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How to Approach the Challenge of Minimizing Non-Thermal Health Effects of Microwave Radiation from Electrical Devices

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ABSTRACT

Dozens of reviews and thousands of primary literature studies have shown the existence of many different non-thermal health effects of microwave and lower frequency electromagnetic fields (EMFs); however current safety guidelines and standards only recognize thermal effects. This leaves both individuals and companies unprotected, particularly with the very large increases in microwave frequency exposures that are occurring over time. It has recently been shown that many, perhaps even all non-thermal health effects are produced by activation of voltage-gated calcium channels (VGCCs) in the plasma membranes of cells, with EMFs activating these channels, producing large increases in intracellular calcium levels [Ca2+]i. The voltage sensor controlling the VGCCs is thought to be extremely sensitive to activation by weak EMFs. Diverse health effects are thought to be produced by downstream effects of increased [Ca2+]i produced by VGCC activation. It is difficult if not impossible to currently predict the biological effects of different EMFs because pulsation patterns, frequencies and EMF polarization each have strong influences on biological effects; there are also windows of exposure producing maximum biological effects within the exposure window. While decreasing exposures on the order of 100 to 1000-fold will no doubt be useful, we also need to have genuine biological measures of damage to allow optimization of both the type of EMF exposures as well as intensities. Biological optimization should be done by studying cells in culture that have high densities of various types of VGCCs, measuring such effects as increases in [Ca2+]i and increases in nitric oxide (NO) production following EMF exposures. Such cell culture-based assessment of biological damage should allow progressive improvement of wireless communication devices and various other electronic devices by choosing designs that lower biological responses.

Keywords

Microwave frequency EMFs, calcium signaling, nitric oxide, peroxynitrite, oxidative stress

1. There Is a Widespread Literature on Non-Thermal Effects Being Produced by Low-Intensity Microwave/RF Exposures

The earliest major report of widespread non-thermal effects of microwave frequency radiation exposures was the 1971 Naval Medical Research Institute (NMRI) Research Report [1] which listed 40 apparent neuropsychiatric changes produced by non-thermal microwave frequency exposures, including 5 central/peripheral nervous system (NS) changes, 9 central NS effects, 4 autonomic system effects, 17 psychological disorders, 4 behavioral changes and 2 misc. effects [1,2]. It also listed cardiac effects including ECG changes and cardiac necrosis as well as both hypotension and hypertension, and also 8 different endocrine effects. Changes affecting fertility included tubular degeneration in the testis, decreased spermatogenesis, altered sex ratio, altered menstrual activity, altered fetal development and decreased lactation. Many other non-thermal changes were also listed for a total of over 100 non-thermal effects. This NMRI report also provided a supplementary document listing over 2300 citations documenting these and other effects of microwave exposures in humans and in animals, with approximately 2000 of these documenting apparent non-thermal effects.

Tolgskaya and Gordon [3] published a long and detailed review of effects of microwave and lower frequency EMFs on experimental animals, mostly rodents. They report that non-thermal exposures impact many tissues, with the nervous system being the most sensitive organ in the body, based on histological studies, followed by the heart and the testis. They also report effects of non-thermal exposures on liver, kidney, endocrine and many other organs. The nervous system effects are very extensive

and are discussed in Reference [2,3] and more modern studies reporting extensive effects of such non-thermal EMF exposures on the brain are also cited in [2]. There are also many modern studies showing effects of non-thermal exposures on fertility in animals.

The Raines 1981 National Aeronautics and Space Administration (NASA) report [4] reviewed an extensive literature based on occupational exposures to non-thermal microwave EMFs. Based on multiple studies, Raines [4] reports 19 neuropsychiatric effects to be associated with occupational microwave/radiofrequency EMFs, as well as cardiac effects, endocrine including neuroendocrine effects and several other effects.

The Bolen 1994 report put out by the Rome Laboratory of the U.S. Air Force [5], acknowledged the role of non-thermal effects of microwave EMFs on humans. This report states in the Conclusion section that "Experimental evidence has shown that exposure to low intensity radiation can have a profound effect on biological processes. The nonthermal effects of RF/MW radiation exposure are becoming important measures of biological interaction of EM fields." Clearly Bolen [5] rejects the claim that only thermal effects occur. So we can see from these four reviews (1,3-5), that there was already a well accepted literature on non-thermal effects of microwave frequency EMFs back in the 1970's through the mid-1990's but it is still the case that U.S. and international safety guidelines and standards are based solely on thermal effects.

