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Scientific evidence contradicts findings and assumptions of Canadian Safety Panel 6: microwaves act through voltage-gated calcium channel activation to induce biological impacts at non-thermal levels, supporting a paradigm shift for microwave/lower frequency electromagnetic field action

Abstract: This review considers a paradigm shift on microwave electromagnetic field (EMF) action from only thermal effects to action via voltage-gated calcium channel (VGCC) activation. Microwave/lower frequency EMFs were shown in two dozen studies to act via VGCC activation because all effects studied were blocked by calcium channel blockers. This mode of action was further supported by hundreds of studies showing microwave changes in calcium fluxes and intracellular calcium [Ca2+]i signaling. The biophysical properties of VGCCs/similar channels make them particularly sensitive to low intensity, non-thermal EMF exposures. Non-thermal studies have shown that in most cases pulsed fields are more active than are non-pulsed fields and that exposures within certain intensity windows have much large biological effects than do either lower or higher intensity exposures; these are both consistent with a VGCC role but inconsistent with only a heating/thermal role. Downstream effects of VGCC activation include calcium signaling, elevated nitric oxide (NO), NO signaling, peroxynitrite, free radical formation, and oxidative stress. Downstream effects explain repeatedly reported biological responses to non-thermal exposures: oxidative stress; single and double strand breaks in cellular DNA; cancer; male and female infertility; lowered melatonin/sleep disruption; cardiac changes including tachycardia, arrhythmia, and sudden cardiac death; diverse neuropsychiatric effects including depression; and therapeutic effects. Non-VGCC non-thermal mechanisms may occur, but none have been shown to have effects in mammals. Biologically relevant safety standards can be developed through studies of cell lines/cell cultures with high levels of different VGCCs, measuring their responses to different EMF exposures. The 2014 Canadian Report by a panel of experts only recognizes thermal effects regarding safety standards for non-ionizing radiation exposures. Its position is therefore contradicted by each of the observations above. The Report is assessed here in several ways including through Karl Popper's assessment of strength of evidence. Popper argues that the strongest type of evidence is evidence that falsifies a theory; second strongest is a test of "risky prediction"; the weakest confirms a prediction that the theory could be correct but in no way rules out alternative theories. All of the evidence supporting the Report's conclusion that only thermal effects need be considered are of the weakest type, confirming prediction but not ruling out alternatives. In contrast, there are thousands of studies apparently falsifying their position. The Report argues that there are no biophysically viable mechanisms for non-thermal effects (shown to be false, see above). It claims that there are many "inconsistencies" in the literature causing them to throw out large numbers of studies; however, the one area where it apparently documents this claim, that of genotoxicity, shows no inconsistencies; rather it shows that various cell types, fields and end points produce different responses, as should be expected. The Report claims that cataract formation is produced by thermal effects but ignores studies falsifying this claim and also studies showing [Ca2+]i and VGCC roles. It is time for a paradigm shift away from only thermal effects toward VGCC activation and consequent downstream effects.

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Introduction

There has been a literature reporting various non-thermal effects of microwave/radiofrequency radiation exposures starting with the Soviet literature in the 1950s. Subsequently, there have been thousands of international published studies reporting non-thermal or what are sometimes called micro-thermal effects producing therapeutic responses, changes in calcium fluxes and signaling, increased oxidative stress, and a wide variety other health-related responses in humans and animal models.

Nevertheless, there has been a series of medical reports, arguing that only thermal effects need be considered when setting guidelines or safety standards for microwave electromagnetic field (EMF) exposures. These have been based mainly on two types of arguments:

- That there cannot be any biophysically viable mechanism for any such non-thermal effects and therefore that reports of such effects should be viewed with great skepticism.
- That there are many "conflicts" or "inconsistencies" in the literature which according to these reports, justify rejection of the various thousands of publications showing apparent non-thermal effects.

The focus of this review is to consider whether it is time for a "paradigm shift" away from strictly thermal effects toward non-thermal effects. Specifically, it is focused on the recent finding that most, possibly all non-thermal effects can be produced by microwave activation of voltage-gated calcium channels (VGCCs). It is also focused on the 2014 Report of the Canadian Panel of Experts on Safety Code 6 as the most recent and therefore up-to-date summary of the evidence supporting the strictly thermal point of view.

EMFs act via stimulation of voltage-gated calcium channels (VGCCs)

Calcium provides an essential role in cell function, being normally maintained at very low, circa 10^{-7} M intracellular levels, but also with transient intracellular calcium ([Ca2+]i) increases being used for widespread and important regulatory signaling. A recent review (1), noted that in two dozen studies, calcium channel blocking drugs block a wide range of electromagnetic field (EMF) effects on cells and organisms by blocking voltage-gated calcium channels (VGCCs which are also known as voltage-operated, voltage-dependent or voltage-regulated calcium channels). In most but not all cases, L-type VGCCs were studied, but T-type, N-type and P/Q-type channels can also have roles, as shown by channel blockers specific for these other channels (1). In each of these studies, calcium channel blockers blocked or greatly lowered each of the responses studied, showing that VGCC activation is required for low intensity fields to produce a wide range of responses (1). Each of these channel blockers is thought to be highly specific, such that with two different types of L-type blockers being used that act at different sites on the L-type VGCCs and also one each of the T-type, N-type and P/Q type blockers being used, with each showing activity in blocking or greatly lowering EMF responses, it is highly unlikely that a non-VGCC mechanism is involved here.

VGCC activation is thought to act mainly by increasing [Ca2+]i. Other considerations also support VGCCs as a major EMF target, accounting for numerous biological impacts of microwave exposures (1–3) at levels not producing substantial changes in temperature.

Pilla published a very important paper, suggesting in retrospect that these low-level fields directly activate the VGCCs (4, see also 1–3). He showed that cells in culture when exposed to a low intensity pulsed microwave field, produce an almost instantaneous Ca^{2+}/calmodulin-dependent increase in nitric oxide (NO), occurring in <5 s. The NO increase is produced by the [Ca2+]i activating the two Ca^{2+}/calmodulin-dependent NO synthases, which can occur almost instantaneously. These results show that the [Ca2+]i increases must also occur almost instantaneously, providing strong evidence that the VGCCs are directly activated by the low intensity field in this study. The known properties of the VGCCs are discussed below, properties that are expected to make them particularly susceptible to activation by such low intensity fields.

In addition to calcium channel blocker studies, the important role of VGCC activation for the biological effects of microwave radiation at levels that do not produce measured changes in temperature is also supported by a large number of studies, some of which were reviewed earlier (5, 6), showing that low level microwave EMF exposures lead to measured changes in calcium signaling and/or calcium fluxes consistent with VGCC activation. There are

also hundreds of studies of oxidative stress responses to low intensity field exposures, which can also be produced by downstream effects of increased [Ca2+]i (1–3). The mode of microwave action via VGCC activation also confirms earlier predictions of Panagopoulos et al. (7, 8) that EMFs may act via voltage-gated ion channel activation. The whole issue of the biophysics of VGCCs and other voltage-gated ion channels is discussed in some detail below.

