms modulating gene expression following exposure to environmental toxics are frequently involved in the pathogenesis of a number of chronic diseases, mainly in the case of early exposures determining developmental effects and the onset of chronic diseases later during life (Bianco-Miotto et al., 2017; Bird, 2007; Di Ciaula and Portincasa, 2014). Of note, the epigenome seems also to have a relevant role following RF-EMF exposure, which is able to produce micro-RNA modulation(Dasdag et al., 2015a, b), chromatin remodeling and alterations of DNA repairing processes (Belyaev et al., 2009; Markova et al., 2005) and to affect the DNA methylation pattern (Mokarram et al., 2017).

Further experimental and epidemiologic studies are urgently needed in order to better and fully explore the health effects caused in humans by the exposure to generic or specific (i.e. MMW) RF-EMF frequencies in different age groups and with increasing exposure density.

However, underestimating the relevance of available results (in particular those from *in vitro* and animal models) do not appear to be ethically acceptable since, as has been observed reasoning in terms of primary prevention, it “is equivalent to accepting that a potential hazardous effect of an environmental agent can be assessed only *a posteriori*, after the agent has had time to cause its harmful effects”(Tomatis, 2002).

Results already available should be sufficient to invoke the respect of the precautionary principle(Hau et al., 2014; Lo, 2009) considering the large number of subjects involved in this form of environmental exposure and classifiable as “vulnerable”(Bracken-Roche et al., 2017), and possible interactions between multiple and heterogeneous exposures, overcoming the single-pollutant approach with the measurement of the absorbed internal dose of multiple pollutants (the concept of exposome(Wild, 2012)).

In the respect of the WHO principle “health in all policies”, the development of new RF-EMF communication networks should be paralleled by adequate and active involvement of public institutions operating in the field of environmental health, by a revision of the existing exposure limits and by policies aimed to reduce the level of risk in the exposed population.

On the other hand, an adequate knowledge of pathophysiological mechanisms linking RF-EMF exposure to health risk should also be useful in the current clinical practice, in particular in consideration of evidences pointing to the role of extrinsic factors as heavy contributors to cancer risk(Wu et al., 2016) and to the progressive epidemiological growth of noncommunicable diseases(Pruss-Ustun et al., 2017).

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