22 additional scientific published reviews have each reviewed various types of non-thermal microwave effects in humans and/or experimental animals in various contexts [2,6-26], as have 26 studies in a recently published book [27]. It can be seen from this that there is a widely held consensus in much of the scientific community that various non-thermal effects of microwave EMFs are well documented.

2. Safety Guidelines and Standards Are Based Only On Thermal Effects

Nevertheless, U.S., ICNIRP and almost all other safety guidelines/standards for microwave/lower frequency EMFs have been based solely on thermal (heating) effects, not on non-thermal effects. These have, therefore left both the general public and also companies designing devices emitting electromagnetic fields unprotected by genuine scientifically-based standards. It is the central focus of this paper as to how such companies should respond to this situation.

There have been many scientific statements that have expressed great concern about the inadequacy of these safety guidelines/standards because of their failure to include what in the views of many scientists, are well established non-thermal effects. For example, Havas in a 2013 paper [6] lists 14 statements of this type, written between 2002 and 2012 by various groups of international scientists, each expressing concern about non-thermal effects and the inadequacy of safety guidelines and standards. In addition, recently, there was a petition from various scientists, arguing that the World Health Organization should reclassify microwave EMFs as a Class 1 human carcinogen; 53 scientists signed a petition that the 2014 Canadian Report (discussed further below) had inadequate protection standards for human health; and 206 international scientists signed a statement sent to the United Nations Secretary General and to member states, stating that international safety guidelines and standards are inadequate to protect human health.

3. Four Important Factors Which Make the Biological Activity of EMFs Unpredictable in Terms of Intensity and Unpredictable in General

Many have assumed that it is possible to predict the effects of such EMFs based simply on EMF exposure intensities but such assumptions are clearly false. Empirical observations have shown that four types of factors greatly influence biological responses to microwave EMFs , with all four reviewed by Belyaev [28] and 3 of the 4 each reviewed elsewhere [24,25].

1. One of these is that pulsed fields are *in most cases* more biologically active than non-pulsed fields. The literature on comparing pulsed fields with non-pulsed fields goes back to the 1960's [3] and continues right up to the present [24-26,28,29]. One example of pulsation effects is from studies of therapeutic effects of non-thermal microwave frequency EMFs [26], when they are of the right type and intensity and focused on the right tissue. Such therapy was standardized using pulsed microwave fields back in the mid-1970s because these pulse fields were more active, a standardization that continues to the present day [26]. There are some 4000 studies of pulsed microwave therapy which make up the largest literature on non-thermal biological effects. Unfortunately we don't have enough detailed knowledge of these pulsation effects to be able to predict how biologically active EMFs with different patterns of pulsation will be. With very complex pulsed fields like those from smart meters or smart phones, prediction becomes still more difficult. Panagopoulos et al [29] have argued that complex pulsation patterns are consistently more biologically active than are simpler patterns. There is some evidence that very low frequency pulsations (10 Hz or less) may lower biological responses, which if confirmed may be useful for lowering biological effects of electronic

devices. Because all wireless communication devices communicate via pulsations, pulsation effects may be inherent factors with such devices.

2. There are non-linearities in dose response curves and specifically there are specific intensity windows of exposure which produce greater biological effects than exposures of either **higher** or **lower** intensity [24,28,29]. In one experiment, an effect seen within a window was studied and it was found that increasing intensity to even to 150 times higher intensity of exposure lead to lower biological responses than was found in the window. Clearly these intensity windows also create important uncertainties in trying to predict biological effects of EMF exposures.
3. It has also been shown that different frequencies have different biological effects [28]. While this is a simpler issue, than either pulsations or the window effects, it may well add substantial complexity in combination with each of these other two factors.
4. Perhaps most importantly, artificial EMFs are polarized and can be linearly or circularly polarized. However most naturally occurring EMFs are non-polarized or only weakly polarized. Polarized fields can produce much stronger forces on charged groups, which, as discussed below, are likely to have central roles in producing non-thermal biological effects [28,29]. One of the other effects discussed by Belyaev [28] is that circularly polarized fields can be either right handed or left handed and that the handedness of specific fields have extremely large effects on the biological responses, such that fields that are identical in intensity and frequency and differ only in their handedness of circular polarization can have almost completely different biological effects.

