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Biological Effects of Millimetric Waves: Considerations on the Bibliography, For the Period 2017-2022

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ABSTRACT

The evolution of fast communication technologies (5G, 6G) has led to a very significant interest in waves in the millimetre ranges. At the same time, biological effects are experiencing a new interest, particularly in terms of therapy, due to technological progress in miniaturization. Here we present a bibliography overview (not a review) of different aspects of the biological effects of MMW. This communication can be seen as a complement to our previous communication on mechanistic aspects of MMW [1].

Introduction

Among electromagnetic radiation, the domain of "millimetre waves" (MMW) corresponds to frequencies ranging from 30 to 100 GHz. Until the 2010s, millimetre wave applications were mainly intended for the military domain (e.g., radar detection, non-lethal crowd control systems). Other civilian applications such as car driving assistance had been developed since the 1970s, and especially more recently the advances of 5G brought into play these frequency bands (up to 27GHz currently) and higher in the near future 6G, up to THz) with the aim of improving communications in terms of number and speed. Conversely, medical applications, especially pain control- identified in the 1980s [2] had fallen into oblivion for the benefit of classical pharmacological treatment. Research results proposed a plausible mechanistic support for these effects, mainly related to the peripheral nervous stimulation induced by the MMW, leading to central endorphin secretion and thus to a hypoalgesia effect. The miniaturization of electronic transmitting systems led to

more manageable and even ambulatory use. In terms of biological or medical applications, the consequences were to relaunch research work both in terms of effectiveness and the evaluation of possible side effects. We present here studies from the last 5 years, covering fundamental works (dosimetry , mechanistic) , experimental results (cells, animals , human clinical) and also normative data edited by international non ionizing committees.

Dosimetry

General Modeling: Regarding the validity of exposure levels and the reproducibility of experiments, some teams are working on more reliable or more adapted methods, especially at the cutaneous level [3]. Proposes a 4-layer model, including the subcutaneous tissue, valid above 6GHz. The model is based on the bio-thermal equations (Pennes) and the thermal conductivity of blood and shows that the increase in surface temperature is, in many circumstances, determined by the thermal resistance of the subcutaneous tissue even though the RF energy can be deposited almost entirely in the

skin layer [4]. From the same team, used the same methods for pulsed systems and showed that the bioheat equations (Pennes 1948) are not applicable to pulsed systems. Other transfer functions appeared necessary, as well as a reconsideration of the current standards [5]. Studied age effects (from 5 to 70 years) on MMW skin absorption and transmission. He found that specific absorption rate (SAR) and heating in the near-surface tissues are limited 10–15%, mainly due to the tissue permittivity and blood flow change with age. Besides, between 26 and 60GHz, the peak SAR decreased while transmitting power was increasing with frequency.

For a purpose of standardization (5G), [6] investigated how the temperature rise was affected by exposure duration at frequencies in the 6-100 GHz range, by considering the effects of polarization, exposure duration and depth MMW penetration below the skin surface. He proposed to use subcutaneous temperature measurement for developing human exposure guidelines at frequencies higher than 6 GHz. In terms of exposure heterogeneity, 3 studies [7-9], took into account the possible role of sweat ducts leading to a local increase in skin SAR: the coiled part of the sweat duct in the upper layer of the skin was considered as a helical antenna in the sub-THz band. The reflectance of human skin in the sub-THz region would depend on the intensity of sweating, related to the conductivity of the sweat duct, and correlate with human stress levels. They concluded that there are potential risks to be considered before developing the bands (5G-6G).

Animal Studies: [10] studied the absorption of MMW between 2 and 120GHz on 4 types of insects; he found a dependence of the absorption on frequency (stronger above 6GHz), with very important absorption jumps for a little modified exposure power. Olrlacchio [11] was interested in vitro dosimetry in continuous or pulsed mode, and in the importance of convection. Under continuous wave (CW) exposure conditions, it appears that temperature rise precedes convection, whereas in pulsed mode convection and temperature rise depend on the duration of the pulse and thermal relaxation time. [12] Developed in his thesis methods for the analysis and dosimetry of electromagnetic waves with biological tissues, with a resolution of a few tens of microns, based on the calculation of SAR from the fluorescence of rhodamine for applications in the design of applicators (arrays) for biomedical use. Hirata's review [13] summarized recent advances in thermal and electromagnetic modelling of exposure at frequencies > 6 GHz. It also commented on the strengths and weaknesses of thermal models for predicting temperature rise of tissues exposed to MMW. A new physical quantity, i.e. absorbed power density/epithelium, has been adopted as a dose measure. The permissible levels of external field strength/power density are derived from this in practice. A new physical quantity, fluence or absorbed energy density, is introduced for protection against short pulses (especially for durations of less than 10s) to avoid excessive increases in tissue temperature. He concluded that further studies are needed to propose more suitable standards. In the 5G environmental framework, various scenarios are studied, especially in 2 articles [14,15], which consider the heterogeneities introduced by reflections and the presence of fingers (the presence of the hand increases the absorption at the head level).