Various frequencies, intensities and pulse patterns of EMFs act via VGCC activation (1), including extremely low frequency fields of 50 or 60 Hz electrical wiring, microwave frequency EMFs also referred to as radiofrequency (RF), very short "nanosecond" pulses, and even static electric or magnetic fields. Given recent global increases in exposures to microwave/RF EMFs, the findings for microwave EMFs create the most concerns for both human and environmental health.

We are therefore in a situation where the paradigm of EMF action focused solely on heating (9–13), should be replaced by one based on VGCC activation of microwave and other EMFs (1–3).

In addition to impacts of EMFs directly involving VGCCs, there are a number of other related mechanisms which should be explored. For instance, Pilla reviewed 2 studies in which microwave EMFs increased apparent calmodulin activation (14). Calmodulin is regulated by [Ca2+]i such that calmodulin activation may act along with VGCC activation in two related pathways of action discussed below.

Three other types of observations that contradict the assumptions of current safety standards

Current safety standards are based on the assumption that all important biological effects of microwave and lower frequency EMFs are due to tissue heating (thermal effects) and that specific absorption rates (SARs) of EMFs are therefore a measure of their ability to produce all important biological effects. While the VGCC studies, discussed above clearly invalidate that assumption, there are three other distinct types of observations that also contradict that assumption. As discussed below, an extensive scientific literature reports biological microwave EMF effects at exposure levels well within safety standards and that therefore should not occur according to current safety standards. Two other types of falsifying evidence are the findings that pulsed fields are often much more biologically active than non-pulsed fields and that certain intensity windows of exposure are more biologically active than are exposures of both lower and higher intensities. These two are each discussed in some detail immediately below.

It has been known for well over 30 years that pulsed microwave fields are often much more biologically active than are continuous non-pulsed fields. This was shown, for example, by Seaman and Wachtel in studies of microwave exposures of Aplysia pacemaker cells (15). Pacemaker cells have a very high density of VGCCs, suggesting that the pulsed microwave exposures may in this study act via VGCC activation. This was shown by Bassett et al. (16) and by Pilla (17) both in 1974 studies of augmentation of bone repair, that pulsed field microwaves were much more active than continuous field microwave exposures. Both Baranski (18) and Czerski (19) showed that microwave pulsed field exposures were more active than non-pulsed fields in terms of their impact on blood forming cells. Micro pulsed field exposures were also more effective than non-pulsed continuous wave (CW) fields in producing a breakdown of the blood-brain barrier (20). Adey's review (21) stated that "There is evidence of interactions with radio and microwave fields pulse-modulated at higher frequencies from 500 to 1500 Hz and an absence of similar effects with CW fields of the same average power density at the same carrier frequency." Several other studies are cited in the Adey (21) review documenting higher biological activity of pulsed fields than non-pulsed CW fields at identical power levels. A recent study showing that pulsed microwave EMFs acted via activation of L-type VGCCs (22) suggests that all these inconsistencies of the pulsed field findings with any heating mechanism may be due to their action in VGCC activation.

More than four decades ago, the biological impact of non-thermal levels of pulsed fields was sufficiently well documented that it became the basis for a number of therapeutic applications of microwave pulses. Therapies currently employed include a wide range of bone growth and orthopedic rehabilitation regimens as well as some applications to enhance the uptake of chemotherapeutic agents (14). These numerous therapeutic effects are well established to be non-thermal and operate through increased levels of [Ca2+]i and nitric oxide (NO) signaling (2, 14). The medical use of these pulsed fields provides therefore prima facie evidence that such fields are often more active in VGCC activation than are non-pulsed fields.

The greater biological activity of pulsed field exposures were sufficiently well documented 30–48 years ago, such that it influenced safety standards of the 1960s and 1970s. For example, the Canadian Standards Association 48 years ago in 1966, adopted lower standards [see Table 2 in ref. (23)] for occupational exposure to pulsed field exposures (1 mWhr/cm^2, limited to 6 min exposure) in contrast to those for continuous, that is non-pulsed exposures

(10 mW/cm^2, for which there was no time limitation). In 1974, in the United States, the American National Standards Institute (ANSI) adopted essentially identical standards as had Canada for occupational pulsed field and non-pulsed field exposure (23). In 1970, the Czechoslovakian government adopted more stringent occupational and general public standards for pulsed field exposures vs non-pulsed field exposures (23). Pulsed fields are, of course, produced by any type of wireless communication device since it is the pattern of pulsations that conveys the information. Different devices often use different types of pulsation patterns. However, we do not know how biologically active the different pulsation patterns are, because this has not been systematically studied. As a result, we cannot rationally compare the dangers of one device vs another.

Furthermore, Barrie Trower, a retired military intelligence expert from the United Kingdom, has stated that classified research indicates that different wavelengths vary in their biological activities as well. He reports that the specific details about the biological impacts of variations in pulsed electromagnetic fields are classified by multiple countries because of "national security". Thus much of what research appears to have been done in this field remains unavailable to decision makers charged with setting standards on such devices that emit pulsed electromagnetic fields.

It has been shown that there can be intensity "windows" where biological activity is greater than at intensities both higher and lower than the window intensity (24–32). This again argues against a heating mechanism as there are no known thermal dose-response curves with similar windows. In addition, these window effects are also found at levels where there is extremely low heating. For example, Blackman et al. (28) state that "Because of the extremely small increments of temperature associated with positive findings [less that 4×10(−4) degrees C], and the existence of more than one productive absorption rate ("window"), a solely thermal explanation appears extremely unlikely". It is (31) stated that "Since there was no detectable temperature increase during exposures, the recorded effects are considered non-thermal". The suggested mechanism (31) may involve a role of voltage-gated ion channels such that "the action of external EMF on cells is dependent on irregular gating of membrane electrosensitive ion channels whenever a force on the channel sensors exceeds the force exerted on them by a change in the membrane potential of about 30 mV which is necessary to gate the channel normally. If in some kind of cells there is an upper limit for this value of membrane potential change, then the channel would be gated whenever the force exerted on its sensors is within this 'window'". Five of these studies show effects on [Ca2+] i fluxes (24–28), consistent with possible roles of VGCCs. These studies provide strong evidence that these window effects occur at levels where there is either no measured change in temperature or extremely low heating.

Perhaps the strongest evidence for non-thermal effects of EMFs comes from studies on animal female and human male reproduction. This literature indicates that sperm exposed to microwave radiation emitted by approved mobile phones die three times faster and develop significantly more damage to their mitochondrial DNA (33). Studies of pregnant mice, rats and rabbits report that prenatally exposed offspring develop significantly more damage to their eyes, skin and liver (33) with hippocampus and pyramidal cell formation are impaired as well.

