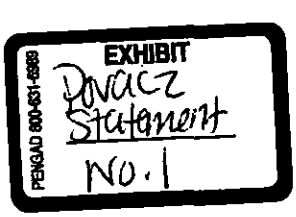
POVACZ STATEMENT NO. 1

BEFORE THE
PENNSYLVANIA PUBLIC UTILITY COMMISSION

Maria Povacz	:	
	:	
v.	:	Docket No. C-2015-2475023
	:	
PECO Energy Company	:	

DIRECT TESTIMONY OF MARTIN L. PALL, Ph.D. ON BEHALF OF COMPLAINANT MARIA POVACZ

April 18, 2016



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DIRECT TESTIMONY
OF
MARTIN L. PALL, Ph.D.

A. INTRODUCTION AND PURPOSE OF TESTIMONY

1. Q. Please state your full name, occupation and business address.

A. My name is Martin L. Pall. I am Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University. My address is 638 NE 41st Avenue, Portland, OR 97232.

2. Q. Please state your professional and educational background and experience.

A. My professional qualifications and experience are set forth in my CV, attached hereto as Appendix A. I would like to emphasize here, several important aspects to my scientific background: I received by B.A. degree in Physics from Johns Hopkins University (with high honors, Phi Beta Kappa), taking much Chemistry and Biology as well as Physics and Mathematics. I received my PhD in Biochemistry & Genetics from Caltech.

3. Q. Have you published any scientific papers?

A. Yes, as of this writing, I have published ninety-nine (99) papers, including five (5) different papers on how low-intensity, microwave frequency electromagnetic fields (EMFs) impact the cells of our bodies and how this leads to multiple health impacts. The first of those papers, published in mid-2013, was honored by being placed on the Global Medical Discovery web site as one of the top medical papers of 2013. That paper has been largely responsible for my being invited and giving 25 different professional talks in part or in whole on health impacts of EMFs in the U.S. and eight (8) European countries. At this writing, the 2013 paper has been

cited 74 different times, according to the Google Scholar database. Based largely on that paper, I have been asked to contribute EMF studies to six (6) special issues of journals, three of which I have accepted, another substantial honor.

4. Q. What is the purpose of your testimony?

A. I am submitting testimony to discuss the health and safety concerns which have arisen in the U.S. because the Federal Communications Commission (FCC) safety guidelines only take into consideration thermal (that is heating) effects of EMFs and therefore do not protect us from non-thermal effects. This limitation of FCC safety guidelines has been confirmed by an Environmental Protections Agency (EPA) document on: http://www.emrpolicy.org/litigation/case_law/docs/noi_epa_response.pdf. This document is included as Appendix B. The failure to address non-thermal effects has been an issue of concern discussed in Appendix C, which comes from: http://apps.fcc.gov/ecfs/document/view?id=7022311506 Additional concerns on this point will be addressed in each of the other sections of my testimony.

B. NON-THERMAL EFFECTS OF EMFS

5. Q. Can you give an overview of the scientific literature on non-thermal effects of microwave frequency EMFs including EMFs from smart meters?

A. There is extraordinarily abundant literature on health-related impacts of non-thermal exposures, going into many thousands of primary literature studies (that is direct empirical studies). I have listed in Appendix D sixty-three (63) different reviews on non-thermal health-related effects that each describe a substantial primary literature ranging from at least a dozen to

over 1000 studies each reporting such non-thermal effects. Among the non-thermal health-related effects that are documented in these 63 reviews are:

1) Widespread different neuropsychiatric effects, including changes in brain structure and function, changes in various types of psychological responses and changes in behavior.

2) At least eight (8) different endocrine (hormonal) effects.

3) Cardiac effects influencing the electrical control of the heart, including changes in electrocardiograms (ECGs) producing arrhythmias, changes that can be life threatening.

4) Chromosome breaks and other changes in chromosome structure.

5) Histological (microscopic) changes in the testes.

6) Cell death (what is now called apoptosis, a process important in neurodegenerative diseases).

7) Lowered male fertility including lowered sperm quality and function and also lowered female fertility (less studied). There are also reports of high levels of spontaneous abortion.

8) Oxidative stress.

9) Changes in calcium fluxes and calcium signaling.

10) Cellular DNA damage including single strand breaks and double strand breaks in cellular DNA and also 8-OHdG in cellular DNA.

11) Cancer, which is likely to involve these DNA changes, but also increased rates of tumor promotion-like events.

12) Therapeutic effects including stimulation of bone growth.

13) Cataract formation (previously thought to be thermal, now known not to be).

14) Breakdown of the blood-brain barrier.

15) Melatonin depletion and sleep disruption.

6. Q. Does this mean that there is a scientific consensus on the existence of each of these fifteen (15) non-thermal health impacts of low-intensity microwave frequency EMFs?

A. This shows that there is very extensive body of scientific literature showing that there are many non-thermal effects produced by low-intensity microwave frequency EMFs. However most of us in science are often focused on one, two or perhaps three aspects of a field of study, so most people are not familiar enough with all of these to judge them all. But what should be clear is that there is a consensus of opinion among independent scientists that there are various non-thermal effects, and that the FCC and other safety guidelines are, therefore deeply flawed, because they only consider thermal effects.

C. FLAWS OF THE FCC SAFETY GUIDELINES

7. Q. Has the scientific community expressed concern regarding the FCC safety guidelines?

A. Yes. It has happened many times. For example, Dr. Magda Havas in Ref.40 of Appendix D, lists fourteen (14) groups of scientists, who between 2002 and 2012 have each expressed deep concern about the current safety guidelines because they are based on only considering thermal effects. There have been several others since 2012, leading up to the 2015 Appeal to the United Nations and Member States, signed by 220 scientists from 41 different countries, which states, in brief, that the current safety guidelines are inadequate because they fail to consider non-thermal effects. These scientists were all active scientists doing research in the area of health-related impacts of microwave frequency EMFs, having published a total of over 2000 peer-reviewed papers in this area. It can be seen from this that there is a consensus

among independent scientists from many countries on both the existence of non-thermal effects and the inadequacy of current safety guidelines, including, of course, the FCC safety guidelines. Further information on the Appeal can be found at: http://www.icmfa.org/emf-scientist-appeal-to-the-united-nations/

8. Q. Do you believe the FCC is biased in favor of industry?

A. Yes. For instance, Thomas Wheeler, who previously headed the CTIA, the wireless telecommunications industry lobbying organization, is the Chairman of the FCC. Furthermore, the Harvard University Safra Center for Ethics, published a long document written by Norm Alster, entitled "Captured Agency: How the Federal Communications Commission (FCC) Is Dominated by the Industries It Presumably Regulates." The full text of this document, with citations, can be obtained from: http://ethics.harvard.edu/files/center-for-ethics/files/capturedagency_alster.pdf *and is also provided as Appendix E. It describes the* revolving door between the telecommunications industry and the FCC (Mr. Thomas Wheeler is only one example). Hundreds of meetings occur each year between telecom industry representatives and the FCC. There is a diverse and substantial case arguing that the FCC and other U.S. government agencies have been essentially co-opted by the wireless telecommunications industry.

9. Q. Why is this important?

A. This is important because PECO relies on the FCC safety guidelines to argue that its smart meters are safe for customers. *See*, Appendix L (answers to Povacz Interrogatories, Set I). In fact, there is no scientific basis for this conclusion.

10. Q. Are there examples of studies that support the view that only thermal effects should be considered?

A. Yes. The latest example of such a study is the 2014 Report of the Canadian Panel of Experts on Safety Code 6 (2014 Canadian Report), which argues that only thermal effects need be considered when setting guidelines or safety standards for microwave EMF exposures.

11. Q. What is your opinion of the 2014 Canadian Report?

A. I published a critique of the 2014 Canadian Report in a peer-reviewed paper (pp.104-110 of my 2015 Reviews on Environmental Health paper (Appendix F)). It seemed to me that as the most recent of such reports supporting only thermal effects, it should have the strongest evidence and arguments for that point of view. However, the Report fails to individually assess the thousands of studies each containing evidence that apparently falsifies their thermal/heating paradigm. The Report fails to provide any "risky prediction" type of evidence – the second strongest type of evidence - in favor of its point of view. The Report bases its conclusions on the weakest type of evidence – evidence that something could be caused by heating but in no way rules out other interpretations. The only specific area that the Report claims to be thermal, that of cataract formation, the Report fails to cite three studies each of which clearly show that cataract formation is not thermal; they also fail to consider the voltage-gated calcium channel (VGCC) mechanism, explained further below, which provides a much stronger explanation for cataract formation. The Report claims there is no biophysically viable alternative mechanism to its thermal paradigm, a claim shown to be false elsewhere in the paper. The Report claims widespread inconsistencies in the literature, but in the only area where it attempts to document this, the area of genotoxicity (cellular DNA damage), there are no inconsistencies to be found in

their cited literature. The Report fails to use its own inconsistency argument in the heart of the Report, the part that argues for a strictly thermal mechanism, where the Report should consider the thousands of studies that individually argue against its point of view. The Report fails to give the reader enough information in the Report or in the literature cited therein, to allow the reader to assess its scientific merit.

12. Q. Do you have anything positive to say about the 2014 Canadian Report?

A. I concluded, later, that "Still, it can be argued, that the Panel of Experts (authors of the Report) 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 (Refs deleted). Of course, the weakness of the Panel's case means that the current safety standards are based on quicksand." See, Appendix F.

D. BIOLOGICAL EFFECTS OF LOW-INTENSITY EMFS

13. Q. Before getting into your own mechanism of action for EMFs, are there other types of evidence that should influence our understanding of the health-related impacts of low-intensity microwave frequency EMFS?

A. There are four of them. Let's start with the one that has probably the most relevance with regard to understanding the impact of smart meters. Pulsed microwave frequency EMFs

are, in most cases, much more biologically active than non-pulsed EMFs. There is an extensive body of scientific literature on this that goes back at least to 1960 and includes many studies. This effect of pulsations was important in that therapeutic studies of microwave EMFs have standardized on the use of pulsed EMFs, with this standardization being adopted at the end of the 1970s; this is still being followed now, over 35 years later. Around that same time period, three countries; Canada, the U.S. and Czechoslovakia each adopted different safety standards for pulsed EMFs as opposed to non-pulsed (also known as continuous wave) EMFs, recognizing this difference. I reviewed much of this literature on pp. 101-102 of Appendix F. Other authors have also documented this in various reviews, including numbers 1, 3, 55 and 57 in Appendix D. Review 57 inferred that the more complex the pulsation pattern, the more biologically active it is likely to be. This may be right, but in my view it is premature to infer this based on the available data. This whole issue is terribly relevant to smart meters which can be seen to put out very sharply spiked pulses, as shown by Dr. Karl Maret in this slide presentation: https://vimeo.com/132039697. It is not uncommon for industry to average smart meter exposure intensities over the time during which communication is occurring; or much worse, over much longer time periods when most of the time nothing is happening. Not only is such averaging highly misleading, it may well be the case that the sharp spikes seen in the video may produce the bulk of the biological effects. There were three (3) studies discussed in my 2013 EMF paper (Appendix G), in which extremely short, nanosecond pulses produced biological effects via the same mechanism that I have shown is activated by other microwave/lower frequency EMFs.