Mecanistical Aspects

The effects induced by low intensity millimetre radiation on biological systems have given rise to numerous studies and several reviews, the main part of which were reported at the beginning of the 2000s, e.g. the involvement of membranes as a target for MMW, even at low levels (less than 10 mW/cm2), via intracellular calcium fluxes (calcium protein channels or not). The role of bound water and phospholipid organization has also been discussed. A global model derived from Fröhlich's theory implies the existence of collective oscillations in biological systems as a possible target of MMW by inducing coherent electrical vibrations. These tracks remain globally theorical bases, but more recent works have allowed to bring some precisions, in the absence of a precise global model. Direct action of MMW on Ca2+, membrane voltage-gated calcium channels (VGcc) and consequences. [16] Proposed a theory questioning the low MMW penetration well accepted through the skin (a fraction of a millimetre at 60 GHz), by considering separately the electrical (E) and magnetic (H) components of MMW (CW). According to him, while E is easily damped and absorbed in the first few mm of skin (dielectric constant of water 79), H would not be and could therefore induce forces on the ions present in the biological environment, the resulting movement constituting local currents from which a local electric field result.

Although the expected field may appear weak, a local amplification related with both physical laws (Coulomb, Ohm), and to the presence of 20 charges in VGcc (5 net charges for each of the 4 intramembrane alpha segments S4) provides in 7.2 million amplification (20 (charges in the voltage sensor) X 120 (of the dielectric constant) X 3000 (amplification at the plasma membrane) = 7.2 million) of the local EMF forces [17]. The result would then be [18]) «a sliding helix mechanism for electromechanical coupling in which outward movement of triggering charges in the S4 transmembrane segments catalysed by sequential ion pair formation stretches the S4-S5 bond, bends and twists the S6 segment, thereby opening the pore.» This «transduction» mechanism would operate without involving a change in transmembrane potential. The immediate consequence is an influx of calcium, local changes in intracellular calcium concentration leading to Ca2+-dependent signalling cascades and the release of chemical neurotransmitters. This theory was criticized by various authors [19,20], both on the basis of electromagnetism (questioning of Maxwell's equations, non-consideration of coupling and damping of E, H..., existence of temporo-spatial coherences/incoherences...), and on the ethical level with respect to previous works (in which he himself would have participated and then neglected); the critics asked for the withdrawal of the article published in 2021.

Indirect Stimulation: The Membrane as the First Target

Previous work has suggested two different routes for MMW membrane interaction, directly or via collective membrane interactions. The cell membrane was early considered as a «major target» for MMW at low power, through membrane associations both resulting in Ca2+ influx and collective electromagnetic interactions.

Structure and Dynamics of The Membrane

Passive Diffusion: It was admitted [21] (on model membrane systems) that passive diffusion of ions or small molecules was favoured by exposure to MMW, directly linked to surface hydration or to a change in the environment of the polar head due to the modification of the curvature of the membrane, itself linked to the water bound in the glycerol region of the phospholipid. [22] Performed integrative metabolomic and lipidomic studies (UPLC-Q-Exactive) on human HaCaT keratinocytes in culture exposed for 24 hours to 60 GHz 20mW/cm2. It revealed a limited number of altered features in the lipidomic sequences and in the intracellular metabolomic analyses. In contrast, significant dysregulations appear in extracellular metabolomic profiles, unrelated to the slight changes that could be reported throughout the transcriptomic studies. He deduced that MMW could modify the permeability of cell membranes.

Induced Diffusion: Cell membranes show an asymmetric distribution of phospholipids; in particular, phosphatidylserine (PS) is mainly located at the inner layer. Following Ca2+ influx (natural or induced by MMW), calcium-associated PS tends to externalize. It is important here to highlight the particular properties of PS. [23] Highlighted in his NMR study that PS commonly interacts with proteins via nonspecific electrostatic interactions as well as via specific binding. In the presence of calcium ions, PS can induce membrane fusion and phase separation. The polar head of PS is more rigid than that of phosphatidylcholines, by electrostatic interactions or formation of a hydrogen bond network between the head groups. This is particularly the case in the presence of divalent cations -such as Ca2+ - which can form «strong dehydrated molecular complexes with PS lipids», even leading to phase separation. Local fusions of isotropic (cubic) or axially fast transmembrane structures (hexagonal) result in an increase in fluidity, all in favour of the equalization of the membrane potential (depolarization) and of a facilitated mobility in S4 helix bending of VGcc, and finally of the setting up of the action potential.