All of these things – the effects of pulsations, of window effects, of frequencies and of linear and circular polarization argue compellingly that we cannot predict biological effects based simply on the intensity of EMFs and certainly not on heating effects of EMFs. An attractive approach to measuring biological effects empirically is discussed below.

4. How Do Non-Thermal EMF Exposures Produce Biological Effects?

The above discussed studies, clearly show that there has been a consensus in the scientific literature from the early 1970s up to the present time on the existence of widespread non-thermal EMF health effects but it has been unclear what mechanism(s) generated these health effects. There were various suggestions about how these might be generated but no confirmation that those suggested mechanisms were correct. The author stumbled onto the mechanism in 2012 and published on it in mid-2013. This 2013 paper [30] was honored by being placed on the Global Medical Discovery web site as one of the most important medical papers of 2013. At this writing, it has been cited 42 times according to the Google Scholar database, with 18 of those citations during the first half of 2015. So clearly it is having a substantial and rapidly increasing impact on the scientific literature. I have given 26 professional talks, in part or in whole on EMF effects in 10 different countries over the last 2 1/4 years. So it is clear that there has been a tremendous amount of interest in this.

What the 2013 study showed [30], was that in 24 different studies (and there are now 2 more that can now be added [2]), effects of low-intensity EMFs, both microwave frequency and lower frequency EMFs could be blocked by calcium channel blockers, drugs that block what are called voltage-gated calcium channels (VGCCs). There were a total of 5 different types of calcium channel blocker drugs used in these studies, with each type acting on a different site on the VGCCs and each thought to be highly specific for blocking VGCCs. What these studies tell us is that these EMFs act to produce non-thermal effects by activating the VGCCs. Where several effects were studied, when one of them was blocked or greatly lowered, each other effect studied was also blocked or greatly lowered. This tells us that the role of VGCC activation is quite wide – many effects go through that mechanism, possibly even all non-thermal effects in mammals. There are a number of other types of evidence confirming this mechanism of action of microwave frequency EMFs [2,24,30]. It is now apparent [24] that these EMFs act directly on the voltage sensor of the VGCCs, the part of the VGCC protein that detects electrical changes and can open the channel in response to electrical changes.

The voltage sensor (and this is shown on pp. 102-104 in [24]) is predicted, because of its structure and its location in the plasma membrane of the cell, to be extraordinarily sensitive to activation by these EMFs, about 7.2 million times more sensitive than are single charged groups elsewhere in the cell. What this means is that arguments that EMFs produced by particular devices are too weak to produce biological effects [31], are immediately highly suspect because the actual target, the voltage sensor of the VGCCs is extremely sensitive to these EMFs.

How, then can the stimulation of the VGCC mechanism lead to health impacts? When the VGCCs are activated, they open up a channel and leads to large increases in intracellular calcium ([Ca2+]i) and it is the excessive intracellular calcium that leads to most if not all of the biological effects. Calcium signaling is very important to the cell, with some effects of it

being produced through increases in nitric oxide (NO) as seen in Fig. 1 and Ref 2.

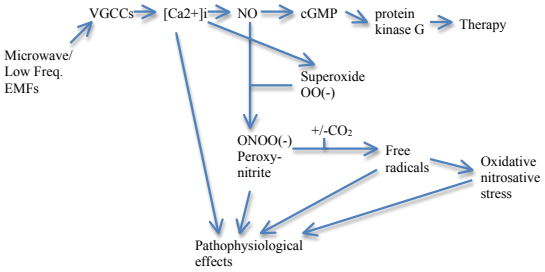

Figure 1. EMFs Act via Downstream Effects of VGCC Activation to Produce Pathophysiological and Therapeutic Effects. Taken from Ref. [24] with permission.

There are non-thermal therapeutic effects produced by these EMFs where they are at the appropriate level and where they are focused on the proper tissue; Such therapeutic effects are produced by the NO signaling pathway across the top of the Figure. However NO can also react with superoxide (which is also elevated by excessive Ca2+]i) to form peroxynitrite, ONOO(-), a potent oxidant. Peroxynitrite can break down to produce reactive free radicals and cause oxidative stress, with all of these acting to produce pathophysiological (that is disease causing) effects (Fig.1). Excess calcium signaling by elevated [Ca2+]i can also contribute to pathophysiological effects.