In summary, four distinct types of evidence provide contradictory information about the basic assumption underlying current US, Canadian and International Commission on Non-Ionizing Radiation Protection (ICNIRP) safety standards that non-thermal effects do not exist: Microwave and other lower frequency EMFs act via VGCC activation rather than by heating; there are numerous papers in the scientific literature reporting biological effects with exposures well within safety standards where substantial heating cannot occur. Moreover, pulsed fields are, in most cases, more biologically active than non-pulsed fields that produce equal heating; windows of exposure intensities occur which are more active than both higher and lower exposures of the same fields. While, in general, lower intensities are safer than higher intensities, this "window" effect shows that there are some major, biologically and medically important exceptions to this pattern. The pulsed field effects and the window effects make it impossible to currently predict biological activity without doing actual measurements of biological activity of specific devices at specific exposure intensities. The question of how to best approach and evaluate such biological effects is discussed below.

The properties of VGCCs and other voltage-gated ion channels may make them uniquely susceptible to low intensity MF activation

There has been an argument repeatedly put forth that there cannot be a biophysically viable mechanism for low intensity, apparently non-thermal effects. This claim

is argued as follows [see Sheppard et al., ref. (34)]: While they acknowledge that EMFs can exert forces on charged groups, they argue that weak EMFs produce only weak forces that are less than are exerted by thermal motion produced at normal body temperature. They argue therefore that the only effects that can be produced by weak EMFs would be dwarfed by a high background noise created by random thermal motion. One of the problems with the Sheppard argument comes from a consideration of the structure of the voltage-gated ion channels and how these channels detect electrical changes, which may lead to opening the channel. The structure of the alpha-1 subunit containing the channel has been modeled and discussed (35–38).

What can be seen is that there are four similar domains in this protein, with each domain containing six transmembrane alpha helixes in it. These four domains are thought to have been produced evolutionarily by two tandem duplications, starting with a gene encoding a protein with one such domain. The fourth helix in each domain contains five positively charged amino acid side chains which collectively make up the voltage sensor (37, 38). It is thought that 20 (4×5) charges make up the voltage sensor, each of which must be pushed in approximately the same direction (and the right direction) at the same time in order for the channel to open. Changes in the membrane potential across the plasma membrane can do this, as can EMFs, because the fields will produce forces on these different charged groups in the same direction at a particular time. Random thermal motion, in contrast, is random in three dimensions and will only extraordinarily rarely produce forces on 20 groups in approximately the same direction at the same time. So you can see the thermal motion argument is clearly at best highly questionable when it is applied to voltage-gated ion channels including VGCCs.

There are other issues that come into play, both influencing the effects of fields on the VGCC voltage sensor. One is that the plasma membrane has high electrical resistance whereas both the aqueous extracellular fluid and the aqueous cytoplasm, with their dissolve salts are good electrical conductors. EMFs only traverse plasma membranes with great difficulty (39, 40). Therefore, fields will produce rapid movement of charges in the intracellular and extracellular aqueous phases which will be blocked by the plasma membrane such that voltage sensor will be influenced by greatly amplified electrical forces, in a direction perpendicular to the plain of the plasma membrane. That circa 3000-fold amplification is recognized by Sheppard et al. (34) immediately before their Conclusion section. The only example of an integral membrane that may be influenced in this way, that they give (34) is that of bacteriorhodopsin, where light exposure leads to the pumping of a proton across the plasma membrane. They attempt to estimate the effects of voltages on the proton pumping, by looking a the effects of voltages on the absorption changes that occur in bacteriorhodopsin (34); however, the cycling of bacteriorhodopsin is a complex process (41) where the proton pumping is not rate-limiting and therefore these studies give little insight into the actual effects on proton pumping.

Bacteriorhodopsin differs from the voltage-sensor in the VGCCs in several important ways:

- The voltage sensor has evolved to respond to voltage changes across the plasma membrane, whereas bacteriorhodopsin has evolved to respond to light exposure.
- There are 20 charged groups in the VGCC voltage sensor (37, 38), whereas there is one charge involved in the bacteriorhodopsin mechanism.
- Whereas the bacteriorhodopsin has considerable water in the center of its structure, water seems to be excluded near the helix 4 structures that constitute the voltage sensor.

The third way, above, is important because the force on charged groups, as shown by Coulomb's law, is inversely proportional to the dielectric constant of the surrounding material. The charged groups of the voltage sensor are found in the lipid region of the plasma membrane. The dielectric constant of the lipid section of the membrane is similar to the dielectric constant of hydrocarbon solvents (41), whereas the water dielectric constant is about 40 times higher than that of hydrocarbon solvents (41). The dielectric constant of the extracellular fluid is 2.5–3.5 times that of water, because of the dissolved salts (42, 43) and the measured dielectric constant of cytoplasm is quite similar to the dielectric constant of extracellular fluid. It follows from this that the aqueous phase where most charges exist in cells has about 120 times the dielectric constant of the membrane where the voltage sensor resides. Therefore, the forces on the voltage sensor charges are on the order of 120 times higher than the forces on most charges in the cell.

It follows from this that if one wants to compare the forces on the voltage sensor with that produced by EMFs on most other charged groups in the cell, the voltage sensor forces are approximately 3000×120×20=7.2 million times greater. [Please note again that the 3000 figure is recognized by Sheppard et al. (34); 120 is the effect of the dielectric constant and 20, the number of charges in the voltage sensor.]

The above considerations in this section, clearly show that Sheppard et al. (34) provide no evidence arguing for biophysical implausibility of the VGCC voltage sensor as

a target of low-intensity EMFs, such that when we have compelling empirical evidence that it is the main target, that evidence should be taken at face value. Furthermore, the VGCC voltage sensor is likely to be many orders of magnitude more sensitive to EMF effects than are any non-plasma membrane localized target. Because heating is produced by the joggling of charged/partially charged groups almost all of which are outside the plasma membrane, the much greater forces on the VGCC voltage sensors show that fields 6–7 orders of magnitude lower than produce heating may activate the VGCC voltage sensors.

Have others been influenced by somewhat similar considerations? I believe it is likely that W.R. Adey was influenced by the plasma membrane properties when in the 1980s he proposed that a plasma membrane protein was the likely target of weak EMFs. Panagopoulos et al. (7, 8) may have been influenced by these plasma membrane and voltage sensor considerations when they decided to do biophysical modeling on voltage gated ion channels. The two reviewers of this paper each had some criticisms of the Panagopoulos et al. (7, 8) modeling, and some of the things in their papers go beyond my biophysics understanding, so I am unable to judge. What I would say is that the modeling studies came to three important predictions: That voltage-gated ion channels may be targets of low-intensity EMFs, that the VGCCs may be particularly activated because of the mechanism of the actual calcium flux through the channel and that pulsed fields may be more active than non-pulsed fields. Biophysical modeling of such complex membrane proteins as the voltage-gated ion channels is, at best a work in progress, given their complexity.

At this point, there is much evidence implicating VGCC activation but no apparent evidence implicating other voltage-gated ion channels in low intensity EMF responses (1–3). Possible reasons for this should be assessed elsewhere.

What is most needed at this point is not more biophysical modeling, although that would be useful, but extensive detailed information on the effects of various fields on VGCC activation. Such information can be obtained via the types of studies advocated below for biologically-based safety standards.