Collective Electromagnetic Interactions: [24] proposed the concept of electromagnetic homeostasis, as «the ability of the human body to maintain the balance of highly complex electromagnetic interactions internally, despite the noisy external electromagnetic environment». This would lead to a dynamic - metastable electromagnetic homeostasis directly supported by cellular and molecular physiological properties. In fact, external electromagnetic interactions could affect normal functions and health, in a deleterious or favourable way. (Geesinck, et al. [25]) in their extensive metaanalysis (724 publications, 2021) built a descriptive model of the effects of non-thermal electromagnetic fields on biological systems, covering an extremely wide frequency range (from static to UV); the fundamental physical basis was based on the «Bose-Einstein condensates» calculated by Einstein, stating that at extremely low temperatures (several µK or less), when the length of the Broglie waves was smaller due to the available space, the bosons preferentially occupied the lowest energy state; this property was confirmed for inorganic systems (the 2-slit Young's slit experiment showing interference necessarily related to coherent systems) and also directly observed later in macroscopic constructions. Fröhlich later postulated and calculated that this concept could be applied to biology, leading - to oversimplify - to the idea that part of the energy of electromagnetic waves could be used, not in thermal production, but rather in order/structuring properties. Current metabolic processes would provide the existence of these coherent -collective-states directly involving ionic and molecular movements. This would imply resonances in MMW (orientational modes), THz-IR frequencies (vibrational modes).

Such a constantly dynamic «equilibrium» - i.e., without a definitive state of equilibrium - could be related to the high sensitivity of living cells to external waves with non-thermal millimetre waves (MMW) and higher frequency resonances. Numerous studies have been published in this framework, which Geesink's meta-analysis pooled, covering all frequencies from quasi-static fields to the visible and ultraviolet bands. He proposed a general descriptive equation formalizing some coherent/incoherent oscillation modes of the energy (frequency) distributions in the manner of a 3D semi-harmonic oscillator, using a discrete set of integers, some of which are not determined. The result was a classification into roughly coherent, incoherent and intermediate frequency ranges «Coherent and decoherent (chaoslike) frequencies could be aligned on a frequency scale and arranged in alternating order; besides, transition frequencies would be located just between coherent and decoherent frequencies, with strong variations depending on modulation or overlays, for example « [26].

Mainly, the authors insisted on 3 essential points:

- The existence of a dynamic electromagnetic balance in biological systems, including charge movements/currents.
- A potential structuring effect by MMW, even at low power exposure levels (i.e. less than 10 mW/cm2);
- The role of water, via water structure, hydrogen bonding, hydration of biomolecules, free cluster/water balance... Unlike THz/IR bands that interact with vibrational modes, MMW (up to 300 GHz) can only act on rotational modes. However, many criticisms, like those pointed out in Pall's model (see above), made this "theory questionable, to say the least" [16]; for example, the term temporospatial «coherence» is inappropriate, directly evoking the MASER domain. From the Geesinck equation are identified (...) alternating deleterious/beneficial frequency domains, which no direct mechanistic element allows to attribute in the causal sense of the term.

Role of Water: Mechanisms of MMW interaction with (or via) water involve several different concepts, such as «formations/ dissociations of assemblies, free or bound water, coherent/incoherent domains, differing yet closely overlapping» (Geesinck 2021, see terminological caveats in the previous chapter) (Mae wan Ho, et al. [27]). Prepared and observed by electron microscopy the formation of water clusters at room temperature and pressure. They noticed

that electromagnetic fields could induce the formation of «large stable coherent domains (CDs) of about 100 nm in diameter at ordinary temperature and pressure, and these CDs could be responsible for all the peculiar properties of water (translated from the author).» According to the theories of Frölich and Davidov, they considered that these CDs could trap MMW since «the photon acquires an imaginary mass, so the frequency of the MMW CD becomes much smaller than the frequency of the free field with the same wavelength. The two states of water, i.e., CD and non-CD, must be in equilibrium. Electron microscopy photographs of these CD structures were presented in various forms in this paper, about 100nm in diameter. Ninno5 also considered water as an equilibrium between two states, but from an energetic point of view. He proposed that in the ground state all electrons are tightly bound, whereas in the excited state configuration «the electrons are only 0.54 eV below the ionization threshold (Eexc = 12.6 eV); thus, they can be considered 'quasi-free' or very weakly bound.» The result is a coherent state which is a superposition of the ground state (83%) and the excited state (17%). It is also necessary to consider the existence of surface layers of water on biomolecules and membranes, called «vicinal water».