A number of repeatedly reported effects of effects of microwave EMF exposures can be generated by these mechanisms, as shown in Ref. [24].

Table 1. Apparent Mechanisms of Action for Microwave Exposures Producing Diverse Biological Effects (See Fig. 1)

Reported Biologic Response	**Apparent Mechanism(s)**
Oxidative stress	Peroxynitrite & consequent free radical formation
Single strand breaks in cellular DNA	Free radical attack on DNA
Double strand breaks in cellular DNA	Same as above
Cancer	Single and double strand breaks, 8-nitroguanine and other pro-mutagenic changes in cellular DNA; produced by elevated NO, peroxynitrite
Breakdown of blood-brain barrier	Peroxynitrite activation of matrix metalloproteinases (MMPs) leading to proteolysis of tight junction proteins
Male and female infertility	Induction of double strand DNA breaks; Other oxidative stress mechanisms; [Ca2+]i mitochondrial effects causing apoptosis; in males, breakdown of blood-testis barrier
Therapeutic effects	Increases in [Ca2+]i and NO/NO signaling
Depression; diverse neuropsychiatric symptoms	VGCC activation of neurotransmitter release; other effects?; possible role of excess epinephrine/norepinephrine
Melatonin depletion; sleep disruption	VGCCs, elevated [Ca2+]i leading to disruption of circadian rhythm entrainment as well as melatonin synthesis; elevated [Ca2+]i may also lead to elevated night time levels of norepinephrine
Cataract formation	VGCC activation and [Ca2+]i elevation; calcium signaling and also peroxynitrite/oxidative stress
Tachycardia, arrhythmia, sometimes leading to sudden cardiac death	Very high VGCC activities found in cardiac (sinoatrial node) pacemaker cells; excessive VGCC activity and [Ca2+]i levels produces these electrical changes in the heart

Taken from ref [24] with permission.

A large number of these repeatedly reported effects of such EMF exposures can be caused by various downstream effects of VGCC activation as shown in Fig. 1. This suggests that both Fig. 1 and also Table 1 may explain many of the effects produced by non-thermal exposures to microwave frequency EMFs. These apparent mechanisms of action provide further support that most if not all effects of microwave and lower frequency EMFs are likely to be produced via downstream effects of VGCC activation.

In contrast to this, when the author examined the evidence supporting a strictly thermal mode of action of these microwave frequency EMFs in the 2014 Canadian Report [32], that evidence was found to be deeply flawed [24].

5. Biologically-Based EMF Safety Standards – Why Industry Needs to Look at These and How They May Be Useful

Hardell and Sage [34], the Scientific Panel on Electromagnetic Health Risks [17] and the author [24] have called for biologically-based EMF safety standards, standards that are based on genuine biologically relevant responses to low-level microwave and other EMFs. The best approach to doing so, in the author's view, as discussed earlier [24] involves looking at biological responses of

VGCC-containing cells in culture (using methods outlined below). The initial focus here is on how such responses should be useful in quantifying biological effects of electronic devices that produce EMFs.

The goal here is both to use such cell culture studies to quantify biological effects of various EMFs, with regard to effects of frequency, intensity, pulsation pattern and polarization. A wide variety of electronic devices can be tested, so as to improve designs by lowering biological effects. These would include various types of broadcasting devices including antennae, all types of wireless communication devices and also many other electronic devices that inadvertently broadcast EMFs and/or dirty electricity. Smaller devices such as cell phones, cordless phones, cordless phone bases, smart meters, Wi-Fi fields and computers/tablets generating Wi-Fi signals but also many other devices. Panagopoulos et al [25] have recently argued that complex pulsation patterns such as produced by smart phones and smart meters produce higher biological activity. A wide variety of factors should be investigated for improved safety, including improved antenna design, use of frequencies producing lowered biological effects, use of shielding materials and changes in polarization and pulsation patterns. Improved sensitivity of receivers can allow lowered intensities to be used.

