Scientific Evidence Contradicts Findings and Assumptions of Canadian Safety Panel 6: Microwaves Act through VGCC Activation to Induce Biological Impacts at Non-Thermal Levels

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Abstract

The 2014 Report of the Canadian Panel of Experts on Safety Code 6 accepts the ICNIRP safety standards that rest solely on avoiding heating but ignores an important literature on voltage-gated calcium channels (VGCCs) and other calcium-related effects, oxidative stress, nitric oxide and a wide range of other effects that take place at non-thermal levels. Microwave/low frequency electromagnetic fields (EMFs) act via activation of VGCCs to produce biological effects. ICNIRP and other safety standards only consider heating and are contradicted by an extensive literature on RF/MW effects produced at exposure levels well within current safety standards. Pulsed EMFs are often more biologically active than are continuous fields and distinct "window effects" take place with maximum responses at specific exposure levels; both observations contradict current safety standards. Biological responses are also influenced by cell type/physiological state, consistent with the VGCC mechanism. The Canadian Report fails to analyze thousands of studies each of which apparently falsify their position, studies widely considered to be the most important type of scientific evidence. The Report falsely claims that there is no biophysically viable mechanism by which low level effects can occur. The genotoxicity part of the Report falsifies claims of inconsistencies in the literature.
The new VGCC paradigm of microwave action produces plausible and probable mechanisms for microwaves to produce: oxidative stress, therapeutic effects, single and double strand breaks in cellular DNA, cancer, male and female infertility, low melatonin/sleep disruption, blood-brain barrier breakdown, cardiac changes including tachycardia, arrhythmia and sudden cardiac death, diverse neuropsychiatric changes and cataract formation. Cell lines or other cells in culture with VGCCs should be investigated for their responses to microwave and other EMFs, to develop much needed biologically based safety standards.

Key Words: oxidative and nitrosative stress, calcium and nitric oxide signaling, peroxynitrite, excessive calcium effects, calcium channel blockers, voltage-gated calcium channels, low level non-ionizing radiation; microwave/radiofrequency radiation

Running Title: Microwave EMFs act via calcium channel activation, not heating: Critique of Canadian report

EMFs Act via Stimulation of Voltage-Gated Calcium Channels (VGCCs)

Calcium provides an essential role in cell function and homeostasis and serves as a critical gatekeeper of membrane integrity and metabolism. A recent review (1), noted that in 2 dozen studies, calcium channel blocking drugs block a wide range of electromagnetic field (EMF) effects on cells and organisms by affecting voltage-gated calcium channels (VGCCs which are also known as voltage-operated, voltage-dependent or voltage-regulated calcium channels). Because measured effects were significantly lowered by calcium channel blocking drugs, this indicates that activation of these channels accounts, at least in part, for the wide-ranging impacts of EMF effects (1). In most but not all cases, L-type VGCCs were primarily involved. Such VGCC activation is thought to act mainly by increasing intracellular calcium ([Ca2+]i). Other considerations also support VGCCs as a major EMF target, accounting for numerous biological impacts of microwave exposures (2,3) at levels not able to produce substantial changes in temperature.

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 induce measured change in temperature is also supported by a large number of studies reviewed earlier (4,5), showing that elevated intracellular calcium levels follow low level microwave EMF exposures, leading to changes in calcium signaling and calcium efflux. The mode of microwave action via VGCC activation also supports earlier predictions of Panagopoulos et al (6,7) that EMFs, including microwave EMFs, may affect charged amino acid residues that in turn control and activate voltage-gated ion channels. These are biophysical modeling studies (6,7) which support these VGCC findings and also argue that the activation of these channels by microwave and various low frequency EMFs is biophysically plausible. In this mechanism, the fields as a whole rather than individual low energy photons, influence charged amino acid residues that regulate channel activation.

Various frequencies, powers 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 (8-12), should be replaced by one based on VGCC activation of microwave and other EMFs (1-3).