The water/surface interaction leads to changes in dielectric constants (10 to be compared to 80 of free water), and a partial structuring -lower entropy- compared to free water. Such changes exceed the 0.1 to 0.2 nm thickness expected from exclusively electrostatic interactions. As mentioned above, Geesink [21] supports the Mae Wan Ho [25] and De Ninno [5] approaches, considering well-defined coherent and incoherent structures (corresponding to frequency domains) as well as less well-defined intermediate states. Water associated with ions, charged groups of proteins, and DNA modify the dielectric properties. MMW in sub-thermal intensity could lead to resonances capable of inducing electron tunnelling and finally ionic rearrangements in DNA protein complexes (as already suggested by Belayev in 2010). He concluded that the main targets of the influence of electromagnetic fields on aqueous DNA solutions are water molecules. The energy transfers would take place (according to the theory of Davidov 1977) via solitons: «a self-reinforcing solitary wave that moves at constant speed without changing its shape», which can be illustrated in the manner of the transfers existing in optical fibres.

Another aspect developed by (Babakyan, et al. [28-30]). concerns the dehydration of Na+ ions and nucleic acids induced by MMW, even at non-thermal levels, in the resonant ranges of water 64.5 and 50.3 GHz (90min) compared to non-resonant frequencies (48.3 GHz). The thermodynamic study involved binding of anticancer drugs mitoxantrone (MTX), netropsin (Nt), doxorubicin (DX) and Hoechst 33258 (H33258) (2018), and methotrexate (2016) to nucleic acids from healthy liver, sarcoma, and synthetic poly ribonucleotides. Exposure to resonant frequencies increases binding, which could be a therapeutic lead. (Betski, et al. [31]) had already observed this dehydration phenomenon in vitro on saline solutions in the THz and millimetre ranges at low exposure levels.

Metrology: In terms of exposure assessment, (Shrivastava, et al. [32,33]), in the context of 5G-6G assessment, have mapped specific absorption rate (SAR) and temperature elevations from an antipodal linear cone slot antenna (ALTSA) at 60 GHz on different parts of the body using EM calculations and thermal cameras. (Hamed, et al. [34]). followed the same goal using terms of specific absorption rates (SARs) studied using the finite difference time domain (FDTD) method in single and layered human tissues by examining 1 g SAR (gram mass average) and point SAR (no mass average) at frequencies of 28, 40, and 60 GHz. The Bioheat equation was used to calculate the temperature rise in the tissues. In both cases, the temperature rise never exceeded 1°C in all configurations, which was well below the threshold value for generating adverse thermal effects in tissues. At radiated power of 20 and 24 dBm, the SAR levels (without mass averaging) in tissues at 28 GHz are lower than at 40 and 60 GHz. The temperature rise in the three-layer model is 2-3 times higher than that in the single-layer model.

Cellular/In Vitro Studies

The majority of the studies have involved cancer lines or skin and skin-like cells (keratinocytes, fibroblasts), with the remainder divided between bacteria, other tissues and plant cells. The team of Y. Le Drean's team was particularly interested in keratinocytes; [35] evaluated the impact of MMW exposure (24 h of exposure at 60.4 GHz, at 5 mW/cm²) on neuronal metabolism and on the dopaminergic renewal of PC12 cells treated with NGF. After exposure to MMW, the intracellular and extracellular contents of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were studied by HPLC and the effect on dopamine transporter (DAT) expression by immunocytochemistry. Dopamine turnover was assessed by the ratio of DOPAC to DA and by measuring the accumulation of DOPAC in the medium. Neither dopamine turnover nor DAT protein expression levels were affected by MMW exposure. However, the extracellular accumulation of DOPAC was found to be slightly, but not significantly, increased. This result was related to the thermal effect and no evidence of non-thermal effects of MMW exposure was observed on dopamine metabolism.