Canadian Royal Society Expert Panel Report on radiofrequency fields

This Royal Society Expert Panel was charged with reviewing Safety Code 6 (2013) safety limits for exposure to radiofrequency (primarily microwave frequency) fields, following the charge to "advance knowledge, encourage integrated interdisciplinary understanding and address issues that are critical to Canadians". The Expert Panel Report (44) can be judged based on these charges and also the requirements that apply to authors of all purportedly scientific documents:

- The need to provide documentation that it has given as objective an assessment of the science as possible;
- The need for clarity of thought and clarity of expression, such that it will be clear to the reader what the Report is trying to say;
- The need to provide the reader of the Report with sufficient information in the Report and in the citations provided in the Report such that the reader can make an independent assessment of the quality of the science;
- And perhaps most importantly, the need to follow widely accepted principles for assessing scientific evidence.

This paper considers both the charges to the panel and these more generally applicable scientific principles to judge the scientific merit of the Report.

What is in the report?

The Report is, in the author's view, stronger on opinion than on evidence (44). Let us consider some specifics.

The Report states that "The Panel considered an 'established adverse health effect' as an adverse effect that is observed consistently in several studies with strong methodology. With this definition in mind, the Panel reviewed the evidence for a wide variety of negative health impacts from exposure to RF energy, including cancer, cognitive and neurologic effects, male and female reproductive effects, developmental effects, cardiac function and heart rate variability, electromagnetic hypersensitivity, and adverse health effects in susceptible regions of the eye." Despite this claim to have reviewed a broad array of biological impacts, in fact the Report does not provide a comprehensive review. Rather it engages, as documented below, in what can be referred to as "cherry-picking" – selecting studies consistent with its assumptions. Moreover, it often ignores studies that are not consistent with its assumption that there are no biological effects excepting those that, in their view, may be tied to heating. Thus the Report completely excludes many different studies on prenatally exposed animals and those on spermatogenesis, on oxidative stress, changes of calcium fluxes and

thousands of studies on therapeutic effects, all at non-thermal levels of exposure.

The Report uses the existence of what it calls "inconsistent," and others have called "conflicting" studies to argue that conflict *per se* indicates a lack of established health impact. This paper considers below whether there are any genuine "inconsistencies" in this literature. Henry Lai and Devra Davis have documented that "conflicting" scientific evidence in the field of bioelectromagnetics relating to mobile phones has been carefully cultivated (45), an inference that may also explain the data of Huss et al. (46). Huss et al. stated "We found that the studies funded exclusively by industry were indeed substantially less likely to report statistically significant effects on a range of end points that may be relevant to health. Our findings add to the existing evidence that single-source sponsorship is associated with outcomes that favor sponsors' products." The panel ignores these findings and considers that conflicting evidence about effects of exposure to RF energy on cancer or other end points means that effects are possible but are not 'established' in accordance with its definition of 'established health effects'. Similarly, while the Report notes that effects of exposure to RF energy on aspects of male reproductive function have been found, it concludes that "the evidence has not been established to indicate that these translate into fertility or health effects" even when such aspects are used clinically to assess male fertility.

The Panel reviewed "inconsistent" evidence about effects of exposure to RF energy on cancer, concluding that effects are possible but are not 'established in accordance with its definition of 'established health effects'. The Report states that the Panel's conclusion on cancer is in agreement with a recent report from the International Agency for Research on Cancer (47). In fact, the Report's characterization of the IARC (47) position does not agree with the IARC actual position. IARC states that "In the text, the Working Group provides comments on those findings that are of greatest relevance to the evaluation, e.g., risk in the overall exposed group, patterns of change in risk with increasing exposure (such as a monotonic increase in risk with increasing exposure), and changes in risk with duration of exposure or latency." Furthermore, the Report ignores the fact that WHO considers microwave radiation to be a Class 2B carcinogen, and the Report also ignores the fact that four prominent reviews on this topic (48–51) all come to the conclusion that microwave exposures can cause cancer. It is apparent therefore that the Panel of Experts on Safety Code 6 has allowed its assumptions to greatly influence its assessment here, rather than providing an objective assessment of the literature.

There are complexities here that the Expert Panel fails to consider. For example, oxidative stress produced by microwave EMF exposure is likely to have a role in causation of cancer. For decades, it has been established that low level oxidative stress can lower oxidative stress markers below initial, pre-stress levels and protect the body from subsequent higher level oxidative stress, a phenomenon known as hormesis that has been recently shown to act by raising the activity of a transcriptional regulator, Nrf2; it has been suggested that this may explain some observations that low level cell phone use may lower cancer incidence via this mechanism, whereas higher level, long-term cell phone use may produce major elevation of cancer incidence. However, the Expert Panel apparently considers these studies to be conflicting, when to the contrary, these studies may raise the issue of biological complexity and a possible U- or J-shaped dose-response curve.

Another even clearer example where inferences of "inconsistencies" or "conflicts" in the literature have been misconstrued regarding the induction of single strand breaks in cellular DNA, measured by what are known as alkaline comet assays, a well-documented method for such studies (1). This literature was reviewed by the author (1), who found 19 different studies where greatly elevated levels of such single strand breaks were found following exposure as well as eight studies where they were not found. However, in examining these studies in detail, it is clear that the differences can be easily explained. For instance, regarding in vitro studies of DNA damage, some of the studies have used different cell types and studied different microwave source EMFs. Thus adult lymphocytes appear relatively resistant to EMF, while neural stem cells are much more susceptible. Different cell types differ from one another in how many and what types of VGCCs may be present and they may differ as well in how the VGCCs are regulated and so may be expected to differ widely in terms of response. All of these studies were done using exposures that were well within current safety standards. Consequently, each of these 19 positive findings contradict the assumptions behind the current safety standards, assumptions that are being defended by the Expert Panel Report, but the Report ignores all of these studies. Moreover, in two of the 19 positive studies, results were positive in some cell types but not others (1), clearly showing that in measurements using identical methodologies, the properties of the cells being studied are critical in determining the biological response found.

Thus the Panel has failed to take into account important nuances regarding scientific research in this field. It has limited considerations to what the Panel calls

"established health effects" defined in terms of consistent responses of various cell and tissue types (44). Where apparent conflict exists, the Panel uses its existence as proof that an effect is not established. In doing so, the Panel fails to take into account scientific details that account for many "inconsistent" results. Such details are likely to include, in addition to the factors discussed above in this section, such factors as the role of different pulsation patterns in different types of exposures, the presence of "window effects" providing very complex dose-response relationships and the role of field frequencies in determining biological response. In effect, the panel dismisses science that does not comport with their underlying assumptions that only thermal effects are relevant.

Genotoxicity of non-thermal microwave exposures: examples of inconsistency?

This inconsistency issue is central to the Report's consideration of genotoxicity of non-thermal microwave exposures. This is one of the two areas (pp. 80–82) where the Report cites substantial numbers of primary citations (22 in this case). It lists 13 citations where studies found genotoxicity following exposure levels, well within safety standards. It also lists nine citations where the Report states that no genotoxic effect was found. The Report only cites a small fraction of the overall literature on genotoxicity. For example, it only cites one of the 19 studies reviewed earlier by the author (1) on induction of single strand DNA breaks in microwave frequency exposed cells [that of Kesari et al. (52)]. In overall outline, the literature cited in the Report on this topic reflects fairly well this overall much larger literature. There are, however, a number of ways in which the Report is problematic in dealing with this subject. The author has looked up all 22 of these studies to determine from the original papers what the original authors stated.