14. Q. What are the other three other factors that influence EMF biological effects?

A. One of them is that there are what have been called exposure windows, where exposures within an exposure window to a specific type of EMF produce maximum biological

effects, whereas exposure levels that are ***either lower or higher*** produce lower biological effects (reviewed in review 55 and 56 in Appendix D). The consequence of this is that biological dose-response curves can be extremely complex such that predicting such biological responses is not currently possible – one needs direct empirical studies to measure actual effects. One consequence of this is that dose-response curves are not only non-linear, they are also non-monotone (that is biological effects do not always increase with increasing exposure). Industry often assumes monotone dose-response relationships (that is it assumes that higher doses always produce higher effects) but this is, then, a false assumption. There are also frequency effects (reviewed in review 55 in Appendix D). And there are also effects of polarization of EMFs (see review 55, 63). All artificial EMFs produced electronically are polarized which gives them special properties. Among those properties (review 63) is that these polarized EMFs produce larger electrical forces on charged groups. When these polarized EMFs reflect off of smooth surfaces, they can produce what is called constructive interference, producing unusually high intensities (review 63). Most such polarized EMFs are linearly polarized, but circularly polarized EMFs can also occur; there are examples where a clockwise circularly polarized EMF produced very different biological effects from an identical EMF but with counterclockwise circular polarization. You can see, then, some of the complications seen when trying to predict biological effects of such EMFs.

15. Q. How do these factors influence industry's predictions of EMF effects?

A. Industry's predictions of EMF effects are flawed. It is very common for industry-linked people to make predictions of relative biological effects of EMFs with a particular frequency and different intensities based on frequency and intensity alone. Most commonly they make the flawed prediction that higher intensities always produce higher effects. The current

impossibility of making predictions based solely on frequency and relative intensity can be clearly seen because of the effects of pulsation patterns, window effects and polarization.

E. THE MECHANISM FOR BIOLOGICAL EFFECTS OF EMFS

16. Q. How do microwave and low-frequency EMFs act to produce biological effects?

A. *Microwave and lower frequency EMFs act via activation of voltage-gated calcium* channels in cells.

17. Q. Can you explain this conclusion?

A. I have made this conclusion in five (5) of my papers (Appendix F, G, H, I and J), with Appendix G, the first to be published (in 2013). What has been found now in 26 different studies, is that biological effects of EMFs can be blocked or greatly lowered by calcium channel blockers, drugs thought to be highly specific for blocking voltage-gated calcium channels (abbreviated VGCCs). These include not only prolonged exposure to microwave frequency EMFs, but also nanosecond microwave pulses as well as exposures to extremely low frequency EMFs such as 50 Hz and 60 Hz exposures from our power wiring and even static electrical fields and static magnetic fields. There are five (5) different types of calcium channel blockers that have been used in these studies, each structurally distinct from the others and each acting on a different site on the VGCC proteins. There is no known or even postulated mode of action for these five (5) classes of calcium channel blockers that can explain their action here other than that they are acting to block voltage-gated calcium channels. It may be concluded from this that these various EMFs each act to activate voltage-gated calcium channels, such that their effects are blocked or greatly lowered by calcium channel blockers. Furthermore it has been found that when several effects of EMF exposures have been examined, when one is blocked or greatly

lowered each of the others examined are also blocked or greatly lowered. This argues that VGCC activation by EMFs is a very general mechanism of action, not just one that is involved in producing only a few of the consequences of EMF exposure.

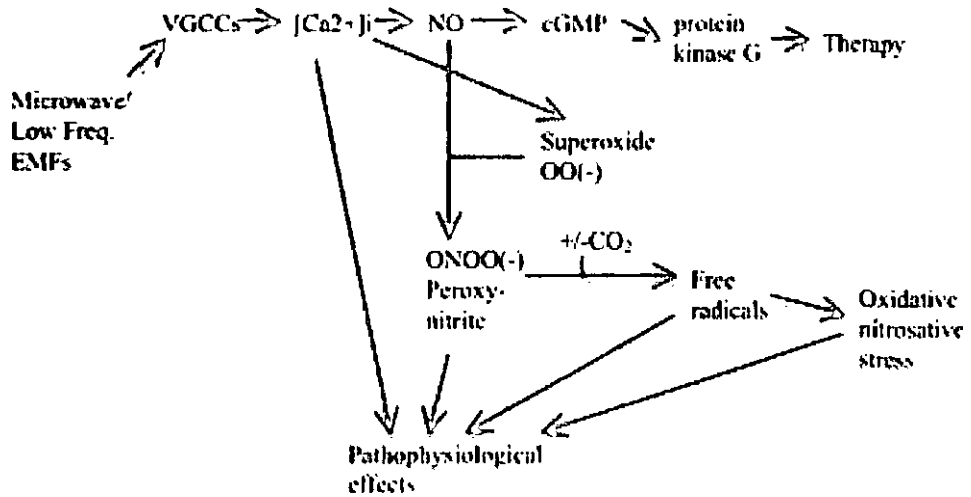
18. Q. Are there other studies that support your conclusions?

A. Yes. As an example, Dr. Arthur Pilla published an important paper in 2012, showing that cells in culture exposed to a pulsed microwave EMF produced an almost instantaneous (less than five (5) seconds) activation of calcium/calmodulin dependent nitric oxide (NO) production; this almost instantaneous response argues that EMFs act directly to produce VGCC activation rather via some indirect mechanism which would require much more time. There are hundreds of studies (reviewed in reviews 7, 9, 11 in Appendix D) showing changes in calcium fluxes and calcium signaling following EMF exposure, that can be explained as being due to VGCC activation.

19. Q. Are the effects of low-intensity EMFs direct or indirect?

A. Activation of VGCCs by low-intensity EMFs is direct. Health impacts of low-intensity EMFs are indirect. A wide range of reported EMF effects can be explained as being

produced by indirect (downstream) effects of EMFs, as shown in Figure 1, below:



It can be seen from Figure 1, that EMFs activate the VGCCs such that the activated channels in the plasma membranes of cells allow calcium ions to flow into the cell from outside, increasing intracellular calcium levels [Ca2+]i. All of the effects diagrammed here follow from the increases in [Ca2+]i. These include increases in nitric oxide (NO) and the NO signaling pathway (across upper right) leading to therapeutic effects (see Appendix H). Pathophysiological (disease-causing) effects are produced both by NO reacting with superoxide to form peroxynitrite, free radicals and oxidative stress (lower right). Pathophysiological effects can also come from excessive calcium signaling from excessive [Ca2+]i. Figure 1 is discussed further below.

20. Q. How do low-intensity EMFs activate the VGCCs?

A. The voltage sensor of the VGCC has a key role here. The voltage sensor is the structure that normally detects electrical changes across the plasma membrane in cells, detects those electrical changes and opens the channel in response to them. It is reasonable, therefore, to

assume that this is likely to be the structure that detects and responds to electrical forces placed upon it by the low-intensity EMFs.

21. Q. *How do you respond to the claim that low-intensity EMFs are too weak to produce biological effects?*

A. Industry has been arguing for over two decades, that the forces produced by these low intensity EMFs are too weak to produce biological effects. (Note: This is discussed in substantial detail and shown to be incorrect on pp. 102-104 of Appendix F.) The argument made by industry has two parts to it. Industry acknowledges that EMFs can place electrical forces on either positively or negatively charged chemical groups. But it also argues that: (1) Such forces will be swamped out by random thermal movement of atoms and molecules that occurs at normal body temperatures; (2) Industry argues that the forces placed on such charged groups by these low-intensity EMFs are too weak to produce biological changes. The voltage sensor has twenty (20) different positively charged groups, with five (5) charges on each of four (4) alpha helixes each located in the lipid bilayer of the plasma membrane of the cell. These charges all need to be pushed or pulled approximately perpendicular to the direction of the plasma membrane in order to open the channel. Such coordinated highly directional forces can be produced both by the charge across the plasma membrane and by the EMFs. <u>However, thermal motion will be ineffective because thermal motion is random in three dimensions</u>. Furthermore, the forces on the voltage sensor are predicted to be much larger than the forces on singly charged groups elsewhere in the cell (these are essentially all in the aqueous phase of the cell). One section of the law of physics known as Coulomb's law, predicts that forces on charged groups are inversely proportional to the dielectric constant of the medium in which those charged groups occur. The dielectric constant of the lipid bilayer section of the membrane is about $1/120^{th}$ of the

dielectric constant of the aqueous phase of the cell. This causes the forces placed on the charged groups of the voltage sensor to be about 120 times higher than assumed by industry.

22. Q. Is there another factor which produces even larger increases in the forces on the voltage sensor?

A. Yes. The plasma membrane has a very high electrical resistance whereas the aqueous phases in the cell and in the extracellular fluid are highly conductive because of the polar nature of water and the salts dissolved in those aqueous phases. Because of this difference, the electrical forces across the very thin, four nanometer (4 nm) thickness of the plasma membrane are estimated to be concentrated about 3000-fold. Therefore the electrical forces on the charges of the voltage sensor are estimated to be increased by another factor of about 3000. Consequently, in comparing the electrical forces on the VGCC voltage sensor with those on singly charged groups in the aqueous phase of the cell, the forces on the voltage sensor are approximately: 20 (for the number of charges in the voltage sensor) X 120 (dielectric constant effect) X 3000 (for the electrical amplification across the plasma membrane) = 7.2 million times stronger. It follows from this that industry calculations of force on the actual biological target of the EMFs are low by a factor of about 7.2 million.

23. Q. Why is this important?

A. This is important for three reasons: (1) Rather than the physics arguing against these non-thermal health effects, as claimed by industry, the physics actually argues strongly for the actual target of the low-intensity EMFs, the VGCC voltage sensor. (2) This provides further confirmation that the VGCCs are the main target low-intensity EMFs. (3) The safety guidelines are based on heating, and heating is produced mainly by forces placed on singly charged groups

in the aqueous phase of the cell; it follows that the safety guidelines are allowing us to be exposed to EMF intensities that are approximately 7.2 million times too high. The vast majority of the human population on earth is being exposed to these EMFs based on safety guidelines that are terribly far off from where they need to be and the consequences for all of humanity are tremendous.

24. Q. How can these various reported health impacts of low-intensity EMFs be generated by VGCC activation?

A. This mechanism is explained in Figure 1, above. Below is a listing of plausible mechanisms of action for microwave exposures producing diverse biological effects.

Table 1. Plausible Mechanisms of Action for Microwave Exposures Producing Diverse Biological Effects

Reported Biologic Response	Apparent Mechanism(s)
Oxidative stress	Peroxynitrite & consequent free radical formation
Single strand breaks in cellular DNA	$OH^{\cdot}$ and other free radical attack on DNA backbone.
Double strand breaks in cellular DNA	Same as above
8-OHdG in cellular DNA	$OH^{\cdot}$ and other free radical or oxidant attack of guanine base in DNA
Cancer	Single and double strand breaks, 8-OHdG and 8-nitrodG pro-mutagenic changes in cellular DNA; produced by elevated NO, peroxynitrite; tight junctions help prevent tumor promotion, but peroxynitrite-mediated AP-1 activation leads to increased matrix metalloproteinases (MMPs) synthesis leading, in turn, to proteolysis of tight junction proteins; oxidant/free radical activation NF-kappaB leads to inflammatory cytokine increases, leading in turn to increased protein kinase C, which acts in many cell types to cause tumor promotion; most of these mechanisms of carcinogenesis are similar or identical those found in inflammatory carcinogenesis
Breakdown of blood-brain barrier	Peroxynitrite-mediated AP-1 activation leads to increased matrix metalloproteinases (MMPs) synthesis leading, in turn, to proteolysis of tight junction proteins

Male and female infertility	Induction of double strand DNA breaks; Other oxidative stress mechanisms; [Ca2+]i mitochondrial effects causing apoptosis; in males, breakdown of blood-testis barrier
Therapeutic effects	Increases in $[Ca]_i$ and NO/NO signaling via protein kinase G
Depression; diverse neuropsychiatric symptoms	VGCC activation of neurotransmitter release; other effects including peroxynitrite pathway; possible role of excess epinephrine/norepinephrine
Melatonin depletion; sleep disruption	VGCCs, elevated $[Ca]_i$ leading to disruption of circadian rhythm entrainment as well as melatonin synthesis
Cataract formation	VGCC activation and $[Ca]_i$ elevation; calcium signaling and also peroxynitrite/oxidative stress action on the proteins of the lens of the eye
Tachycardia, bradycardia, arrhythmia, sometimes leading to sudden cardiac death; also heart palpitations	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; heart palpitations may also involve activation of voltage-gated potassium channels
Hormone (endocrine) effects	Release of many hormones is controlled by VGCC activation & [Ca2]i; This initially leads to large increases in hormone secretion but can over time "exhaust" the endocrine cells, leading to very subnormal secretion
Steroid hormones	Steroid hormones are not controlled as described above, but their synthesis via cytochrome P450s can be inhibited by NO
Apoptosis (programmed cell death)	Can be produced by elevated levels (within a certain range) of Ca2+ in the mitochondria; can also be produced by cellular DNA changes including 8-OHdG.