(Soubere Mahamoud, et al. [36]) Analysed by DNA microarray methods the whole genome changes of a human keratinocyte model that was exposed to 60.4 GHz-MMW at 20 mW/cm2, 3 hours under athermal conditions, alone or in the presence of metabolic stress (2 deoxy glucose, which decreases cellular ATP content and alters the transcriptome on 632 coding genes). No modification of the keratinocyte transcriptome was observed in the presence of MMW. The MMW/2dG combination did not alter the ATP content of keratinocytes, but it did slightly alter the transcriptome, reflecting the ability of MMW to interfere with the bioenergetic stress response (validated by RT PCR on 6 sensitive genes that encode transcription factors or inhibitors of cytokine pathways). The question is the potential impact of long-term or chronic exposure to MMW on metabolically stressed cells.

Cancer lines: [37] Compared, on neuroblastoma cells, the effects of sine wave irradiation in the frequency range 100GHz - 3 THz with Gaussian pulses covering the same frequency range. The frequency response (after Fourier transform) is also Gaussian while the side bands are more homogeneous than the sinc signals. He observed the variation of membrane potential, transmembrane calcium fluxes through VGcc and intracellular calcium concentration. He found that THz pulses had a much higher efficiency than CW in all observed parameters. In addition, he pointed out that «for relatively large amplitudes, THz Gaussian pulse irradiation reduces the simultaneous temperature rise compared to THz sine wave irradiation.

This would help to reduce the side effects of the THz-induced temperature rise.» The pulse shape should therefore be selected a priori start/cut (square pulse), spectrally continuous to cover (Gaussian) with better homogeneity over the selected bandwidth (Gaussian of revolution). (Franchini, et al. [38]) studied possible in vitro effects of MMW (25GHz) on human foetal fibroblasts from the point of view of genotoxicity and overall cellular toxicity: direct DNA damage was excluded (comets, H2AX phosphorylation, frequency of micronuclei negatives to the anti-kinetochore antibody (CREST). No induction of apoptosis or changes in pro-survival signalling proteins were detected. CREST analysis showed an increase in the total number of micronuclei and centromere-positive micronuclei in the exposed samples, indicating induction of aneuploidy due to chromosome loss. (Hovpanian, et al. [39]) exposed E. hirae ATCC 9790 bacteria to low-intensity MMW (0.06 mW cm-2 at 51.8 and 53 GHz) and monitored the rate of bacterial growth; a stronger effect was observed with 53 GHz, regardless of the duration of exposure (0.5 h, 1 h or 2 h). Scanning electron microscopy analysis of these effects was performed; the cells were spherical in shape. The electromagnetic field at 53 GHz, but not at 51.8 GHz, changed the size of the cell - the diameter was enlarged 1.3 times at 53 GHz. These results suggest the difference in mechanisms of action on bacteria for the 51-8 GHz and 53 GHz electromagnetic fields.

A stronger inhibitory effect of the low-intensity electromagnetic field on Enterococcus hirae ATCC 9790 bacterial growth rate was observed with 53 GHz compared to 51-8 GHz, regardless of the exposure duration. Scanning electron microscopy analysis showed that almost all of the irradiated cells in the population had similar spherical shapes to the unirradiated cells, but they had increased diameters in the case of cells irradiated at 53 GHz, but not at 51-8 GHz. These different results for MMW of different frequency could be applied in the processing of foods and products in veterinary medicine, where E. hirae plays an important role. [40] was interested in the design of liposomes loaded with superparamagnetic iron oxide nanoparticles as a means of magnetically triggerable delivery of active ingredients. He studied by electron microscopy image analysis the MMW-induced movements on giant lipid vesicles in suspension containing or not maghemite iron oxide (y-Fe2O3) nanoparticles (MNP). Exposure to MMW induces a collective reorientation of the movement of control vesicles at the onset of MMW activation. No change was observed at the onset of the first MMW activation of MNPs, but secondary evolution shows a directional orientation of the vesicles was induced (planar motion, absence of gravitational effects, and trajectories spanning a narrower range of deflection angles than the control vesicles). The authors suggest as an explanation the possible interaction of MNPs with lipid membrane components influencing, phospholipid density and membrane stiffening, and ultimately to modify vesicle movement.

(Vlasova, et al [41]). investigated by luminol chemiluminescence and morphological examination the effects of MMW (32.9-39.6 GHz, 15min, 100 W/m2) on opsonized zymosan- or E. coli-induced neutrophil activation in ex vivo whole blood. Immediately after exposure the neutrophil response to both agonists was intensified without morphological modification. This result was interpreted as thermal. [42] Realized a re-exposure to MMW (150 minutes, 55 or 66GHz, 0.066 W/m2) of germinating seeds: at 66 GHz increases their resistance to the stressful effects of sub-zero temperatures: germination, survival, total and aerial mass biological productivity have values indistinguishable from control. Exposure to 55 GHz reduces their resistance to thermal stress, worsens growth and development. The results obtained allow the development of recommendations on the irradiation of agricultural plants to enhance their potential to adapt to adverse environmental factors, increase productivity, improve crop quality, and improve the economic and energy efficiency of plant production.