Scientists often look at genotoxicity because of its importance in carcinogenesis and this section of the Report is part of a larger section on carcinogenesis. However, the Panel of Experts nowhere considers that many of the authors of these studies discuss their own work as strengthening the case that such fields are carcinogenic. A second connection, to male infertility, is also hidden in the report. Two of the positive studies (53, 54) are falsely stated in the Report as being on blood formation but what was actually being studied in both of these studies was testicular sperm formation. The positive study Liu et al. (55) which shows genotoxicity in a spermatocyte cell line may also have implications regarding male infertility, because of the cell type being studied. There is also a connection with male infertility of one of the negative studies (56). This study of effects of mobile phones, found no genotoxic effects on human sperm, but the same group published two earlier studies showing that other EMFs had substantial effects that suggested lowered fertility as a consequence of exposure. The Report cited the Falzone et al. (56) study but not the two earlier studies. Perhaps this is an overreaction, but the Report seems to be hiding studies providing substantial support for the view that these EMFs can substantially impact male fertility and also hiding the implications of many of these studies on carcinogenesis.

There are other aspects of this section that are problematic. The Report listed the Franzellitti et al. (57) study as a negative one but it is not; it reports increased single strand DNA breaks as measured by alkaline comet assays following exposure. The Report accurately lists the Bourthoumieu et al. (58) study as being negative, but that study cites other studies by the same research group using other cell types as being positive; these positive studies are not cited or discussed in the Report. Similarly, the Report correctly lists two studies by Zeni, Sannino and their colleagues as being negative for apparent genotoxicity; however, this same research group published 6 additional studies, with three showing positive effects, depending on the cell type being studied. The Xu et al. (59) study found genotoxicity in two cell types but not in four other cell types. These studies clearly show that different types of cells respond differently to low level microwave exposures, but for some reason, the Panel of Experts seems unable to draw this very important conclusion. The cell type differences are discussed above in relation to the role of VGCCs in producing single strand breaks in cellular DNA (1). Another problematic aspect of this part of the Report, is that it lists seven of the 13 positive studies as studies providing evidence for "genotoxic or epigenetic" changes but none of those seven have anything to do with epigenetics.

We have here 13 (14 actually when the Franzellitti study is added) studies each of which provide clear evidence for genotoxic activity of non-thermal microwave fields and each of which therefore falsify the heating/thermal hypothesis underlying the Report and also falsify current safety standards. Therefore, based on widely accepted scientific standards, the heating/thermal hypothesis and the safety standards should be rejected.

What conclusion does the Panel draw? It concludes that "Extensive in vitro studies have generated inconsistent evidence that RF energy has genotoxic or epigenetic potential". There is, however, no inconsistent evidence whatsoever. When one studies different cell types, different fields with different pulsation patterns, and different end points, even an elementary understanding of biology argues that different results are likely to be obtained. This section of the Report makes very clear on what basis the Panel is inferring "inconsistency". The authors of the Report are simply looking at superficial similarities of studies and falsely inferring that differences should be interpreted as "inconsistencies" or "conflicts", when they are not inconsistent or conflicting at all. The only type of studies that can produce clear evidence of inconsistency are identical studies that produce different results. Neither the Report nor, to my knowledge, its predecessors have provided any examples of such identical studies. Because this inconsistency argument underlies so much of the Report, one can see that this argument and the Report and also the current safety standards are each deeply flawed.

Karl popper and how to assess scientific evidence

What is the responsibility of the Expert Panel as a group of scientists attempting to produce a scientifically defensible Report? Probably the most influential work on this topic comes from the famous philosopher of science Karl Popper. In his work, *Conjectures and refutations*, Popper argues that scientific hypotheses cannot be proven, but they can be falsified (60). Thus science is to be regarded as tentative information that can always be advanced through further research. Falsifying information, information that apparently falsifies a theory, is the most important type of scientific information and needs therefore to be considered very carefully. The next more important type of evidence is what he calls "risky predictions" where one makes a prediction based on a hypothesis, a prediction that is not likely to be made based on any other unrelated hypothesis. Confirmation of such a risky prediction provides substantial support whereas lack of confirmation can again lead to falsifying the hypothesis. Finally, there are confirmatory evidence studies where multiple hypotheses may explain any confirmation and consequently such confirmation is of low scientific significance.

When considered against the Popperian framework, all of the evidence supporting the heating/thermal hypothesis, favored by the Expert Panel (44) is of the third type. It is widely established therefore that a scientific assessment of this area needs to consider in detail each apparently falsifying study and unless each of them can clearly be shown to be deeply flawed, the inference that should be drawn is that the heating hypothesis should be rejected. This rejection is the one aspect of this that may need to be modified in biology, given the inherent complexity of biology. It is possible that rather than rejection, the hypothesis needs instead to be modified in such a way that the information no longer falsifies the new hypothesis. However, in this situation where perhaps thousands of such modifications may be needed because of thousands of apparent falsifying studies, the difference in practice from outright falsification by each study may be trivial. It is clear, in any case that the Expert Panel has completely avoided doing its scientific duty here, failing to assess each of the thousands of apparent falsifying studies, and opting instead, as seen above, to make specious arguments. That is tragic, in my view, failing to protect the health of many Canadians, and indeed others around the world.

Some other aspects

Most of the Report is focused on their heating/thermal interpretation of microwave radiofrequency effects (44). That is, perhaps, not surprising. What is however very surprising, is that having made such a fetish out of the "inconsistencies" in dealing with various topics, nowhere does the Expert Panel consider in this very large section of the Report, the thousands of findings that clearly conflict with their own favorite hypothesis. What sections of data should be thrown out that may be relevant to this section? The Panel of Experts seem to be completely oblivious that if in its view "inconsistencies" are sufficient to throw out many studies in one area, it should have at least a little consistency in dealing with "inconsistencies" in the heart of their own Report.