These health effects attack each of the four things that we most value as individuals and as a species: (1) They attack our health; (2) they attack our brain function; (3) they attack the integrity of our genomes; and (4) they attack our ability to produce healthy offspring.

25. Q. Is there evidence of cumulative effects of low-intensity EMF exposures?

A. Yes. There are four (4) types of studies, each of which supports the view that there are cumulative effects of low-intensity EMF exposures, each dealing with different time frames. Two of these types of studies were performed in humans, two others in rodents. In the U.S. NASA review published in 1981 (review #8 in Appendix D), there were three human

occupational exposure studies where humans were exposed to a particular level and type of non-thermal EMF exposure over time and the effects were studied over two time periods. In each of these three studies, there was a substantial increase in severity of effects with increasing time. In the Tolgskaya and Gordon document (review # 3 in Appendix D) there were numerous rodent (mostly rat) studies where it was found that relatively brief exposure (often circa a month) produced modest changes in brain structure, changes that were reversible by simply removing the exposures. However, with increasing time of exposure, the effects on brain structure became more and more severe with time and these more severe effects became irreversible. In the Magras and Xenos 1997 study (RF radiation-induced changes in the prenatal development of mice. Bioelectromagnetics. 1997;18(6):455-61), mating pairs of mice were put in small cages at ground level in two locations in an antenna park. Both locations were locations where exposures were well within current safety guidelines. It takes about a month for mice to go through gestation. At the higher exposure site, the pairs of mice successfully produced two litters, albeit with decreasing numbers of progeny in the second litters; after that the mice were completely sterile. At the lower exposure site the mouse pairs successfully produced 4 litters, again with decreasing numbers of progeny over time; after that they were completely sterile. None of these progressive declines in fertility should have happened if our safety guidelines had any scientific merit whatsoever. It can be seen from these studies that there is substantial evidence for cumulative health effects of low-intensity intensity EMFs. A fourth type of study, on headaches caused by cell phone usage, was discussed in Appendix I, which referred to three primary literature citations plus a review that considered earlier literature studies. People develop headaches during or following long cell phone conversations. These headaches develop on the side of the head where the cell phone is used and with most people, they only develop after long

(typically over one hour) cell phone continuous conversations. The side of the head on which the headaches develop provides strong evidence for causality of cell phone usage and the length of continuous cell phone usage time required before headaches occur in most people argues strongly for cumulative effects.

F. HEALTH EFFECTS OF SMART METERS

26. Q. What are the effects of smart meters on human health?

A. Smart meters have only been investigated for health effects twice, to my knowledge; once in Australia (Lamech, 2014 in Appendix I) after they were deployed there, and once in the U.S. (Conrad, 2013 in Appendix I), also after they were deployed here. Both studies showed multiple neuropsychiatric effects, similar to those produced by other types of low-intensity microwave frequency EMFs and both were cited in my neuropsychiatric paper (Appendix I). The Australian study also found cardiac effects (these have also been reported in many human and animal studies following low-intensity EMF exposure).

In the U.S. study the following information was provided about the smart meter involved:

10. What was the Brand/Manufacturer of the closest Electric smart meter?

Value	Count	Percent %
Don't know or n/a	89	42.4%
Itron	24	11.4%
Landis+Gyr	22	10.5%
Other Brand	16	7.6%
GE	15	7.1%
Centron (Itron)	12	5.7%
Sensus	11	5.2%
Elster	9	4.3%
OpenWay (Itron)	6	2.9%
ABB	2	1.0%
Schlumberger (Centron)	2	1.0%
Tantalus	1	0.5%
Westinghouse	1	0.5%
Siemens	0	0.0%

11. What was the TYPE of the closest Electric smart meter? AMI = Advanced Metering Infrastructure type of meter (data automatically sent to utility), AMR = Automated Meter Reading type of meter (data read remotely by reader from vehicle or on foot)

Value	Count	Percent %
AMI	113	53.8%
AMR	20	9.5%
Other	6	2.9%
Don't know or n/a	71	33.8%

Statistics	
Total Responses	210
Skipped	0
Unanswered	0

Table 2 – Comparison of health symptoms from smart meter and cell phone antenna studies.

Neuropsychiatric study Appendix I	**Conrad 2013 U.S. smart meter study**	**Lamech 2014 Australian smart meter study**	**Santini 2003 cell phone antenna exposures**
Sleep disturbance/ insomnia Headache Fatigue/tiredness Depression/depressive symptoms Dysesthesia (vision/ hearing/olfactory dysfunction) Concentration/attention /cognitive dysfunction Dizziness/vertigo Memory changes Restlessness/tension/ anxiety/stress/ agitation/feeling of discomfort Irritability Loss of appetite/ body weight Skin tingling/burning/ inflammation/ dermographism Nausea	Fatigue Insomnia Concentration attention difficulty Headache Agitation Dizziness Ear ringing, tinnitus Head pressure Eye, vision Numbness Skin tingling, burning	Insomnia Headache Tinnitus Fatigue Cognitive disturbances Dysesthesias (abnormal sensation) Dizziness	Fatigue Irritability Sleep disturbance Headache Memory loss Depressive symptoms Memory loss Concentration difficulty Feeling of discomfort Skin problems Visual disturbance Dizziness Nausea
Not included	Tachycardia, arrhythmia, high and low blood pressure	Not studied	Cardiovascular problems

28. Q. How are smart meter health effects similar to other non-thermal microwave exposure effects?

A. The many different neurological/neuropsychiatric effects and the cardiac effects found from smart meter exposure are similar to effects reported following many different non-thermal microwave exposures, giving increased credence to these observations following smart meter exposure.

29. Q. How are individuals with electromagnetic hypersensitivity (EHS) affected by smart meters?

A. The U.S. smart meter study also strongly suggests that electromagnetic hypersensitivity (EHS), which they call ES, also appears to be greatly exacerbated by smart meter exposures. Table 2 above shows a variety of neurological, neuropsychiatric and cardiac effects of exposure to smart meters. These effects are similar to those experienced by people living near cellular antennae.

30. Q. Have the health effects of smart meters been studied sufficiently?

A. More studies on the health effects of smart meters are needed. In my view, it was completely irresponsible for PECO and other companies to deploy these smart meters without even a single biological safety study being done. That is not unique to smart meters, of course. No wireless communication devices are tested biologically for safety before they are foisted on or marketed to an unsuspecting public.

31. Q. What is your opinion about electromagnetic hypersensitivity (EHS)?

A. I have prepared a document on EHS (Appendix K). All of my opinions on the probable mechanism of EHS are presented in that document.

32. Q. Can Maria Povacz' EHS symptoms be caused by smart meter exposures?

A. Maria Povacz reports being very healthy until approximately September 2012 when AMI smart meters were installed at her neighbor's house (10-12 feet away), near her home and throughout her neighborhood. She reports the following symptoms developed rapidly after that

time and continue today: Buzzing in the ears, lack of sleep, exhaustion, headache, visual disturbances, fatigue, heart palpitations, widespread pain, severe lethargy, memory loss and lack of concentration. There is a striking similarity between her symptoms and those found in the two smart meter studies, the one from the U.S. and the one from Australia, described in Table 2. She also reports suffering from severe endocrine problems including thyroid dysfunction and adrenal exhaustion. This sort of endocrine exhaustion was described in reviews 2 and 3 in Appendix D, as well in Table 1 above. Furthermore, the U.S. smart meter study reported large numbers of people developing EHS following smart meter installation. Maria Povacz reports developing a severe case of EHS, following smart meter installation. The evidence in the previous two sentences as well as in Appendix K provides strong evidence, in my opinion, that here EHS case was caused by the PECO smart meter. In summary, then, the evidence presented here, provides for a very strong inference, in my opinion, that most, if not all, of Maria Povacz' symptoms were caused by smart meter installation in her neighbor's home and all around her.

33. Q. Does that conclude your direct testimony?

A. Yes.

APPENDIX A

NAME: Martin L. Pall **DATE:** Nov. 2015

martin_pall@wsu.edu
Phone: 503-232-3883

EDUCATION
Institutions, degrees, dates

Organization and Location	Degree	Date
Johns Hopkins University Baltimore, MD	B.A.	1962
California Institute of Technology, Pasadena, CA	Ph.D.	1968

EXPERIENCE
Positions and dates

Reed College, Portland, OR	1967-72	Assistant Professor of Biology
Department of Botany, Indiana University, Bloomington, IN	May-June 1971	Visiting Research Associate
Program in Genetics and Department of Chemistry, Washington State University, Pullman, WA	9/16/72-9/156/75	Assistant Professor of Genetics and Chemistry
Program in Genetics and Program in Biochemistry/Biophysics, Washington State University, Pullman.WA	4/12/73	Elected to Graduate Faculty in Genetics and Biochemistry
	9/16/75-1/31/81	Associate Professor of Genetics and Biochemistry
Program in Genetics, Washington State University, Pullman, WA	9/16/78-9/15/79	Acting Chairman, Program in Genetics
Department of Physiology, Yale University, New Haven, CT	9/16/79-9/15/80	Visiting Associate Professor (during professional leave)
Departments of Genetics and Cell Biology and Biochemistry/Biophysics, Washington State University, Pullman, WA	2/1/81-9/15/83	Associate Professor of Genetics and Cell Biology and Biochemistry
	9/16/83-8/15/96	Professor of Genetics and Cell Biology and Biochemistry
Department of Pharmacology, University of California, San Francisco, Ca	5/15/86 12/31/86	Adjunct Professor of Pharmacology (professional leave)

Washington State University, Vancouver, WA	8/16/94-5/16/96	Coordinator of Sciences
Department of Biochemistry/Biophysics and Basic Medical Sciences Program	8/16/96-99	Professor of Biochemistry and Basic Medical Sciences
School of Molecular Biosciences and Basic Medical Sciences Program	8/16/99-8/15/08	Professor of Biochemistry and Basic Medical Sciences
Professor Emeritus of Biochemistry and Basic Medical Sciences, WSU and Research Director, The Tenth Paradigm Research Group, Portland, OR	8/15/08-	

CURRENT WEB SITE:
thetenthparadigm.org

HONOR SOCIETIES

Phi Beta Kappa
Alpha Epsilon Delta
Sigma Xi
Member of Panel of Advisors of Environmental Law Centre in London
Clinician of the Month, Healthcomm International (October, 1999),
Member Scientific Advisory Board of Ariston Pharmaceuticals

PROFESSIONAL SOCIETIES AND OTHER HONORS
American Society of Biochemistry and Molecular Biology
International Association for Chronic Fatigue Syndrome

RECENT HONORS REGARDING ENVIRONMENTAL MEDICINE:

1. 2005: Pall was appointed to the Advisory Board of the Environmental Law Centre in London.
2. May 2008: Pall was the only person from outside of Europe, invited to address a special session of the European Union Parliament ("Council of Nations") as an "Expert" in Environmental & Health.
3. 2009: Pall was chosen from all scientists in the world to write an authoritative review on Multiple Chemical Sensitivity for General and Applied Toxicology, 3rd Edition.
4. April 2010: Pall was appointed as "life time, honorary ambassador and member of the Scientific Advisory Board of the International Society for Applied Preventative Medicine (I-GAP)."
5. May 2010: Pall was the meeting honoree at the Fundacion Alborada meeting in Spain, only the second time such an honoree had been chosen.
6. September 2010: Pall was the only person from outside of Europe invited to address a special meeting at the National Institute of Health in Rome on Environmental Medicine.
7. 2012 and onward. Pall was chosen to be a founding faculty member of the new Environmental Medicine Faculty in Italy. He started in that function in March 2013.
8. 2013: Chosen to be the Jonathan Forman award recipient, the highest award given by the American Academy for Environmental Medicine.
9. Publication #89 was honored by inclusion at the "Global Medical Discovery" as one of the top medical publications of 2013.