Animal Studies

[43] evaluated the effects of 94 GHz on their gene expression. Exposure to 94GHz CW, was continued for 5 months with rats exposed 3 h per day for 3 days per week to an incident power density of 10 mW/cm², using two populations of rats (young/adult) with sham/ exposed distribution in each group. At the end of the experiment, skin explants were collected, and RNA was extracted and gene expression profiles analysed with a gene expression microarray. In the absence of changes in animal temperature, long-term chronic exposure to 94 GHz-MMW did not significantly alter skin gene expression in either young or adult rats. (Kojima, et al. [44]). studied the changes in ocular temperature in the eyes (cornea, lens, vitreous) of rabbits exposed to different frequencies (18 to 40 GHz, 2 independent systems, 200mW/ cm2)) with a fluoroptic thermometer. The highest ocular temperature was induced by 40 GHz, followed by 35 GHz, the least at 18GHz. The heat induced by MMW exposure is frequency dependent and is transmitted not only to the cornea but also to the lens.

[45] was also interested in the frequency dependence of the absorption on arthropod model (bee and 2 insects) in the 2-120GHz bands by modelling, X-ray tomography, FTDD; he finds a frequency dependence of the absorption (stronger above 6GHz), with very important absorption jumps for a little modified exposure power.

(Debouzy, et al. [46]), exposed hairless rats to MMW (CW) under acute high power conditions (3sec at 10kW/m2) and under low power environmental/occupational exposure conditions (4 hours per

day, 5 days per week, for 6 months at 10 mW/cm2). Acute exposure to 94 GHz caused the disappearance of the upper corneal layers of the epidermis and increased SOCS-3 inflammatory gene expression after 3 hours. A thermal effect is observable, associated with a localized inflammatory response. Chronic low-power exposure induces a hypoalgesia effect, possibly related to an increase in brain plasticity. The mechanistic hypothesis is a low-noise stimulation of thermal pain receptors at a subthreshold level. Conversely, neither inflammation nor direct changes in skin cell gene expression were found.

Tumanyants [47] exposed molluscs (helix albescens) to Yav- 1 radiation 42GHz, 10 mW/cm2) in 3 groups of 20 (control, placebo, exposed 1hr), in each group 1 subgroup receiving naloxone. The nociceptive state of the animals was judged by the threshold (P) and latency (LP) of the avoidance response (AR) in the hot plate test. He found a pronounced antinociceptive effect in the regulatory mechanisms and the importance played by the opioid system, a role that differs according to the developmental stages during exposure. [48], was interested in the intracellular calcium of the ganglion of leeches exposed to 60GHz -(100mW at the output of the guide, DSP?). He finds an upregulation of free intracellular calcium in an ex vivo experiment (thermal effect?) MMW could affect cell volume regulation mechanisms, such as Na/K-ATPase, PMCA, ion balance inside and outside the cell and many signalling pathways controlled by calcium and calcium-dependent processes. [49] observed the effect of MMW (30min/d 15days) on tumour growth in rat transplanted sarcoma-37 in the absence of cytostatic treatment. He observed a difference of 1/3 in tumour growth and 200% in DNA methylation. He invokes a mechanism of hypermethylation of tumour DNA by MMW through activation of cell-specific molecular mechanisms, leading to a decrease of undesirable structural changes in tumour DNA and inhibition of tumour growth.

Human Studies/Clinical Results

(Partyla, et al. [50]) exposed the sternal skin of healthy volunteers to MMW (42.25 GHz: active generator, 17.2 mW/cm2; or 50-75 GHz: noise generator with power less than 100mW; or an inactive MMW device: placebo generator) in a randomized, double-blind, crossover fashion. The pain threshold, measured with the Cold pressure test -CPT-, was the primary endpoint. Other CPT parameters, heart rate, blood pressure, incidence of subjective sensations (paraesthesia) during exposure, as well as the quality of blinding of the volunteers were also recorded. The end points of the condition with 42.25 GHz exposure were compared to baseline; 50-75 GHz noise exposure; and the placebo generator. An increase in pain threshold during exposure to the 42.25-GHz generator compared with baseline was found: median difference (MD), 1.97 seconds (95% confidence interval [CI], 0.35 to 3.73) and noise generator: DM, 1.27 seconds (95% CI, 0.05 -2.33) but not compared with the placebo generator. Time to onset of cold and increasing pain sensations and diastolic blood pressure increased under 42.25 GHz generator exposure compared with baseline and noise generator. Other outcome measures were comparable between study conditions. These results confirm the previously suggested

hypoalgesia effects of low-intensity electromagnetic MW. However, the effect here was indistinguishable from the placebo condition.