In the first paragraph in the conclusion section, the Panel of Experts state that (44) "No viable biophysical mechanism has been proposed for carcinogenic effects for exposure below the levels of SC6 that are supported by results in experimental systems," citing three earlier studies but neglecting to consider the VGCC mechanism of microwave EMF action. The VGCC mechanism is clearly a viable biophysical mechanism, because of the properties of the voltage sensor located in the plasma membrane. VGCC activation produces downstream effects including [Ca2+]i elevation, NO elevation and peroxynitrite/oxidative stress/

free radical elevation (1–3), see Figure 1. It has been shown that NO and peroxynitrite/oxidative stress/free radical elevation are central to the mechanism of inflammatory carcinogenesis (61–64), the type of carcinogenesis that occurs in chronically inflamed tissues and therefore causes cancer in such tissues. It follows that it is biophysically and physiologically plausible, that microwave caused VGCC activation may cause cancer via the same mechanisms shown to cause cancer in inflammatory carcinogenesis. It has also been shown that free radicals formed through Compton scattering by ionizing radiation have essential roles in ionizing radiation carcinogenesis (65–67), providing probable mechanistic similarities between microwave EMF carcinogenesis and ionizing radiation carcinogenesis, as well. There have been many arguments made by the advocates of the heating/thermal mechanism of action, emphasizing the correct fact that the individual microwave photons have insufficient energy to perturb the chemistry of our bodies and they infer from this that these photons cannot cause cancer or many other pathophysiological responses. But what the Panel of Experts and others fail to realize is that the microwave fields as a whole, acting through downstream effects of VGCC activation, lead to high densities of intracellular free radicals (Figure 1) and can produce therefore similar effects on the body to those produced by ionizing radiation exposure. In any case, it follows from this paragraph, that the statement, in the Report, that there is no viable biophysical mechanism for low level microwave exposure to cause cancer or other diseases is false, with that falsehood apparently based on the failure of the Panel of Experts to consider the information provided to the panel by the author (Refs. 1 and 3).

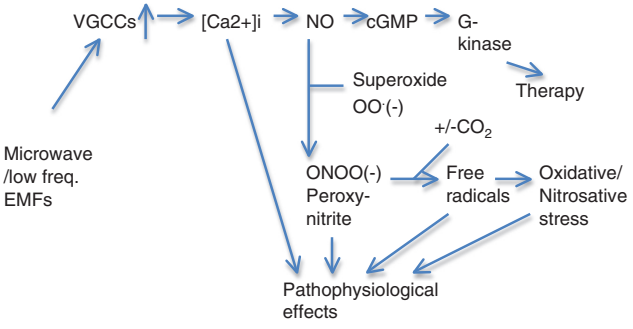

Figure 1: Mechanisms of action for microwave EMFs leading to diverse pathophysiological responses and therapeutic responses. Microwave/lower frequency electromagnetic fields (EMFs) act to stimulate voltage-gated calcium channels (VGCCs), increasing levels of intracellular calcium [Ca2+]i. Elevated [Ca2+]i increases nitric oxide (NO) synthesis which can act along two pathways. The NO signaling pathway, raises cyclic GMP (cGMP) levels and G-kinase activity, producing therapeutic effects. In the other pathway of action of NO reacts with superoxide to form peroxynitrite [ONOO(0)], which either before or after reaction with carbon dioxide (CO_2) can break down to form free radicals, producing oxidative/nitrosative stress. The excessive calcium signaling produced by [Ca2+]i and the peroxynitrite/free radical/oxidative stress pathway each contribute to pathophysiological responses.

This issue of biophysical plausibility of a mechanism for such low intensity exposures is a terribly important one. In the Report, there is a quote from a 2009 Health Canada document, which authors of the Report essentially adopt as their own [p. 78, ref. (44)]; "At present, there is no scientific basis for the occurrence of acute, chronic and/or cumulative adverse health risks from RF field exposure at levels below the limits outlined in Safety Code 6. The hypothesis of other proposed health effects occurring at levels below the exposure limits in Safety Code 6 suffer from lack of evidence of causality, biological plausibility and reproducibility and do not provide a credible foundation for making science-based recommendations for limiting human exposures to lower-intensity RF fields (Safety Code 6)." Whether or not this was a defensible position in 2009, it clearly is not defensible in 2014. This issue of biological/biophysical plausibility is a key one in considering various types of epidemiological evidence, such as were considered in the Report, whenever the role of such stressors in initiating disease is being considered based on studies of groups of people. Hennekens and Buring (68), on p. 40 in their textbook *Epidemiology in Medicine* state "The belief in the existence of a cause and effect relationship is enhanced if there is a known or postulated biologic mechanism by which the exposure might reasonably alter risk of developing disease." Consequently, all of the epidemiological evidence considered in the Report and elsewhere needs to be reconsidered in the light of the biophysical and physiological plausibility of the VGCC mechanism and downstream effects produced by VGGC activation.

Cataract formation as claimed effects of microwave-caused heating

The Report presents a fairly extensive specific case, arguing that microwave exposure produced cataract formation is produced by their heating/thermal mechanism (44). Unlike most other areas of the Report, the Panel considers substantial amounts of the primary literature on this topic. The studies discussed, provide evidence for the third and weakest test, according to Karl Popper's analysis

(60), namely that the exposures studied are mostly within the range that produce substantial tissue heating and may therefore produce both cataracts and lens opacification via heating. This type of evidence is considered to be the weakest of the three types of evidence in Popper's schema, because alternative mechanisms are not in any way ruled out.

What is interesting is that there are three published studies which argue strongly against a heating mechanism for cataract formation by microwave exposures. One of these, a study by Cleary and Mills (69), showed that in comparison with other treatments raising lens temperatures, microwave radiation "appears to exert a unique component of thermal stress in the induction of opacification in the mammalian lens," arguing against a strictly thermal mechanism. Two studies have been published testing in effect the "risky prediction" that microwave-induced cataracts are produced by heating. One of these showed that neither eye-localized or whole-body hyperthermia to 42° produced any cataract-like opacity in the rabbit (70). The other showed that localized eye heating in the rabbit, producing the same temperature for the same duration as cataractogenic microwave exposures, produced no opacity in the rabbit eye (71). Both of these "risky predictions" failed to confirm the prediction and strongly suggest falsification of the hypothesis that microwave-induced cataracts are produced through heating. What is particularly disturbing about the Report is that it fails to cite any of these three studies (44) despite the fact that each of them has been cited by others in this context, according to the Google Scholar database. Clearly, the literature the Expert Panel cites regarding cataract formation, which includes the second most extensive primary literature in the Report, does not provide an objective assessment of the scientific literature in this area.

In contrast to studies discussed in the previous paragraph, the equally "risky prediction" that VGCCs and excessive [Ca2+]i have roles in such cataract formation have produced validation of the hypothesis that microwave-induced VGCC activation causes cataracts. Walsh and Patterson (72) demonstrated that elevated [Ca2+]i in the lens of the frog eye has a central role in cataract formation and that calcium channel blockers, which of course block VGCC activation, can block cataract formation. In a recent review, it was shown that excessive [Ca2+]i in the lens of the human and mammalian eye plays a major role in the opacification process producing cataracts and that VGCCs can have a substantial role in this process (73). While these studies do not directly relate to microwave exposures, they clearly show that excessive [Ca2+]i in the lens of the eye has essential roles in cataract formation and that excessive VGCC activity causes cataract formation in experimental animals. Much of the action of [Ca2+]i in cataract formation has been shown to occur through the action of several calcium receptors that act independently of NO. However, there is also an established role of oxidative stress in cataract formation, and it is thought that peroxynitrite also has a role because of the elevation of a marker for peroxynitrite, 3-nitrotyrosine in cataracts (74). It is likely therefore that microwaves act to produce cataracts via calcium signaling as well as via downstream effects involving peroxynitrite and oxidative stress (see Figure 1). The difference in confirmation of these "risky predictions" clearly shows that the VGCC/[Ca2+]i role in producing cataracts is far better documented than any possible heating role.