10. One of two keynote speakers for the Building Biology Conference, (International Institute for Building Biology & Ecology) Bainbridge Island, WA 2015 and voted the favorite speaker at the meeting by meeting participants.

Publications from 2001:

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APPENDIX B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 8 2002

OFFICE OF
AIR AND RADIATION

Janet Newton
President
The EMR Network
P.O. Box 221
Marshfield, VT 05658

Dear Ms. Newton:

Thank you for your letter of January 31, 2002, to the Environmental Protection Agency Administrator Whitman, in which you express your concerns about non-thermal effects of radiofrequency (RF) radiation and the adequacy of the Federal Communications Commission's RF radiation exposure guidelines. The Administrator has asked us to critically examine the issues you bring to our attention, and we will be responding to you shortly.

We appreciate your interest in the matter of non-thermal RF exposure, possible health risks, and Federal government responsibility to protect human health.

Sincerely,

Frank Marcinowski, Director
Radiation Protection Division

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 16 2002

OFFICE OF
AIR AND RADIATION

Ms. Janet Newton
President
The EMR Network
P.O. Box 221
Marshfield, VT 05658

Dear Ms.Newton:

This is in reply to your letter of January 31, 2002, to the Environmental Protection Agency (EPA) Administrator Whitman, in which you express your concerns about the adequacy of the Federal Communications Commission's (FCC) radiofrequency (RF) radiation exposure guidelines and nonthermal effects of radiofrequency radiation. Another issue that you raise in your letter is the FCC's claim that EPA shares responsibility for recommending RF radiation protection guidelines to the FCC. I hope that my reply will clarify EPA's position with regard to these concerns. I believe that it is correct to say that there is uncertainty about whether or not current guidelines adequately treat nonthermal, prolonged exposures (exposures that may continue on an intermittent basis for many years). The explanation that follows is basically a summary of statements that have been made in other EPA documents and correspondence.

The guidelines currently used by the FCC were adopted by the FCC in 1996. The guidelines were recommended by EPA, with certain reservations, in a letter to Thomas P. Stanley, Chief Engineer, Office of Engineering and Technology, Federal Communications Commission, November 9, 1993, in response to the FCC's request for comments on their Notice of Proposed Rulemaking (NPRM), Guidelines for Evaluating the Environmental Effects of Radiofrequency Radiation (enclosed).

The FCC's current exposure guidelines, as well as those of the Institute of Electrical and Electronics Engineers (IEEE) and the International Commission on Non-ionizing Radiation Protection, are thermally based, and do not apply to chronic, nonthermal exposure situations. They are believed to protect against injury that may be caused by acute exposures that result in tissue heating or electric shock and burn. The hazard level (for frequencies generally at or greater than 3 MHz) is based on a specific absorption dose-rate, SAR, associated with an effect

that results from an increase in body temperature. The FCC's exposure guideline is considered protective of effects arising from a thermal mechanism but not from all possible mechanisms. Therefore, the generalization by many that the guidelines protect human beings from harm by any or all mechanisms is not justified.

These guidelines are based on findings of an adverse effect level of 4 watts per kilogram (W/kg) body weight. This SAR was observed in laboratory research involving acute exposures that elevated the body temperature of animals, including nonhuman primates. The exposure guidelines did not consider information that addresses nonthermal, prolonged exposures, i.e., from research showing effects with implications for possible adversity in situations involving chronic/prolonged, low-level (nonthermal) exposures. Relatively few chronic, low-level exposure studies of laboratory animals and epidemiological studies of human populations have been reported and the majority of these studies do not show obvious adverse health effects. However, there are reports that suggest that potentially adverse health effects, such as cancer, may occur. Since EPA's comments were submitted to the FCC in 1993, the number of studies reporting effects associated with both acute and chronic low-level exposure to RF radiation has increased.

While there is general, although not unanimous, agreement that the database on low-level, long-term exposures is not sufficient to provide a basis for standards development, some contemporary guidelines state explicitly that their adverse-effect level is based on an increase in body temperature and do not claim that the exposure limits protect against both thermal and nonthermal effects. The FCC does not claim that their exposure guidelines provide protection for exposures to which the 4 W/kg SAR basis does not apply, i.e., exposures below the 4 W/kg threshold level that are chronic/prolonged and nonthermal. However, exposures that comply with the FCC's guidelines generally have been represented as "safe" by many of the RF system operators and service providers who must comply with them, even though there is uncertainty about possible risk from nonthermal, intermittent exposures that may continue for years.

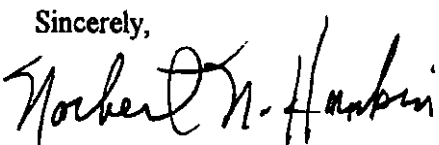
The 4 W/kg SAR, a whole-body average, time-average dose-rate, is used to derive dose-rate and exposure limits for situations involving RF radiation exposure of a person's entire body from a relatively remote radiating source. Most people's greatest exposures result from the use of personal communications devices that expose the head. In summary, the current exposure guidelines used by the FCC are based on the effects resulting from whole-body heating, not exposure of and effect on critical organs including the brain and the eyes. In addition, the maximum permitted local SAR limit of 1.6 W/kg for critical organs of the body is related directly to the permitted whole body average SAR (0.08 W/kg), with no explanation given other than to limit heating.

I also have enclosed a letter written in June of 1999 to Mr. Richard Tell, Chair, IEEE SCC28 (SC4) Risk Assessment Work Group, in which the members of the Radiofrequency Interagency Work Group (RFIAWG) identified certain issues that they had determined needed to be addressed in order to provide a strong and credible rationale to support RF exposure guidelines.

Federal health and safety agencies have not yet developed policies concerning possible risk from long-term, nonthermal exposures. When developing exposure standards for other physical agents such as toxic substances, health risk uncertainties, with emphasis given to sensitive populations, are often considered. Incorporating information on exposure scenarios involving repeated short duration/nonthermal exposures that may continue over very long periods of time (years), with an exposed population that includes children, the elderly, and people with various debilitating physical and medical conditions, could be beneficial in delineating appropriate protective exposure guidelines.

I appreciate the opportunity to be of service and trust that the information provided is helpful. If you have further questions, my phone number is (202) 564-9235 and e-mail address is hankin.norbert@epa.gov.

Sincerely,



Norbert Hankin
Center for Science and Risk Assessment
Radiation Protection Division

Enclosures:

1) letter to Thomas P. Stanley, Chief Engineer, Office of Engineering and Technology, Federal Communications Commission, November 9, 1993, in response to the FCC's request for comments on their Notice of Proposed Rulemaking (NPRM), Guidelines for Evaluating the Environmental Effects of Radiofrequency Radiation
2) June 1999 letter to Mr. Richard Tell, Chair, IEEE SCC28 (SC4) Risk Assessment Work Group from the Radiofrequency Radiation Interagency Work Group

APPENDIX C

Letter from Dr. De-Kun Li, MD, PhD, MPH

Kaiser Permanente Division of Research 2000 Broadway Oakland, CA 94612

Dear Ms. Martin:

Thank you for inviting me to provide my professional opinions on the SmartMeter safety issue. I will address two questions raised in the attached letter. But first, here is some background information:

1. Currently there are no national or international "**standards**" for safety levels of radiofrequency (a range of 3 kHz to 300 GHz) devices. What FCC is currently using are "guidelines" which have much lower certainty than a "standard". One can go to many governmental agencies' websites like NIOSH, EPA, FDA, etc. to verify this. Therefore, for anyone to claim that they meet "FCC" standards gives a false impression of safety certainty compared to "guidelines" which implies that a lot is "unknown."

2. The current FCC "guideline" was adopted by FCC based on EPA's recommendation in 1996. EPA made the recommendation "with certain reservation". There was a letter by Norbert Hankin, Center for Science and Risk Assessment, Radiation Protection Division at EPA describing the current FCC guidelines (The letter can be found through a Google search). According to Hankin's letter, the FCC current guidelines were solely based on "thermal effect" of radiofrequency, a level at which radiofrequency can cause heat injury. As we know, heat injury is not what the public is concerned about regarding radiofrequency safety. Their concerns are about cancer, miscarriages, birth defects, low semen quality, autoimmune disease, etc. Hankin's letter, specifically emphasized that the EPA recommended guidelines that FCC is currently using do not apply to non-thermal effects or mechanisms (e.g., cancer, birth defects, miscarriage, autoimmune diseases, etc) which are the focus of the public's concern. Hankin's letter states **"Therefore, the generalization by many that the guidelines protect human beings from harm by any or all mechanisms is not justified."**

3. In addition to being limited to only the thermal effect, the letter also states that the current FCC guidelines recommended by EPA were only based on experiments on animals in laboratories. Establishing firm safety standards

usually requires evidence from human studies such as epidemiological studies. The current FCC guidelines were based on animal studies only, not human data, which may explain why they are only considered as guidelines rather than standards. Furthermore, the thermal effect, used to establish the FCC guidelines, was based on *acute* thermal effect. It did not even deal with chronic long-term intermittent effect. In fact, Hankin's letter also states **"exposures that comply with the FCC's guidelines generally have been presented as "safe" by many of the RF system operators and service providers who must comply with them, even though there is uncertainty about possible risk from nonthermal, intermittent exposures that may continues for years"**

4. Electromagnetic fields (EMFs) can come from sources with a spectrum of frequencies. EMFs from electric power sources usually have a frequency less than 1 kHz , while radiofrequency (RF) generated by SmartMeters are reportedly in the range 900 MHz to 2.4 GHz. While overall research on the EMF health effect remains limited, there are more reported studies examining the EMF health effect in power line frequencies (< 1 kHz) including some of my research1-3 than in RF. It is not clear at this moment whether the findings on the EMF health effect at lower frequencies (i.e., < 1 kHz) can be applied to RF range. If the underlying mechanisms are similar, the findings in lower frequency EMFs can then be applied to RF range for SmartMeter. Many studies of power frequencies reported associations with childhood leukemia, miscarriage, poor semen quality, autoimmune diseases at a level much lower than those generating thermal damage as used by FCC.