[51] Used MMW: in the management of neuropathic pain in patients with various cancers (stages II/IV) in a palliative care unit; 30 patients (versus 15 controls). He used MMW sessions (42GHz CW 10 sessions of 10 min , transmitter was Pramn M14T-Z 42GHz), and carried out the follow-up by means of analyses by questionnaires DN4, Rivermead pressure mobility index, Beck scale, self-evaluation of depression according to Wakefield, HAM-D, HBV; in front of the significant effect obtained, he underlined the perspective of therapeutic use. [52] even proposed a «mode of use» of MMW systems in various pathologies: vague indications:

- 1. Any long-term illness difficult to treat.
- 2. Inflammatory processes in chronic tissue organs.
- 3. Functional violations of organs and systems.
- 4. Situations with severe pain syndrome.
- 5. Injuries. Operational interventions.
- 6. Vascular disorders.
- 7. Decreased immunity.
- 8. For an improvement of the thermoregulation. The desired effects are: Immunostimulant Protective Anaesthetic Protective Hypotensive Improvement of renal blood flow Stimulant Antistress Influence of psychophysiological state. The sources are similar to those used in the former USSR 4.9 mm (60.12 GHz), 5.6 mm (53.33 GHz) and 7.1 mm (42.19 GHz).

The book by Bukrova and Logatchva [53] considered the clinical applications of MMW from a mechanistic point of view, identifying general principles of interaction, the basis of their informational, thermal and therapeutic properties on the human body, and the mode of action at different frequencies. The proposed applications are treatment of ulcers, wounds, ophthalmic diseases, as a stimulator of bone marrow haematopoiesis, to regulate the enzymatic activity of microorganisms and to strengthen the immunity of the human body. Special attention was paid to modern means of microwave therapy in the field of non-invasive diagnosis and surgery of diseases.

(Debouzy, et al. [54,55]), have published case reports on the beneficial effects of MMW exposure of a commercial portable device (a watch designed device proposed for wellness) on patients with various pathologies: hypoalgesia and functional recovery after surgical or sports trauma, pain and physical rehabilitation of chronic pancreatitis, pain, and rehabilitation of fibromyalgia [56]. The MMW (60 GHz, 14mW/cm2, 3 sessions per day) were emitted by a portable wristband type device, the antennas placed on the palmar side of the wrist. The mechanism is based on the stimulation of thermal nerve endings, the information triggering a central reaction of endorphin secretion responsible for the beneficial effect observed.

Mattsson's [57] very general review covers the potential medical

applications of electromagnetic waves (from 0Hz to 10THz). Very much focused on diathermy but did not deal much with millimetre ranges. At the local level, Gibbons [58] reported a case of back urticaria that occurred when a healthy volunteer was exposed to 95 GHz at thermal levels; it resolved in a few hours and was identified as being of thermal origin (42°C local). [59] Assessed hypoalgesic and parasympathetic effects of MMW applied on the palmar side of the wrist in healthy participants. In a within-subject design, 10 healthy participants had the palmar side of their wrist exposed to MMW (61.25 GHz, 17 mW/cm2) for 30 minutes, 1 h, & 1 h30, and 30 minutes of sham exposure. Experimental pain was induced after the exposure sessions with the Cold Pressor Test, and pain threshold and pain tolerance values were compared to that of the sham condition. Participants' heart rate and blood pressure were measured before and after exposures. Finally, innocuity of the exposure system was controlled with a pre-post exposure visual examination scale and skin temperature measured by a thermal camera. Exposure to 30 minutes, but not 1 h or 1 h30, of MMW led to significant increases in pain thresholds compared to the sham condition, but no increase of pain tolerance. All conditions led to decreased heart rate, while no change in blood pressure was observed. No change in skin state or temperature was observed for any of the conditions. MMW applied on the inner part of the wrist diminish pain sensations more effectively than placebo, and seem to increase parasympathetic activities, while remaining innocuous.