It can be seen from the above, that although the Canadian Panel of Experts seems to argue that cataract formation is the strongest example of a strictly thermal EMF response (44), the case for such a thermal mechanism is to the contrary extremely weak. Their case is totally dependent on ignoring both evidence that falsifies their view and also evidence that confirms "risky predictions" of the VGCC mechanism that is ignoring the two strongest types of evidence. Thus the claimed role for heating being the cause of cataract formation following microwave exposure, advocated by the Expert Panel, has now been apparently debunked.

Summary of the report

In summary, then each of the following failures in the Report can be seen to be important in our rejecting its conclusions:

- It fails to individually assess the thousands of studies that provide evidence apparently falsifying their heating/thermal paradigm. By failing to assess studies containing this most important type of evidence, as shown by Popper (60), this failure provides more than sufficient reason to reject the conclusions of the Report.
- The Report fails to provide any "risky prediction" type evidence (the second most important type of evidence) in favor of the heating/thermal hypothesis, but such risky predictions are available supporting the VGCC mechanism of action.
- The Report bases its conclusion on the weakest type of evidence, evidence that some responses could be generated by heating but does not rule out other types of mechanisms. A close examination of what the Expert Panel considers to be the strongest case for heating,

that of cataract formation, shows that this is another example of a probable VGCC mechanism, not heating.
- The Report repeatedly fails to provide an objective assessment of the scientific literature. Because omitted citations consistently have the effect of weakening their position, it seems unlikely that these omissions are just coincidental.
- The Report claims that there is no biophysically viable alternative to the heating/thermal paradigm, a claim clearly shown here to be false.
- The Report claims extensive inconsistencies (what others have called conflicts) occur in the literature, where what it considers "similar" studies produced different results and it uses these claims of "inconsistencies" to throw out large amounts of the literature. However, these "similar" studies are in fact, dissimilar, differing in cell type being studied, the properties of the fields being studied and/or the end point being studied, with each of these having demonstrated roles in determining outcome. It follows that the Report provides no evidence for any such "inconsistencies." Any claims of such "inconsistencies" are at best undocumented.
- The Report fails to use its own inconsistency argument (6 above) in the heart of the report, the part that argues for a heating/thermal mechanism, thus failing to be consistent in its own treatment of this issue.
- The Report fails to give the reader enough information in the Report itself or in the citations provided to allow the reader to assess its scientific merit.

The author is aware that similar flaws to those described immediately above occur in earlier studies arguing for the heating/thermal/SARs mechanism (9–13). But that only emphasizes the fact that this whole point of view has been on extraordinarily weak ground all along. That makes it crucially important that safety standards on which the health of most Canadians and indeed, most people around the world are dependent, be examined in scientifically defensible ways.

It is perhaps surprising that the case developed by the Panel of Experts is so weak. That is especially so because industry-funded research has been skewed in support of the heating/thermal interpretation (45, 46), so one would think that with a lot of industry-supported research, the Expert Panel would have come up with some stronger evidence.

Let me say that it is my opinion that the Panel of Experts may not have been corrupted by industry influence, but rather it may have fallen victim to a common affliction, that of groupthink. Groups of people each carrying misconceptions in common, act to encourage their common misconceptions in other members of the group. What was apparently lacking in the Panel of Experts was someone who could challenge those misconceptions, rather than encourage them. However the "logic" presented in the Report provides industry with a strategy to indefinitely prevent any true scientific standards from being used to assess safety. Industry need only fund research that ends up making "inconsistent" conclusions, thus allowing all independently funded studies to be thrown out because of these "inconsistencies" and thus indefinitely preventing adoption of safety standards based on genuine, independent science. It is my hope and expectation that this was not the goal of the Expert Panel, but it is nevertheless an apparent consequence of their Report, if it is viewed as being scientific.

Still, it can be argued, that the Panel of Experts has perhaps unwittingly fulfilled a very valuable function. By clearly showing how weak their case is in 2014, the Panel has shown that none of the more recent evidence has substantially strengthened their case. It is still based on a false premise (biophysical implausibility of alternative mechanisms) and circular reasoning, it is still based on the failure to consider large numbers of apparent falsifying studies, it is still based on ignoring large amounts of the relevant literature and it is still based on the failure to provide the most well supported types of evidence needed to establish biological mechanisms in medicine, just as was true earlier (9–13). Of course, the weakness of the Panel's case means that the current safety standards are based on quicksand.

How VGCC activation by microwave/RF exposure can produce a variety of important biological responses

Table 1 summarizes how VGCC activation may plausibly produce a wide range of reported responses to microwave and, in some cases, lower frequency EMF exposures. It can be seen that a wide range of reported responses to low level microwave exposures can apparently all be understood as being a consequence of VGCC activation and downstream effects of such activation that were outlined in Figure 1. These can all be seen as "risky predictions" of the VGCC activation mechanism produced by EMF exposures. While these mechanisms support the inference that all of these effects seem to be produced by VGCC activation, that inference must be viewed as being surprising. After all,

Table 1: Apparent mechanisms of action for microwave exposures producing diverse biological effects (see Figure 1).

Reported biologic response	Apparent mechanism(s)	Citation(s)/Comments
Oxidative stress	Peroxynitrite and consequent free radical formation	(1–3); detected via a large number of oxidative stress markers
Single strand breaks in cellular DNA	Free radical attack on DNA	(1, 3)
Double strand breaks in cellular DNA	Same as above	Same as above; detected from micronuclei and other chromosomal changes
Cancer	Single and double strand breaks, 8-nitroguanine and other pro-mutagenic changes in cellular DNA; produced by elevated NO, peroxynitrite	This paper and (3)
Breakdown of blood-brain barrier	Peroxynitrite activation of matrix metalloproteinases leading to proteolysis of tight junction proteins	(3)
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	(3)
Therapeutic effects	Increases in $[Ca]_i$ and NO/NO signaling	(1–3; 13)
Depression; diverse neuropsychiatric symptoms	VGCC activation of neurotransmitter release; other effects? possible role of excess epinephrine/norepinephrine (75)	These were reported in occupational exposures (22); also reported in people living near cell phone towers
Melatonin depletion; sleep disruption	VGCCs, elevated $[Ca]_i$ leading to disruption of circadian rhythm entrainment as well as melatonin synthesis	(3)
Cataract formation	VGCC activation and $[Ca]_i$ elevation; calcium signaling and also peroxynitrite/oxidative stress	This paper
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	(3)

although low level EMF activation of VGCCs is now well-documented, other possible direct targets of EMFs cannot be ruled out, targets that may produce changes that cannot be easily explained as being caused by VGCC activation and downstream effects of such activation. When the apparent mechanisms summarized in Table 1 are put together with the calcium channel blocker studies and other studies on widespread changes in calcium fluxes and calcium signaling following microwave EMF exposures, we are left without any alternative, non-VGCC target of EMF action that currently can be studied for its role in producing biological effects in humans.