5. Many chronic diseases that the public is concerned about (e.g., cancer) have a long latency period and take decades to show symptoms. Most wireless network and devices have only been used widely in the last 10 to 15 years. Therefore, many studies evaluating RF health effect related to cancer risk previously, if they failed to identify an adverse health effect, are not appropriate to be used as evidence to claim the safety of RF exposure since the latency period has not been long enough to show the effect even if an adverse association does indeed exist.

6. While the underlying mechanisms of the potential EMF health effect are not totally understood at present, skeptics have been focused on the EMF thermal effect, especially those who are NOT in the profession of biomedical research, such as physicists. It is now known that EMFs can

interfere with the human body through multiple mechanisms. For example, it has been demonstrated that communication between cells depends on EMF signals, likely in a very low level. External EMFs could conceivably interfere with normal cell communication, thus disrupting normal cell differentiation and proliferation. Such disturbance could lead to miscarriage, birth defects, and cancer.

To address the two questions raised in the letter:

1. Whether FCC standards for SmartMeter are sufficiently protective of public health taking into account current exposure levels to radiofrequency and electromagnetic fields. First, FCC currently has only "guidelines", not standards as explained above. Second, as described in the background information above, the current FCC guidelines only deal with thermal effect, which was also based on animal studies only. Meeting the current FCC guidelines, in the best-case scenario, only means that one won't have heat damage from SmartMeter exposure. It says nothing about safety from the risk of many chronic diseases that the public is most concerned about such as cancer, miscarriage, birth defects, semen quality, autoimmune diseases, etc. Therefore, when it comes to non-thermal effects of RF, which is the most relevant effect for public concerns, FCC guidelines are irrelevant and can not be used for any claims of SmartMeter safety unless we are addressing heat damage.

2. Whether additional technology-specific standards are needed for SmartMeter and other devices that are commonly found in and around homes, to ensure adequate protection from adverse health effects. Safety standards for RF exposure related to non-thermal effects are urgently needed to protect the public from potential adverse health effects from RF exposure that are increasingly prevalent in our daily life due to installation of ever-powerful wireless networks and devices like SmartMeter. Unfortunately scientific research is still lacking in this area and some endpoints like cancer take decades to study. The safety standards are not likely to be available anytime soon. The bottom line is that the safety level for RF exposure related to non-thermal effect is unknown at present and whoever claims that their device is safe regarding non-thermal effect is either ignorant or misleading.

In summary, we do not currently have scientific data to determine where the safe RF exposure level is regarding the non-thermal effect. Therefore, it

should be recognized that we are dealing with uncertainty now and most likely for the foreseeable future. The question for governmental agencies, especially those concerned with public health and safety, is that given the uncertainty, should we err on the side of safety and take the precautionary avoidance measures? Unknown does not mean safe. There are two unique features regarding SmartMeter exposure. First, because of mandatory installation, it is a universal exposure. Virtually every household is exposed. Second, it is an involuntary exposure. The public that are exposed to SmartMeters do not have any input in deciding whether they would like to have the SmartMeter installed. The installation is imposed upon the public. Governmental agencies for protecting public health and safety should be much more vigilant towards involuntary environmental exposures because governmental agencies are the only defense against such involuntary exposure. Given the uncertainty of the SmartMeter safety, one rational first step of public policy could be to require household consent before installation of SmartMeters. Finally, because of the nature of universal exposure, many susceptible and vulnerable populations including pregnant women and young children are unknowingly exposed 24 hours a day, 7 days a week. Usually, the threshold of harmful level is much lower for susceptible populations.

References

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De-Kun Li, MD, PhD, MPH, is a senior research scientist at the Division of Research, Kaiser Permanente Northern California.

Dr. Li completed his medical training and master's degree in public health at Shanghai Medical University, Shanghai, China. He then received his PhD in

epidemiology from the University of Washington, Seattle. Dr. Li has conducted research in the areas of pregnancy outcomes, sudden infant death syndrome, women's health, breast cancer, pharmacological effects on pregnancy outcomes, genetic etiology, and occupational exposures since 1984. His research interests include: reproductive, perinatal, and pediatric epidemiology, such as etiology of miscarriage, sudden infant death syndrome, preterm delivery, preelcampsia, low birth, infertility, cerebral palsy, birth defects, pediatric diseases (including childhood cancer and neurological disorders), autoimmune diseases in relation to maternal-fetal interaction, breast cancer, and risk factors for low semen quality. Dr. Li' research areas also include pharmacoepidemiolgical effect of medication use during pregnancy, genetic determinants of adverse pregnancy outcomes, the effect of electromagnetic fields on adverse pregnancy outcomes and low sperm quality, and the effect of endocrine disruptors, specifically Bisphenol A (BPA), on male and female reproductive systems. He is currently the associate editor of the American Journal of Epidemiology. Dr. Li has participated in a National Institute of Child Health and Human Development (NICHD) sponsored panel evaluation of "Back to Sleep" campaign and Sudden Infant Death Syndrome risk. He has also served as a member on the Ad Hoc Committee reviewing the NICHD program project, and on several Special Emphasis Panels at National Institute of Occupational Safety and Health and National Institute of Environmental Health and Sciences reviewing grant proposals. He has served as a member of the Policy Committee at the American College of Epidemiology. He was invited by the National Academy of Science to participate as a panel member in the U.S.-China Roundtable on Collaboration of Biomedical Research. In addition, he teaches at Stanford University and supervises doctoral students from the departments of epidemiology at UCB (University of California, Berkeley) and UCLA (University of California, Los Angeles).

Dr. Li has published extensively with 29 first-authored publications. He has obtained, as the principal investigator, numerous grants, ranging from $600,000 to $ 3.49 million from various federal agencies of the National Institutes of Health, as well as the California Public Health Foundation. Many of his publications have been widely reported by the national, international, and local news media including recent studies of caffeine intake and miscarriage, pacifier use and use of a fan in relation to SIDS risk, and depression during pregnancy and preterm delivery. Other examples of work receiving wide media coverage include the risk of miscarriage associated with EMF exposure, NSAID use and the risk of miscarriage, hot tub use during pregnancy and the risk of miscarriage, and maternal-fetal HLA compatibility and the risk of preterm delivery.

Current Position(s):

Research Scientist III, Division of Research, Kaiser Permanente Northern California

Lecturer, Stanford University, Department of Health Research and Policy

Primary Research Interests:

Reproductive, prenatal, and pediatric epidemiology, such as etiology of infertility, miscarriage, preterm delivery, preeclampsia, sudden infant death syndrome, cerebral palsy, birth defects; pediatric diseases, including childhood cancer and neurological disorders; autoimmune diseases in relation to maternal-fetal interaction, and breast cancer.

Health effects of electromagnetic fields

Pharmacological effects of medication use during pregnancy on pregnancy outcome

Genetic determinants of pregnancy outcome

Risk factors for poor semen quality

Health effect of endocrine disruptors, especially Bisphenol A (BPA), on male and female reproductive systems

APPENDIX D

List of 62 Reviews on Non-thermal Effects of Microwave Frequency EMFs

Among the scientific reviews documenting these various non-thermal health effects are 62 that follow. Each of these reviews cites at least a dozen primary literature citations showing non-thermal effects, with many citing 100 or more going up to the 2nd reference which cites approximately 1500 such citations. It can be seen from this that the primary literature citations supporting the existence of various non-thermal health effects cited in these reviews go into several thousands. This list is not and is not intended to be a list of all important such reviews. However it gives some measure of the size of the literature that contradicts the industry contention that there are no non-thermal effects of microwave frequency EMFs.

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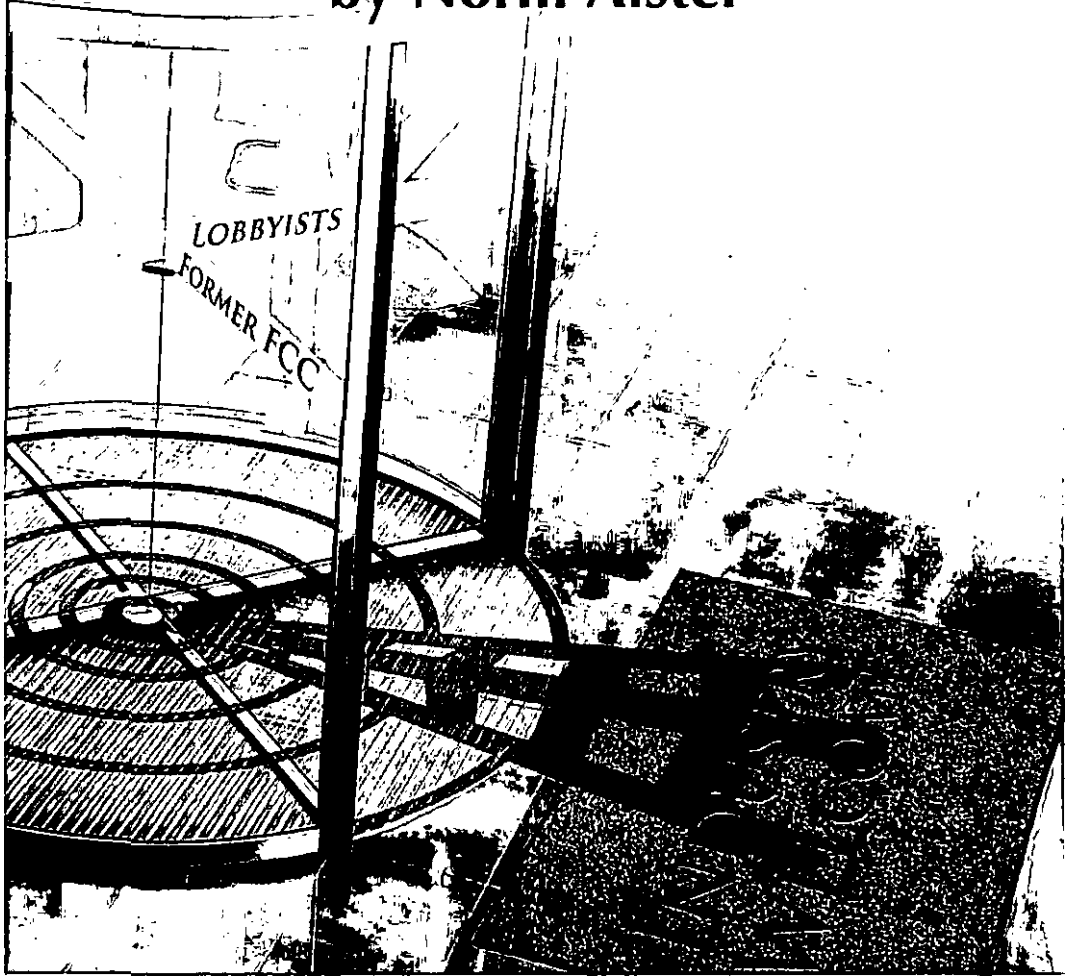
APPENDIX E

Captured Agency:

How the Federal Communications Commission Is Dominated by the Industries It Presumably Regulates

by Norm Alster



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Captured Agency

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Chapter One: The Corrupted Network

Renee Sharp seemed proud to discuss her spring 2014 meeting with the Federal Communications Commission.

As research director for the non-profit Environmental Working Group, Sharp doesn't get many chances to visit with the FCC. But on this occasion she was able to express her concerns that lax FCC standards on radiation from wireless technologies were especially hazardous for children.

The FCC, however, should have little trouble dismissing those concerns.