Normative Aspects

The technological evolution towards 5G, underway, and then towards 6G, incipient, required a re-evaluation by the normative bodies: At the French national level, ANSES (agence nationale de securité sanitaire et environnementale) [60-62], and ANFR (agence nationale des fréquences) [63,64], lead works and reviews: facing the weak bibliography in the millimetre bands (26GHz) specific to the 5G, the millimetre approach was extended to 100GHz. These works did not show a decisive effect outside thermal on the systems considered «(skin, eye, central nervous system, genotoxicity, membrane permeability), ...except for a limited level of evidence for the effect on cell membranes.» The 2019 draft report presents a comprehensive literature review including previous ANSES reports and bands above 40GHz. ANSES concluded that further studies, signal characterization ...were necessary. This need for further research was further emphasized by Miyakoshi [65] and Simmko [66]. The ICNIRP/ WHO (international committee for non-ionizing radiation protection) [67-69], 2020 update is still based on «power (CW) or energy (pulse) density, with identical reference values up to 6GHz (the «switchover» frequency was 20GHz in previous versions such as ICNIRP 1998). While the basic restrictions have remained close in the millimetre bands, the reference levels have been restored to the 1998 values (100W/m2) instead of 50W/m2, for professional levels Table 1.

Table 1: Occupational limits (ICNIRP) or limits for restricted environments (IEEE).

		ICNIRP			IEEE		FCC	
Exposure	WB	Loc	Locl	WB	Loc	Loc	F	
Frequency (GHz)	2- 300	6 - 300	30-300	6 - 300	30-300	6-300	1,5-100	30-300
S(W/m²) or F(kJ/m²)	50			50	decrease from 200 to 100 from 6 to 300GHz respectively	decrease from 400 to 200. from 30 to 300GHz respectively	F vary with pulse width	tp ^{1/2}
Averaging area, cm ²	WB	4	1	WB	4	1	WB	
Averaging time, sec	30	6	6	30	6	6		

Note: WB, whole body; Loc, local exposure; S, power density; F, fluence limit for pulses; tp, pulse width, in s.

IEEE/ IEC (Institute of Electrical and Electronics Engineers) [70,71], the previous document dates from 2007; the latest revision is IEC 2019, and IEEE 2019. All these bodies have adopted a «transition frequency» of 6 GHz. Below this frequency, SAR remains the basic measure of internal exposure. Above this frequency, a new measure of internal exposure has been adopted, the «absorbed/epithelial power density». Both sets of limits were designed to avoid excessive increases in tissue temperature, based largely on electromagnetic and thermal modelling studies (Ziskin, et al. [72]). Note that the article by Hirata [72] details the differences between ICNIRP and IEEE standards, as well as the evolution towards harmonization between these standards. As with the introduction of 4G, pressure groups are concerned about the non-thermal deleterious effects of MMW; there are articles implicating possible mechanisms (see &3)

and a questioning of current standards (&8); Shirin [73] makes an analysis of the reviews covering all the bands used in 5G from VHF to millimetres; among his selection, he concludes (like Naren [74]) that 5G technology can have «calamitous» effects, genetic, biochemical and morphological, and that it is «time to stop» the production, the implementation and the use of any 5G technology as long as the effects are unknown... Pall [75,76], echoes the same views and expands on a review of 197 papers showing that non-thermal exposures well below ICNIRP, FCC or other «safety guidelines» have a significant health effect against any claims that can be made based on ICNIRP, US FCC, EU or guidelines», as do thousands of citations from the primary literature.... At this point Joseph [77] establishes rather a prospective census or doubts than a definite opinion, like Kostoff [78] and Hardell [79] or Franck [80].

Concluding Remarks

In the period under consideration, the explosion of millimetre wave technology (especially the development of 5G-6G) has led to increased interest, both from developers and from various pressure groups, in the health/biological risks of millimetre wave electromagnetic waves (MMW), which are still very incompletely known. This is why many studies are devoted to the exact evaluation of exposure levels, and especially of the possible elementary mechanisms involved in biological effects at low exposure densities (i.e. below 10mW/m2) that cannot be explained by a simple thermal effect. This approach is found in cellular or animal studies showing no genotoxic, metabolomic or lipidomic effect in the absence of a thermal effect, but more global effects that may correspond to a membrane support. The human results were mainly updates of older documents, replication experiments (for hypoalgesia, in particular), collections of potential clinical indications, and case reports describing the beneficial effects of MMW in various pathologies. Moreover by showing probable innocuity of MMW local exposure in human, the work of Minier and coll. Underlines interesting "benefit to cost ratio", that is strong argument for potential, use of MMW in medical applications. Finally, regulatory protection at the population level has, or has begun, the revision of protection criteria, as the simple thermal model no longer seems sufficient. Other dosimetry criteria, intended to define new permissible levels of exposure, are currently being developed.

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