In addition to impacts of EMF directly involving VGCCs, there are a number of other related mechanisms that should be explored. For instance, Pilla reviewed two studies in which microwave EMFs increased calmodulin activation (13). Calmodulin is regulated by intracellular calcium [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 that, there are three other distinct types of observations that also contradict this assumption. As discussed previously (3), an extensive scientific literature that report biological microwave EMF effects at 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 much more biologically active than non-pulsed fields and that certain intensity windows of exposure *are more biologically active 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 (14). Pacemaker cells have a very high density of VGCCs, suggesting that the pulsed microwave exposures may in this study act via VGCC activation. It was shown by Bassett et al (15) and by Pilla (16) both in 1974 studies of augmentation of bone repair, that pulsed field microwaves were much more active than continuous field microwave exposures. Both and Baranski (17) and Czerski (18) showed that microwave pulsed field exposures were more active than non-pulsed fields in terms of their impact on blood forming cells. MicroPulsed field exposures were also more effective than non-pulsed continuous wave (CW) fields in producing a breakdown of the blood-brain barrier (19). Adey's review (20) 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 (that is continuous wave) fields of the same average power density at the same carrier frequency."

Several other studies are cited in the Adey (20) 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 (21) 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 (13). These numerous therapeutic effects are well established to be non-thermal and operate through increased levels of [Ca2+]i and nitric oxide (NO) signaling (2,13). 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 to 48 years ago, such that they 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. 22) for occupational exposure to pulsed field exposures (1 $mWhr/cm^2$, limited to 6 minute 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 U.S., the American National Standards Institute (ANSI) adopted essentially identical standards as had Canada for occupational pulsed field and non-pulsed field exposure (22). In 1970, the Czechoslovakian government adopted more stringent occupational and general public standards for pulsed field exposures vs non-pulsed field exposures (22). 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 don't 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 U.K. 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 (23-31). This again argues against a heating mechanism and these effects are also found at levels where there is extremely low heating. For example, Blackman et al (27) state that "Because of the extremely small increments of temperature associated with positive findings (less that 4 X 10(-4) degrees C), and the existence of more than one productive absorption rate ("*window*"), a solely thermal explanation appears extremely unlikely." Panagopoulos and Margaritis (30) state that "Since there was no detectable temperature increase during exposures, the recorded effects are considered non-thermal." Panagopoulos and Margaritis suggest a role of voltage-gated ion channels stating 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 (23-27), consistent with possible roles of VGCCs. These studies provide strong evidence that these window effects occur at levels where there either no measured change in temperature or extremely low heating.

Perhaps the strongest evidence for non-thermal effects of EMF 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 (32). Studies of pregnant mice, rats and rabbits report that prenatally exposed offspring develop significantly more damage to their eyes, skin and liver (32) 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 U.S., Canadian and international (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.

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 (33) 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 they have 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 general, strong on opinion and weak on evidence (33). Let's 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. Other excluded studies are those 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 they call "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. In fact, as Henry Lai and Devra Davis have documented, conflicting scientific evidence in the field of bioelectromagnetics relating to mobile phones has been carefully cultivated (34), an inference that may also explain the data of Huss et al (35). 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 endpoints 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 (IARC, 2013). In fact, the Report's characterization of the IARC, 2013 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 three prominent reviews on this topic (36-38) 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-shaped dose-response curve.

Another even clearer example where inferences of "inconsistencies" or "conflicts" in the literature have been misconstrued regards 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 as well as 8 studies where they were not. 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. They have limited their considerations to what they call "established health effects" defined in terms of consistent responses of various cell and tissue types (33). Where apparent conflict exists, they have used 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.

The "inconsistency" argument is discussed further below.

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 Refutation*, Popper argues that scientific hypotheses cannot be proven, but they can be falsified (39). 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 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 SARs) hypothesis, favored by the Expert Panel (33) 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/SARS interpretation of microwave radiofrequency effects (33). 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 do they 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 their view "inconsistencies" are sufficient to throw out many studies in one area, they 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 (33) "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 3 earlier studies but neglecting to consider the VGCC mechanism of microwave EMF action. The VGCC mechanism is clearly a viable biophysical mechanism, because it was predicted based on detailed biophysical modeling (6,7) and is based on the activation of VGCC channels by microwave and lower frequency EMFs - the fields as a whole, not the individual low energy photons (6,7). VGCC activation produces downstream effects including [Ca2+]i elevation, NO elevation, and peroxynitrite/oxidative stress/free radical elevation (1-3), see Fig. 1. It has been shown that NO and peroxynitrite/oxidative stress/free radical elevation are central to the mechanism of inflammatory carcinogenesis (40-43), 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 (44-46), 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/SARS 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 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).