Arguing that current standards are more than sufficient and that children are at no elevated risk from microwave radiation, wireless industry lobbyists don't generally have to set up appointments months in advance. They are at the FCC's door night and day.

Indeed, a former executive with the Cellular Telecommunications Industry Association (CTIA), the industry's main lobbying group, has boasted that the CTIA meets with FCC officials "500 times a year."[1]

Sharp does not seem surprised. "There's no question that the government has been under the influence of industry. The FCC is a captured agency," she said.[2]

Captured agency.

That's a term that comes up time and time again with the FCC. Captured agencies are essentially controlled by the industries they are supposed to regulate. A detailed look at FCC actions—and non-actions—shows that over the years the FCC has granted the wireless industry pretty much what it has wanted. Until very recently it has also granted cable what it wants. More broadly, the FCC has again and again echoed the lobbying points of major technology interests.

Money—and lots of it—has played a part. The National Cable and Telecommunications Association (NCTA) and CTIA have annually been among Washington's top lobbying spenders. CTIA alone lobbied on at least 35 different Congressional bills through the first half of 2014. Wireless market leaders AT&T and Verizon work through CTIA. But they also do their own lobbying, spending nearly $15 million through June of 2014, according to data from the Center for Responsive Politics (CRP). In all, CTIA, Verizon, AT&T, T-Mobile USA, and Sprint spent roughly $45 million lobbying in 2013. Overall, the Communications/Electronics sector is one of Washington's super heavyweight lobbyists, spending nearly $800 million in 2013-2014, according to CRP data.

But direct lobbying by industry is just one of many worms in a rotting apple. The FCC sits at the core of a network that has allowed powerful moneyed interests with limitless access a variety of ways to shape its policies, often at the expense of fundamental public interests.

As a result, consumer safety, health, and privacy, along with consumer wallets, have all been overlooked, sacrificed, or raided due to unchecked industry influence. The cable industry has consolidated into giant local monopolies that control pricing while leaving consumers little choice over content selection. Though the FCC has only partial responsibility, federal regulators have allowed the Internet to grow into a vast hunting grounds for criminals and commercial interests: the go-to destination for the surrender of personal information, privacy and identity. Most insidious of all, the wireless industry has been allowed to grow unchecked and virtually unregulated, with fundamental questions on public health impact routinely ignored.

Industry controls the FCC through a soup-to-nuts stranglehold that extends from its well-placed campaign spending in Congress through its control of the FCC's Congressional oversight committees to its persistent agency lobbying. "If you're on a committee that regulates industry you'll be a major target for industry," said Twaun Samuel, chief of staff for Congresswoman Maxine Waters.[3] Samuel several years ago helped write a bill aimed at slowing the revolving door. But with Congress getting its marching orders from industry, the bill never gained any traction.

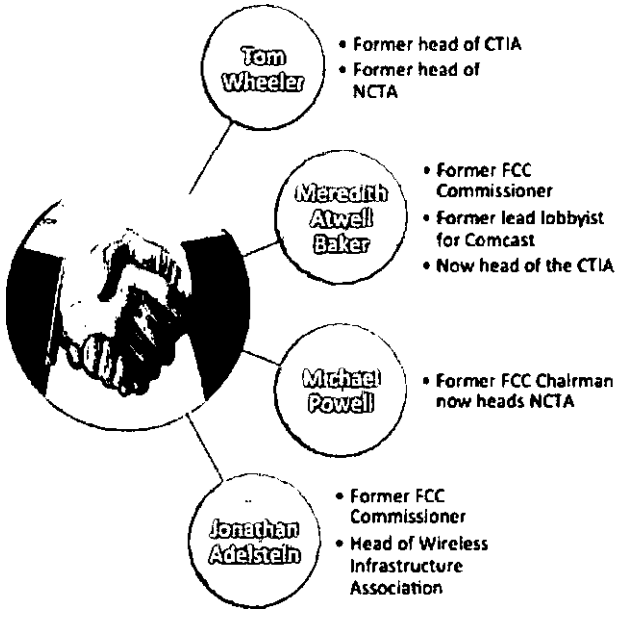
Industry control, in the case of wireless health issues, extends beyond Congress and regulators to basic scientific research. And in an obvious echo of the hardball tactics of the tobacco industry, the wireless industry has backed up its economic and political power by stonewalling on public relations and bullying potential threats into submission with its huge standing army of lawyers. In this way, a coddled wireless industry intimidated and silenced the City of San Francisco, while running roughshod over local opponents of its expansionary infrastructure.

On a personal level, the entire system is greased by the free flow of executive leadership between the FCC and the industries it presumably oversees. Currently presiding over the FCC is Tom Wheeler, a man who has led the two most powerful industry lobbying groups: CTIA and NCTA. It is Wheeler who once supervised a $25 million industry-funded research effort on wireless health effects. But when handpicked research leader George Carlo concluded that wireless radiation did raise the risk of brain tumors, Wheeler's CTIA allegedly rushed to muffle the message. "You do the science. I'll take care of the politics," Carlo recalls Wheeler saying.[4]

Wheeler over time has proved a masterful politician. President Obama overlooked Wheeler's lobbyist past to nominate him as FCC chairman in 2013. He had, after all, raised more than $700,000 for Obama's presidential campaigns. Wheeler had little trouble earning confirmation from a Senate whose Democrats toed the Presidential line and whose Republicans understood Wheeler was as industry-friendly a nominee as they could get. And while Wheeler, at the behest of his Presidential sponsor, has taken on cable giants with his plans for net neutrality and shown some openness on other issues, he has dug in his heels on wireless.

Newly ensconced as chairman of the agency he once blitzed with partisan pitches, Wheeler sees familiar faces heading the industry lobbying groups that ceaselessly petition the FCC. At CTIA, which now calls itself CTIA - The Wireless Association, former FCC commissioner Meredith Atwell Baker is in charge.

Wireless and Cable Industries Have the FCC Covered



And while cell phone manufacturers like Apple and Samsung, along with wireless service behemoths like Verizon and AT&T, are prominent CTIA members, the infrastructure of 300,000 or more cellular base stations and antenna sites has its own lobbying group: PCIA, the Wireless Infrastructure Association. The President and CEO of PCIA is Jonathan Adelstein, another former FCC commissioner. Meanwhile, the cable industry's NCTA employs former FCC chairman Michael Powell as its president and CEO. Cozy, isn't it?

FCC commissioners in 2014 received invitations to the Wireless Foundation's May 19th Achievement Awards Dinner. Sounds harmless, but for the fact that the chief honoree at the dinner was none other than former wireless lobbyist but current FCC Chairman Tom Wheeler. Is this the man who will act to look impartially at the growing body of evidence pointing to health and safety issues?

The revolving door also reinforces the clout at another node on the industry-controlled influence network. Members of congressional oversight committees are prime targets of

industry. The cable industry, for example, knows that key legislation must move through the Communications and Technology Subcommittee of the House Energy and Commerce Committee. Little wonder then that subcommittee chairman Greg Walden was the second leading recipient (after Speaker John Boehner) of cable industry contributions in the last six years (through June 30, 2014). In all, Walden, an Oregon Republican, has taken over $108,000 from cable and satellite production and distribution companies.[5] But he is not alone. Six of the top ten recipients of cable and satellite contributions sit on the industry's House oversight committee. The same is true of senators on the cable oversight committee. Committee members were six of the ten top recipients of campaign cash from the industry.[6]

Cable & Satellite Campaign Contributions

Top House Recipients Funded

Recipient	Amount
John A. Boehner	$135,425
Greg Walden	$108,750
Bob Goodlatte	$93,200
John Conyers Jr.	$84,000
Mike Coffman	$82,137
Fred Upton	**$73,500**
Lee Terry	**$65,916**
Henry A. Waxman	**$65,000**
Cory Gardner	**$64,500**
Anna G. Eshoo	**$60,500**

Cellular Industry Campaign Contributions

Top House Recipients Funded

Recipient	Amount
Henry A. Waxman	**$41,500**
Scott H. Peters	$40,300
Greg Walden	**$35,750**
Fred Upton	**$32,250**
Bob Goodlatte	$31,250
Lee Terry	**$29,600**
Anna G. Eshoo	**$27,000**
Doris O. Matsui	**$25,500**
John Shimkus	**$24,000**
Peter J. Roskam	$21,100

Cable & Satellite Campaign Contributions

Top Senate Recipients Funded

Recipient	Amount
Edward J. Markey	**$320,500**
Kirsten E. Gillibrand	$194,125
Mitch McConnell	$177,125
Harry Reid	$175,600
Charles E. Schumer	$175,450
Mark L. Pryor	**$172,950**
Michael F. Bennet	$159,000
Richard Blumenthal	**$148,800**
Claire McCaskill	**$138,185**
Mark Udall	$136,625

Cellular Industry Campaign Contributions

Top Senate Recipients Funded

Recipient	Amount
Edward J. Markey	**$155,150**
Mark R. Warner	$74,800
Harry Reid	$73,600
Mark L. Pryor	**$71,900**
Roy Blunt	**$57,400**
John McCain	$56,261
Charles E. Schumer	$53,300
Roger F. Wicker	$51,300
Barbara Boxer	$49,578
Kelly Ayotte	$43,333

The compromised FCC network goes well beyond the revolving door and congressional oversight committees. The Washington social scene is one where money sets the tone and throws the parties. A look at the recent calendar of one current FCC commissioner shows it would take very disciplined and almost saintly behavior on the part of government officials to resist the lure of lavishly catered dinners and cocktail events. To paraphrase iconic investigative journalist I.F. Stone, if you're going to work in Washington, bring your chastity belt.

All that free liquor, food and conviviality translates into the lobbyist's ultimate goal: access. "They have disproportionate access," notes former FCC commissioner Michael Copps. "When you are in a town where most people you see socially are in industry, you don't have to ascribe malevolent behavior to it," he added.[7]

Not malevolent in motive. But the results can be toxic. And blame does not lie solely at the feet of current commissioners. The FCC's problems predate Tom Wheeler and go back a long way.

Indeed, former Chairman Newton Minow, enduringly famous for his 1961 description of television as a "vast wasteland," recalls that industry manipulation of regulators was an issue even back then. "When I arrived, the FCC and the communications industry were both regarded as cesspools. Part of my job was to try to clean it up."[8]

More than 50 years later, the mess continues to pile up.

Chapter Two: Just Don't Bring Up Health

Perhaps the best example of how the FCC is tangled in a chain of corruption is the cell tower and antenna infrastructure that lies at the heart of the phenomenally successful wireless industry.

It all begins with passage of the Telecommunications Act of 1996, legislation once described by South Dakota Republican senator Larry Pressler as "the most lobbied bill in history." Late lobbying won the wireless industry enormous concessions from lawmakers, many of them major recipients of industry hard and soft dollar contributions. Congressional staffers who helped lobbyists write the new law did not go unrewarded. Thirteen of fifteen staffers later became lobbyists themselves.[9]

Section 332(c)(7)(B)(iv) of the Act remarkably—and that adverb seems inescapably best here—wrests zoning authority from local governments. Specifically, they cannot cite health concerns about the effects of tower radiation to deny tower licenses so long as the towers comply with FCC regulations.

Congress Silences Public

Section 332(c)(7)(B)(iv) of the Communications Act provides:

> **No State or local government or instrumentality thereof may regulate the placement, construction, and modification of personal wireless service facilities on the basis of the environmental effects of radio frequency emissions to the extent that such facilities comply with the Commission's regulations concerning such emissions.**

In preempting local zoning authority—along with the public's right to guard its own safety and health— Congress unleashed an orgy of infrastructure build-out. Emboldened by the government green light and the vast consumer appetite for wireless technology, industry has had a free hand in installing more than 300,000 sites. Church steeples, schoolyards, school rooftops, even trees can house these facilities.