In dirty electricity, transients produced by various devices, produce transients in electrical power wiring such that the wiring acts as an antenna, producing in turn, human exposure to EMFs. All digital technology has the potential to produce such dirty electricity, but digital technology involving high current flows may be the major challenge, such as broadcasting antennas, digital power supplies and inverters. It may be important to investigate the use of filters to lower such transients in electrical wiring. It is not uncommon for electronic devices to purposefully introduce signals onto electrical power wiring, such that the wiring is used as a communication conduit. Clearly such purposeful use of power wiring needs to be investigated for biological effects. Filters and other technologies should be investigated to see if these lower biological responses. Even static magnetic fields can activate VGCCs [30], possibly because rapid movement of the VGCCs due to movement of plasma membranes in which they are located. The effects, therefore of many types of EMFs can be assessed biologically through testing of such biological responses.

How then should cells in culture be used to monitor biological effects of various EMFs? Studies would use cell lines with such high VGCC levels, such as neuroblastoma cell lines, glioblastoma/glioma hybrid cell lines or perhaps cell lines derived from endocrine cells with relatively high VGCC levels. Among these cell lines should be the neuroblastoma cell lines previously studied by Dutta et al (discussed in [24]) and shown to produce changes in calcium fluxes in response to very low level EMF exposures. PC12 cells, a commonly used chromaffin cell line may also be useful. In addition, it may useful to use cardiac pacemaker cells which have very high activities of VGCCs and can be derived from stem cells [24]. Because the growth conditions of cells may influence their responsiveness, such conditions must be standardized. Standardization should include growth of cells in a Faraday cage such as to prevent, to the extent possible, previous exposures to EMFs.

Two approaches should be used to measure responses of such cells to EMF exposure: Cells in culture could be monitored for nitric oxide (NO) production using an NO electrode in the gas phase over the culture, using methods similar to those used by Pilla [33]. NO synthesis is stimulated by [Ca2+]i elevation because there are two NO synthase enzymes that are each calcium-dependent and therefore increase in activity with increasing [Ca2+]i. Continuous measurements from an NO electrode can be recorded and easily quantified, allowing accumulation of very large amounts of data in very short time periods in response to various EMFs. Therefore, issues such as reproducibility should be quickly resolved.

Another approach to such studies involves using calcium-sensitive fluorescent probes that concentrate into the cytoplasm of cells, allowing assessments of [Ca]i levels with a fluorescence microscope or of multiple cells using a fluorometer. Alternatively, transgenic cell lines containing green fluorescent protein (GFP) can be used, where GFP functions as the calcium-sensitive fluorescent probe. This may allow one of obtain information of different types than described in the previous paragraph. One can get information on heterogeneity of responses at the cellular level and also how raised [Ca]i levels may propagate over time from one part of the cell to another. However a limitation to this approach may occur if the fields generated by the microscope perturb the [Ca2+]i levels and cannot be well shielded using a small Faraday cage that does not cage exposures that are to be studied. So these two approaches are distinct from one another and whether they will complement each other as they develop is uncertain. It is my view that both of these should be investigated if only to explore their strong points and weak points, but that the NO electrode approach may be a very good place to start because it has already been used to assess EMF effects [33] and because it allows easy quantification. These two types of approaches should allow comparison of different wireless communications devices for their relative biological effects, possibly permitting easy improvements in design. There is some evidence that some pulsation patterns may lower biological effects and this type of effect might be studied as well.

From the standpoint of industry and engineering of electronic devices, the four factors we discussed above, that each influence biological responses each

need to be considered: the roles of pulsations, window effects, frequency and polarization. Each of these can be viewed as a challenge, but also as an opportunity. The opportunities come because by manipulating these factors, it may well be possible to develop devices with much lower biological effects than are produced by current devices. A smart company that gets the information early and uses it effectively may well have a marketing advantage over its competitors.

6. Conclusions

Non-thermal effects of EMF exposures have been extensively documented for over 40 years. However only recently has the mechanism of action of such non-thermal effects been demonstrated. These act via EMF activation of VGCCs, producing increases in intracellular calcium [Ca2+]i. This allows the development of techniques using cells in culture with high densities of multiple types of VGCCs, to assess different devices that emit microwave frequency EMFs by measuring either increases in [Ca2+]i or increases in nitric oxide (NO) produced as a consequence of increased [Ca2+]i. It is the author's view that smart companies should use these cell culture techniques to greatly improve the safety of such devices.

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