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 at their own (p. 78, ref. 33) as follows. "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 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 epidemiological evidence, such as we are 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 (47), 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 plausibility of the VGCC mechanism.

<u>Genotoxicity of Non-Thermal Microwave Exposures</u>

This section, pp 80-82 in the report has a substantial number of citations to the primary literature in this area. It lists 13 citations where studies found genotoxicity following exposure levels, well within safety standards. It also lists 9 citations which they state found no genotoxic effect in each study. While in overall outline, the literature cited reflects fairly well this overall literature, there are 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 consider 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 (Kumar et al, 2013; Atasoy et al 2012/2013; citations in this section are referred to using the format given in the Report and the reader should obtain full citations in (33)) are falsely stated in the report as being on blood formation; what was actually being studied in both of these studies was testicular sperm formation. The positive study Liu et al, 2013 study is on genotoxicity in a spematocyte 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 (Falzone et al 2010). 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 2010 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 2010 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, 2011 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 2013 study found genotoxicity in 2 cell types but not in 4 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 make 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. Another problematic aspect of this part of the Report, is that they list 7 of the 13 positive studies as studies providing evidence for "genotoxic or epigenetic" changes but none of those 7 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/SARs hypothesis underlying the Report and also falsify current safety standards. Therefore, based on widely accepted scientific standards, the heating/thermal/SARs hypothesis and the safety standards should be rejected.

What conclusion does the Panel draw? They conclude 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 its predecessors have provided any examples of such identical studies. Because this inconsistency argument underlies so much of the Report, one can see that the argument and the Report and also the current safety standards are each deeply flawed.

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/SARS mechanism (33). Unlike most other areas of the Report, the Panel considers substantial amounts of the primary literature on this topic. The studies that they discuss, provide evidence for the third and weakest test, according to Karl Popper's analysis (39), 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 (48), 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^{o} produced any cataract-like opacity in the rabbit (49). 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 (50). 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 (33) 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. In a 20 year old study, Walsh and Patterson (51) 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 (52). 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 can have a central and important role in cataract formation in humans and experimental animals. Much of the action of [Ca2+]i in cataract formation has been shown to occur through the action of several calcium receptors, 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 (53). 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 Fig. 1 above). The difference in confirmation of these "risky predictions" clearly show that the VGCC/[Ca2+]i role in producing cataracts is far better documented than any possible heating role with any heating role being highly unlikely.

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 (33), 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.

<u>Summary of the Report</u>

In medicine, whenever one wishes to establish biological mechanism of a disease process, one typically needs to have repeated studies of several different types. Usually, this requires genetic evidence, evidence of specific biochemical/physiological changes in the body and evidence based on effects of presumably specific pharmacological agents. Only when each of these repeatedly support a proposed mechanism and there is no substantial contrary evidence, is is possible to conclude that the proposed mechanism is well supported. In earlier times, other multiple types of evidence were used, such as in Koch's postulates. In recent decades, these three have been most important, with the first and third providing important causal evidence and the second having very strong methodology of genuine physiological changes. However the Report of the Canadian Panel of Experts have provided none of these three types of evidence in support of their claim that microwave/RF EMFs act via their heating/thermal/SARs mechanism and that therefore safety standards can be based on that mechanism nor have they provided evidence of any comparable quality to those three. Therefore those well-accepted standards in the science of medicine allow us to confidently reject their claims.