Is there any reason to believe that the relatively low level radiofrequency emissions of these facilities constitute a public health threat? Certainly, cell phones themselves, held close to the head, have been the focus of most concern on RF emissions. Since the impact of RF diminishes with distance, industry advocates and many scientists dismiss the possibility that such structures pose health risks.

But it's not really that simple. A troubling body of evidence suggests exposure to even low emission levels at typical cellular frequencies between 300 MHz and 3 GHz can have a wide range of negative effects.

In a 2010 review of research on the biological effects of exposure to radiation from cell tower base stations, B. Blake Levitt and Henry Lai found that "some research does exist to warrant caution in infrastructure siting."[10] They summarized the results on one 2002 study that compared the health of 530 people living at various distances within 300 meters of cell towers with a control group living more than 300 meters away. "Results indicated increased symptoms and complaints the closer a person lived to a tower. At <10 m, symptoms included nausea, loss of appetite, visual disruptions, and difficulties in moving. Significant differences were observed up through 100 m for irritability, depressive tendencies, concentration difficulties, memory loss, dizziness, and lower libido."[11]

A 2007 study conducted in Egypt found similar results. Levitt and Lai report, "Headaches, memory changes, dizziness, tremors, depressive symptoms, and sleep disturbance were significantly higher among exposed inhabitants than controls."[12]

Beyond epidemiological studies, research on a wide range of living things raises further red flags. A 2013 study by the Indian scientists S. Sivani and D. Sudarsanam reports: "Based on current available literature, it is justified to conclude that RF-EMF [electro magnetic fields] radiation exposure can change neurotransmitter functions, blood-brain barrier, morphology, electrophysiology, cellular metabolism, calcium efflux, and gene and protein expression in certain types of cells even at lower intensities."[13]

The article goes on to detail the effects of mobile tower emissions on a wide range of living organisms: "Tops of trees tend to dry up when they directly face the cell tower antennas. . . . A study by the Centre for Environment and Vocational Studies of Punjab University noted that embryos of 50 eggs of house sparrows were damaged after being exposed to mobile tower radiation for 5-30 minutes. . . . In a study on cows and calves on the effects of exposure from mobile phone base stations, it was noted that 32% of calves developed nuclear cataracts, 3.6% severely."[14]

Does any of this constitute the conclusive evidence that would mandate much tighter control of the wireless infrastructure? Not in the estimation of industry and its captured agency. Citing other studies—often industry-funded—that fail to establish health effects, the wireless industry has dismissed such concerns. The FCC has typically echoed that position.

Keep in mind that light regulation has been one factor in the extraordinary growth of wireless—CTIA says exactly that in a Web post that credits the Clinton Administrations light regulatory touch.

July 25, 2013

CTIA BLOG
CTIA is an international nonprofit trade association that has represented the wireless communications industry since 1984.

But our position as the world's leader was no accident. It started with the Clinton Administration that had the foresight to place a "light regulatory touch" on the wireless industry, which was in its infancy at the time. That light touch has continued through multiple Administrations.

Obviously, cellular technology is wildly popular because it offers many benefits to consumers. But even allowing for that popularity and for the incomplete state of science, don't some of these findings raise enough concern to warrant some backtracking on the ham-fisted federal preemption of local zoning rights?

In reality, since the passage of the 1996 law, the very opposite has occurred. Again and again both Congress and the FCC have opted to stiffen—rather than loosen—federal preemption over local zoning authority. In 2009, for example, the wireless industry convinced the FCC to impose a "shot clock" that requires action within 90 days on many zoning applications. "My sense is that it was an industry request," said Robert Weller, who headed up the FCC's Office of Engineering and Technology when the shot clock was considered and imposed.[15]

And just last November, the FCC voted to further curb the rights of local zoning officials to control the expansion of antenna sites Again and again, Congress and the FCC have extended the wireless industry carte blanche to build out infrastructure no matter the consequences to local communities.

The question that hangs over all this: would consumers' embrace of cell phones and Wi-Fi be quite so ardent if the wireless industry, enabled by its Washington errand boys, hadn't so consistently stonewalled on evidence and substituted legal intimidation for honest inquiry? (See Appendix for online study of consumer attitudes on wireless health and safety.)

Document searches under the Freedom of Information Act reveal the central role of Tom Wheeler and the FCC in the tower siting issue. As both lobbyist and FCC chairman, Wheeler has proved himself a good friend of the wireless industry.

In January of 1997, CTIA chieftain Wheeler wrote FCC Wireless Telecommunications Bureau Chief Michele C. Farquhar citing several municipal efforts to assert control over siting. Wheeler, for example, asserted that one New England state had enacted a law requiring its Public Service Commissioner to issue a report on health risks posed by wireless facilities.[16] He

questions whether such a study—and regulations based on its results—would infringe on FCC preemption authority.

FCC bureau chief Farquhar hastily reassured Wheeler that no such study could be consulted in zoning decisions. "Therefore, based on the facts as you have presented them, that portion of the statute that directs the State Commissioner to recommend regulations based upon the study's findings would appear to be preempted,"[17] the FCC official wrote to Wheeler. She emphasized that the state had the right to do the study. It just couldn't deny a siting application based on anything it might learn.

The FCC in 1997 sent the message it has implicitly endorsed and conveyed ever since: study health effects all you want. It doesn't matter what you find. The build-out of wireless cannot be blocked or slowed by health issues.

Now let's fast forward to see Wheeler on the other side of the revolving door, interacting as FCC chairman with a former FCC commissioner who is now an industry lobbyist.

A March 14, 2014 letter[18] reveals the chummy relationship between Wheeler and former commissioner Jonathan Adelstein, now head of PCIA, the cellular infrastructure lobbying group. It also references FCC Chairman Wheeler seeking policy counsel from lobbyist Adelstein:

Wheeler Still Willing to Help

From: Jonathan Adelstein [mailto:adelstein@pcia.com]
Sent: Friday, March 14, 2014 12:24 PM
To: [redacted]
Cc: Renee Gregory; Jonathan Campbell
Subject: How to Spur Wireless Broadband Deployment

Tom – It was great to see you the other night at the FCBA event, and wonderful to see how much fun you're having (if that's the right word). I know I enjoyed my time there (thanks to your help with Daschle in getting me that role in the first place!).

Thanks for asking how we think the FCC can help spur wireless broadband deployment. The infrastructure proceeding perfectly tees up many of the top issues the FCC needs to address. As you requested, I've summarized briefly in the attached letter some of the key steps you can take now.

"Tom – It was great to see you the other night at the FCBA event, and wonderful to see how much fun you're having (if that's the right word). I know I enjoyed my time there (thanks to your help with Daschle in getting me that role in the first place!)."

"Thanks for asking how we think the FCC can help spur wireless broadband deployment," the wireless lobbyist writes to the ex-wireless lobbyist, now running the FCC.

Adelstein's first recommendation for FCC action: "*Amend its rules to categorically exclude DAS and small deployments* [Ed. note: these are compact tower add-ons currently being widely deployed] *from environmental and historic review.*" Adelstein outlined other suggestions for further limiting local antenna zoning authority and the FCC soon did its part. Late last year, the agency proposed new rules that largely (though not entirely) complied with the antenna industry's wish list.

James R. Hobson is an attorney who has represented municipalities in zoning issues involving the FCC. He is also a former FCC official, who is now of counsel at Best, Best and Krieger, a Washington-based municipal law practice. "The FCC has been the ally of industry," says Hobson. Lobbyist pressure at the FCC was intense even back in the 70s, when he was a bureau chief there. "When I was at the FCC, a lot of my day was taken up with appointments with industry lobbyists." He says of the CTIA that Wheeler once headed: "Their reason for being is promoting the wireless industry. And they've been successful at it."[19]

The FCC's deferential compliance has allowed industry to regularly bypass and if necessary steamroll local authorities. Violation of the FCC-imposed "shot clock," for example, allows the wireless license applicant to sue.

The FCC's service to the industry it is supposed to regulate is evidently appreciated. The CTIA web site, typically overflowing with self-congratulation, spreads the praise around in acknowledging the enabling contributions of a cooperative FCC. In one brief summation of its own glorious accomplishments, CTIA twice uses the word "thankfully" in describing favorable FCC actions.

In advancing the industry agenda, the FCC can claim that it is merely reflecting the will of Congress. But the agency may not be doing even that.

Remember the key clause in the 96 Telecom Act that disallowed denial of zoning permits based on health concerns? Well, federal preemption is granted to pretty much any wireless outfit on just one simple condition: its installations must comply with FCC radiation emission standards. In view of this generous carte blanche to move radiation equipment into neighborhoods, schoolyards and home rooftops, one would think the FCC would at the very least diligently enforce its own emission standards. But that does not appear to be the case.

Indeed, one RF engineer who has worked on more than 3,000 rooftop sites found vast evidence of non-compliance. Marvin Wessel estimates that "10 to 20% exceed allowed radiation standards."[20] With 30,000 rooftop antenna sites across the U.S. that would mean that as many as 6,000 are emitting radiation in violation of FCC standards. Often, these emissions can be 600% or more of allowed exposure levels, according to Wessel.

Antenna standards allow for higher exposure to workers. In the case of rooftop sites, such workers could be roofers, painters, testers and installers of heating and air conditioning

equipment, to cite just a few examples. But many sites, according to Wessel, emit radiation at much higher levels than those permitted in occupational standards. This is especially true of sites where service providers keep adding new antenna units to expand their coverage. "Some of these new sites will exceed ten times the allowable occupational radiation level," said Wessel.[21] Essentially, he adds, this means that nobody should be stepping on the roof.

"The FCC is not enforcing its own standard," noted Janet Newton, who runs the EMF Policy Institute, a Vermont-based non-profit. That group several years ago filed 101 complaints on specific rooftop sites where radiation emissions exceeded allowable levels. "We did this as an exercise to hold the FCC's feet to the fire," she said. But the 101 complaints resulted in few responsive actions, according to Newton.[22]

Former FCC official Bob Weller confirms the lax—perhaps negligible is the more appropriate word—FCC activity in enforcing antenna standards. "To my knowledge, the enforcement bureau has never done a targeted inspection effort around RF exposure," he said.[23] Budget cuts at the agency have hurt, limiting the FCC's ability to perform field inspections, he added. But enforcement, he adds, would do wonders to insure industry compliance with its limited regulatory compliance requirements. "If there were targeted enforcement and fines issued the industry would pay greater attention to ensuring compliance and self-regulation," he allowed.

Insurance is where the rubber hits the road on risk. So it is interesting to note that the rating agency A.M. Best, which advises insurers on risk, in 2013 topped its list of "emerging technology-based risks" with RF Radiation:

> *"The risks associated with long-term use of cell phones, although much studied over the past 10 years, remain unclear. Dangers to the estimated 250,000 workers per year who come in close contact with cell phone antennas, however, are now more clearly established. Thermal effects of the cellular antennas, which act at close range essentially as open microwave ovens can include eye damage, sterility and cognitive impairments. While workers of cellular companies are well trained on the potential dangers, other workers exposed to the antennas are often unaware of the health risks. The continued exponential growth of cellular towers will significantly increase exposure of these workers and others coming into close contact with high-energy cell phone antenna radiation,"* A.M. Best wrote.[24]

So what has the FCC done to tighten enforcement? Apparently, not very much. Though it does follow up on many of the complaints filed against sites alleged to be in violation of standards it takes punitive actions very rarely. (The FCC did not provide answers to written questions on details of its tower enforcement policies.)