Biologically-based EMF safety standards

Hardell and Sage (76), the Scientific Panel on Electromagnetic Health Risks (77) and the author (3) have called for biologically-based EMF safety standards that are based on genuine biologically relevant responses to low-level microwave and other EMFs, rather than SARs. The only approaches we have available for this based on a known biological end point, as shown in the previous section, are approaches based on VGCC activation. There are experimental whole animal approaches based on VGCC activation (3), but my feeling is that initial studies should focus on using cells in culture, cells that have high levels of some VGCCs. Some such studies would use cell lines with such high VGCC levels, such as neuroblastoma 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. (78) and shown to produce changes in calcium fluxes in response to very low level EMF exposures. PC12 cells, a commonly used chromaffin cell line should also be considered for such studies. In addition, it may useful to use cardiac pacemaker cells which have very high activities of VGCCs (35) and can be derived from stem cells (79).

Two approaches suggest themselves for measuring responses of such cells to EMF exposure: Cells in culture could be monitored for NO production using an NO electrode in the gas phase over the culture, both before and following EMF exposure. This approach was used by Pilla in studying effects of pulsed microwave fields (4) in trying to understand the mechanism of microwave therapy. Pilla found that the NO increase in such cultures on EMF field

exposure was almost instantaneous, using a NO electrode in the gas phase (4). With this sort of approach, many different fields can be quickly and easily studied for their ability to produce NO increases, including different frequencies, pulsation patterns and possibly intensities, with the last of these needed to analyze window effects. Different cordless communication devices can be compared for activity using several cell types. 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. Therefore, issues such as reproducibility should be quickly resolved. One might even be able to determine whether previous exposures produce increased sensitivity to exposure, possibly developing a cell culture model of electromagnetic hypersensitivity.

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. 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 [Ca]i levels and cannot be well shielded using a small Faraday cage that does not cage exposures that are to be studied. It is also true that the NO electrode studies are easier to quantify than such fluorescent probe studies. 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 (4) and because it allows easy quantification.

Brief overview

Havas' recent review (80) discusses 14 different documents prepared by international scientists (dated 2002 through 2012) expressing deep concern about various non-thermal effects of microwave radiation exposures and other studies have expressed similar views. W.R. Adey's papers (6, 21) reviewed much of the then current evidence for many non-thermal effects of microwave radiation. But his prescience is most clearly shown by his statement that "Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both extremely low frequency and microwave fields for many neurotransmitters, hormones, growth-regulating enzyme expression, and cancer-promoting chemicals. *In none of these studies does tissue heating appear to be involved causally in the responses*" [italics added, from a talk at the Royal Society of Physicians, London May 16–17, 2002, quoted in ref. (81)]. The recent Herbert and Sage review (81) discusses "the emergence of ever larger bodies of evidence supporting a large array of non-thermal but profound pathophysiological impacts of EMF/RFR in transforming our understanding of the nature of EMF/RFR impacts on the organism." In a second paper (82), Herbert and Sage state that "Our EMF/RFR standards are also based on an outdated assumption that it is only heating (thermal injury) which can do harm. These thermal safety limits do not address low-intensity (non-thermal) effects. The evidence is now overwhelming that limiting exposure to those causing thermal injury alone does not address the much broader array of risks and harm now clearly evident with chronic exposure to low-intensity (non-thermal) effects." The Khurana et al. review (83) states: "The authors reviewed more than 2000 scientific studies and reviews, and have concluded that: (1) the existing public safety limits are inadequate to protect public health; (2) from a public health policy standpoint, new public safety limits on further deployment of risky technologies are warranted based on the total weight of evidence. A precautionary limit of 1 mW/m^2 was suggested ...." The Scientific Panel on Electromagnetic Field Health Risks listed four well-documented central conclusions at the beginning of their publication (77):

- Low-intensity (non-thermal) bioeffects and adverse health effects are demonstrated at levels significantly below existing exposure standards.
- ICNIRP and IEEE/FCC public safety limits are inadequate and obsolete with respect to prolonged, low-intensity exposures.
- New biologically-based public exposure standards are urgently needed to protect public health worldwide.
- It is not in the public interest to wait.

Canadian Panel of Experts do not cite these papers or others providing clear and focused views that contradict the views advocated in the Report, showing again that the Report fails to provide an objective assessment of the scientific literature. The current paper adds a number of specific considerations to the needed debate:

- VGCC activation produces most, possibly even all microwave and lower frequency EMF health-related

responses. Each of the studies on VGCC activation or on changes in calcium fluxes and signaling following low level exposure clearly falsifies the thermal/heating paradigm.
- This VGCC activation mechanism by low level microwave and lower frequency fields, rather than individual photons, is biophysically plausible based on the special properties of the voltage sensor and its localization to lipid region of the plasma membrane.
- Downstream effects of VGCC activation (Figure 1) can generate each of 13 different health effects repeatedly found to be produced by microwave exposure (Table 1).
- Studies document roles of pulsation in influencing biological responses to microwave exposures, influences that are incompatible with these being produced by heating.
- "Window" effects occur, where specific intensities of microwave EMF exposure produce higher biological effects than those produced by both lower and higher intensities, observations incompatible with heating effects.
- Thousands of studies have reported biological effects at intensities well within safety standards, each of which appear to falsify the heating/thermal paradigm, none of which have been considered in this light by the Panel of Experts, despite the scientific requirement to do so under well-accepted scientific principles.
- The claims in the Report that microwave induction of cataracts is produced by heating has been tested in three studies, each contradicting this claim; two of them produce clear falsification, but none of these three studies are cited in the Report. Because VGCC activation can cause cataracts and elevated [Ca2+]i has essential roles in producing cataracts, a VGCC mechanism for microwave-induced cataracts is much more strongly supported than is the claimed heating mechanism.
- The claim in the Report of widespread "inconsistency" in the literature is tested here through examination of the literature cited on genotoxic effects. No inconsistencies were found in this literature despite the Report claiming such. Furthermore, no identical studies are cited anywhere in the Report showing inconsistency of results, these being the only types of studies that can clearly show inconsistency. Claims of widespread "inconsistency" or "conflict" in the literature must be viewed as, at best, undocumented.
- Each of the 8 considerations listed immediately above clearly show that the Report fails to provide anything resembling an objective assessment of the evidence on biological effects of microwave EMF exposures and provides therefore no scientifically valid support for Safety Code 6, ICNIRP or other current safety standards.
- Development of biologically-based safety standards has been called for and approaches to using cell culture-based tests that may be used to develop such safety standards are discussed.

It has been clear for a long time that the heating paradigm is indefensible and that a new paradigm is much needed. We now have that with VGCC activation, and while VGCC activation may not be the entire story behind the biological actions of such EMFs in humans and other mammals, it clearly is most of the story. It is time therefore for a paradigm shift away from strictly thermal effects and toward a central role for VGCC activation in the cellular response to microwave and lower frequency EMFs.

Acknowledgments: I wish to thank Dr. Devra Lee Davis for her many helpful suggestions. Any remaining errors in this are, of course, my own. This paper is dedicated to the memory of W. Ross Adey (1922–2004) whose studies in this area were impressively prescient – someone I regret never meeting.

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