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

1) It has provided none of the three most important types of evidence usually used to document biological mechanism in the biomedical literature (first paragraph in this section).
2) It fails to individually assess the thousands studies that provide evidence apparently falsifying their heating/thermal/SARs paradigm. By failing to assess studies containing this most important type of evidence provides more than sufficient reason to reject the conclusions of the Report.
3) The Report fails to provide any "risky prediction" type evidence (the second most import type of evidence) in favor of the heating/thermal/SARs hypothesis, but such risky predictions are available supporting the VGCC mechanism of action.
4) The Report bases its conclusion on the weakest type of evidence, evidence that some responses could be generated by heating but do not in any rule out other types of mechanisms. A close examination of what they consider to be the strongest case for heating, that of cataract formation, clearly shows that this is another example of a probable VGCC mechanism, not heating.
5) 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.
6) The Report claims that there is no biophysically viable alternative to the heating/thermal/SARS paradigm, a claim clearly shown here to be false.

7) The Report claims extensive inconsistencies (what others have called conflicts) occur in the literature, where what they call "similar" studies produced different results and they use 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 endpoint being studied, with each of these having demonstrated roles in determining outcome. It follows that the Report provides no evidence for any such "inconsistencies" nor does it provide a logical framework for assessing any supposed "inconsistencies", such that any claims of such "inconsistencies" are at best undocumented.
8) The Report fails to use its own inconsistency argument (7 above) in the heart of the report, the part that argues for a heating/thermal/SARs mechanism, thus failing to be consistent in its own treatment of this subject.
9) 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 in numbers 1-9 immediately above occur in earlier studies arguing for the heating/thermal/SARs mechanism (8-12). 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/SARs interpretation (34,35), 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 they 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 reporting "inconsistent" reports, 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, they have 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 (8-12). Of course the weakness of their 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 widely 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 Fig. 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, 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 (55), the Scientific Panel on Electromagnetic Health Risks (56) and the author (3) have called for biologically-based EMF safety standards, 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 (57) and shown to produce changes in calcium fluxes in response to very low level EMF exposures. Alternatively, it may useful to use cardiac pacemaker cells which have very high activities of VGCCs (58) and can be derived from stem cells (59).

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 (60) 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 (60). Whereas NO is quite unstable in the aqueous phase in biological fluids, when using a limited volume of culture medium, the NO quickly diffuses into the gas phase where it is much more stable, allowing continuous NO electrode measurements to be made. 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 are 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 (60) 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.

Brief Overview

W.R. Adey stated 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, quoted from talk at the Royal Society of Physicians, London May 16-17, 2002, quoted in Ref. 61). The recent Herbert and Sage review (61) 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 (62), 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 Scientific Panel on Electromagnetic Field Health Risks listed four well-documented central conclusions at the beginning of their publication (56):

1) *Low-intensity (non-thermal) bioeffects and adverse health effects are demonstrated at levels significantly below existing exposure standards.*
2) *ICNIRP and IEEE/FCC public safety limits are inadequate and obsolete with respect to prolonged, low-intensity exposures.*
3) *New biologically-based public exposure standards are urgently needed to protect public health world-wide.*
4) *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:

1) 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/SARS paradigm.
2) This VGCC activation mechanism by low level microwave and lower frequency fields, rather than individual photons, is biophysically plausible based on the earlier studies of Panagopoulos et al (6,7).
3) Downstream effects of VGCC activation (Fig. 1) can generate each of 13 different health effects repeatedly found to be produced by microwave exposure (Table 1).
4) The long-standing studies on roles of pulsation in influencing biological responses to microwave exposures, influences that are incompatible with these being produced by heating.
5) The long-standing "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.
6) Thousands of studies have reported biological effects at intensities well within safety standards, each of which appear to falsify the heating/thermal/SARs 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.
7) 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.
8) 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 and questionable.
9) 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.

10) 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.

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

Reported Biologic Response	Apparent Mechanism(s)	Citation(s)/Comments
Oxidative stress	Peroxynitrite & 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	[3] and this paper
Breakdown of blood-brain barrier	Peroxynitrite activation of matrix metalloproteinases (MMPs) 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 (54)	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	This paper

	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	[3]

Figure 1

Mechanisms of Action for Microwave EMFs Leading to Diverse Pathophysiological Responses and Therapeutic Responses


QuickTime™ and a
decompressor
are needed to see this picture.