The best ally of industry and the FCC on this (and other) issues may be public ignorance.

An online poll conducted for this project asked 202 respondents to rate the likelihood of a series of statements.[25] Most of the statements were subject to dispute. Cell phones raise the risk of certain health effects and brain cancer, two said. There is no proof that cell phones are harmful, another declared. But among the six statements there was one statement of indisputable fact: "The U.S. Congress forbids local communities from considering health effects when deciding whether to issue zoning permits for wireless antennae," the statement said.

Though this is a stone cold fact that the wireless industry, the FCC and the courts have all turned into hard and inescapable reality for local authorities, just 1.5% of all poll respondents replied that it was "definitely true."

Public ignorance didn't take much cultivation by the wireless industry on the issue of local zoning. And maybe it doesn't matter much, considering the enormous popularity of wireless devices. But let's see how public ignorance has been cultivated and secured—with the FCC's passive support—on the potentially more disruptive issue of mobile phone health effects.

Chapter Three: Wireless Bullies and the Tobacco Analogy

Issues of cable and net neutrality have recently attracted wide public attention (more on that in Chapter Six). Still, the bet here remains that future judgment of the FCC will hinge on its handling of wireless health and safety issues.

And while the tower siting issue is an egregious example of an industry-dominated political process run amuck, the stronger health risks appear to reside in the phones themselves. This is an issue that has flared up several times in recent years. Each time, industry has managed to beat back such concerns. But it's worth noting that the scientific roots of concern have not disappeared. If anything, they've thickened as new research substantiates older concerns.

The story of an FCC passively echoing an industry determined to play hardball with its critics is worth a further look. The CTIA's own website acknowledges the helpful hand of government's "light regulatory touch" in allowing the industry to grow.[26]

Former congressman Dennis Kucinich ventures one explanation for the wireless industry's success in dodging regulation: "The industry has grown so fast its growth has overtaken any health concerns that may have gained attention in a slow growth environment. The proliferation of technology has overwhelmed all institutions that would have attempted safety testing and standards," Kucinich said.[27]

But the core questions remain: Is there really credible evidence that cell phones emit harmful radiation that can cause human health problems and disease? Has the FCC done an adequate job in protecting consumers from health risks? Or has it simply aped industry stonewalling on health and safety issues?

Before wading into these questions, some perspective is in order.

First, there's simply no denying the usefulness and immense popularity of wireless technology. People depend on it for safety, information, entertainment and communication. It doesn't take a keen social observer to know that wireless has thoroughly insinuated itself into daily life and culture.

The unanswered question, though, is whether consumers would embrace the technology quite so fervently if health and safety information was not spun, filtered and clouded by a variety of industry tactics.

To gain some insight into this question, we conducted an online survey of 202 respondents, nearly all of whom own cell phones, on Amazon's Mechanical Turk Web platform (see Appendix). One striking set of findings: many respondents claim they would change behavior—reduce wireless use, restore landline service, protect their children—if claims on health dangers of wireless are true.

It is not the purpose of this reporter to establish that heavy cell phone usage is dangerous. This remains an extremely controversial scientific issue with new findings and revised scientific conclusions repeatedly popping up. Just months ago, a German scientist who had been outspoken in denouncing the view that cell phones pose health risks reversed course. In an April 2015 publication, Alexander Lerchl reported results confirming previous research on the tumor-promoting effects of electromagnetic fields well below human exposure limits for mobile phones. "Our findings may help to understand the repeatedly reported increased incidences of brain tumors in heavy users of mobile phones," the Lerchl team concluded.[28] And in May 2015, more than 200 scientists boasting over 2,000 publications on wireless effects called on global institutions to address the health risks posed by this technology.

But the National Cancer Institute still contends that no cell phone dangers have been established. A representative of NCI was the sole known dissenter among the 30 members of the World Health Organization's International Agency for Research on Cancer (IARC) when it voted to declare wireless RF "possibly carcinogenic."[29] If leading scientists still can't agree, I will not presume to reach a scientific conclusion on my own.

IARC RF working group: Official press release

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 208

31 May 2011

IARC CLASSIFIES RADIOFREQUENCY ELECTROMAGNETIC FIELDS AS POSSIBLY CARCINOGENIC TO HUMANS

Lyon, France, May 31, 2011 -- The WHO/International Agency for Research on Cancer (IARC) has classified radiofrequency electromagnetic fields as **possibly carcinogenic to humans (Group 2B)**, based on an increased risk for **glioma**, a malignant type of brain cancer, associated with wireless phone use.

But let's at least look at some of the incriminating clues that health and biology research has revealed to date. And let's look at the responses of both industry and the FCC.

The most widely cited evidence implicating wireless phones concerns gliomas, a very serious type of brain tumor. The evidence of elevated risk for such tumors among heavy cell phone users comes from several sources.

Gliomas account for roughly half of all malignant brain tumors, which are relatively rare. The annual incidence of primary malignant brain tumors in the U.S. is only 8.2 per 100,000 people, according to the International Radio Surgery Association.

Still, when projected over the entire U.S. population, the public health impact is potentially very significant.

Assuming roughly four new glioma cases annually in the U.S. per 100,000 people, yields over 13,000 new cases per year over a total U.S. population of 330 million. Even a doubling of that rate would mean 13,000 new gliomas, often deadly, per year. A tripling, as some studies have found, could mean as many as 26,000 more new cases annually. Indeed, the respected online site Medscape in January 2015 reported results of Swedish research under the headline: *Risk for Glioma Triples With Long-Term Cell Phone Use.*[30]

And here's some eye-opening quantitative perspective: the wars in Iraq and Afghanistan, waged now for more than a decade each, have together resulted in roughly 7,000 U.S. deaths.

Preliminary—though still inconclusive—research has suggested other potential negative health effects. Swedish, Danish and Israeli scientists have all found elevated risk of salivary gland tumors. One Israeli studied suggested elevated thyroid cancer risk. Some research has found that men who carry their phones in their pockets may suffer sperm count damage. One small study even suggests that young women who carry wireless devices in their bras are unusually vulnerable to breast cancer.

And while industry and government have never accepted that some portion of the population is unusually sensitive to electromagnetic fields, many people continue to complain of a broad range of symptoms that include general weakness, headaches, nausea and dizziness from exposure to wireless.

Some have suggested that the health situation with wireless is analogous to that of tobacco before court decisions finally forced Big Tobacco to admit guilt and pay up. In some ways, the analogy is unfair. Wireless research is not as conclusively incriminating as tobacco research was. And the identified health risks with wireless, significant as they are, still pale compared with those of tobacco.

But let's not dismiss the analogy outright. There is actually a very significant sense in which the tobacco-wireless analogy is uncannily valid.

People tend to forget that the tobacco industry—like the wireless industry—also adopted a policy of tone-deaf denial. As recently as 1998, even as evidence of tobacco toxicity grew overwhelming, cigarette maker Phillip Morris was writing newspaper advertorials insisting there was no proof smoking caused cancer.

It seems significant that the responses of wireless and its captured agency—the FCC—feature the same obtuse refusal to examine the evidence. The wireless industry reaction features stonewalling public relations and hyper aggressive legal action. It can also involve undermining the credibility and cutting off the funding for researchers who do not endorse cellular safety. It is these hardball tactics that look a lot like 20th century Big Tobacco tactics. It is these hardball tactics—along with consistently supportive FCC policies—that heighten suspicion the wireless industry does indeed have something to hide.

Begin with some simple facts issuing from meta-analysis of cellular research. Dr. Henry Lai, emeritus professor of bioengineering at the University of Washington, has reviewed hundreds of published scientific papers on the subject. He wanted to see how many studies demonstrated that non-ionizing radiation produces biological effects beyond the heating of tissue. This is critical since the FCC emission standards protect only against heating. The assumption behind these standards is that there are no biological effects beyond heating.

But Dr. Lai found that just over half—actually 56%—of 326 studies identified biological effects. And the results were far more striking when Dr. Lai divided the studies between those that were industry-funded and those that were independently funded. Industry-funded research identified biological effects in just 28% of studies. But fully 67% of non-industry funded studies found biological effects (Insert Slide—Cell Phone Biological Studies).

A study conducted by Swiss and British scientists also looked at how funding sources affected scientific conclusions on the possible health effects of cell phone usage. They found that of studies privately funded, publicly funded and funded with mixed sponsorship, industry-funded studies were "least likely to report a statistically significant result."[31] "The interpretation of results from studies of health effects of radiofrequency radiation should take sponsorship into account," the scientists concluded.[32]

So how does the FCC handle a scientific split that seems to suggest bias in industry-sponsored research?

In a posting on its Web site that reads like it was written by wireless lobbyists, the FCC chooses strikingly patronizing language to slight and trivialize the many scientists and health and safety experts who've found cause for concern. In a two page Web post titled "Wireless Devices and Health Concerns," the FCC four times refers to either "some health and safety interest groups," "some parties," or "some consumers" before in each case rebutting their presumably groundless concerns about wireless risk.[33] Additionally, the FCC site references the World Health Organization as among those organizations who've found that "the weight of scientific

evidence" has not linked exposure to radiofrequency from mobile devices with "any known health problems."

Yes, it's true that the World Health organization remains bitterly divided on the subject. But it's also true that a 30 member unit of the WHO called the International Agency for Research on Cancer (IARC) was near unanimous in pronouncing cell phones "possibly carcinogenic" in 2011. How can the FCC omit any reference to such a pronouncement? Even if it finds reason to side with pro-industry scientists, shouldn't this government agency also mention that cell phones are currently in the same potential carcinogen class as lead paint?

Now let's look a bit more closely at the troublesome but presumably clueless crowd of "some parties" that the FCC so cavalierly hastens to dismiss? Let's begin with **Lennart Hardell**, professor of Oncology and Cancer Epidemiology at the University Hospital in Oreboro, Sweden.

Until recently it was impossible to gain any real sense of brain tumor risk from wireless since brain tumors often take 20 or more years to develop. But the cohort of long-term users has been growing. In a study published in the International Journal of Oncology in 2013, Dr. Hardell and Dr. Michael Carlberg found that the risk of glioma—the most deadly type of brain cancer—rose with cell phone usage. The risk was highest among heavy cell phone users and those who began to use cell phones before the age of 20.[34]

Indeed, those who used their phones at least 1640 hours (which would be roughly 30 minutes a day for nine years) had nearly three times the glioma incidence. Drs. Hardell and Carlberg also found that gliomas tend to be more deadly among heavy wireless callers.[35]

Perhaps of greatest long-term relevance, glioma risk was found to be four times higher among those who began to use mobile phones as teenagers or earlier. These findings, along with the established fact that it generally takes decades for tumors induced by environmental agents to appear, suggest that the worst consequences of omnipresent wireless devices have yet to be seen.

In a 2013 paper published in *Reviews on Environmental Health*, Drs. Hardell and Carlberg argued that the 2011 finding of the IARC that identified cell phones as a "possibly carcinogenic" needs to be revised. The conclusion on radiofrequency electromagnetic fields from cell phones should now be "cell phones are not just a possible carcinogen." They can now be "regarded as carcinogenic to humans" and the direct cause of gliomas (as well as acoustic neuromas, a less serious type of tumor).[36] Of course, these views are not universally accepted.

The usual spin among industry supporters when presented with research that produces troubling results is along the lines of: "We might pay attention if the results are duplicated." In fact, the Hardell results were echoed in the French CERENAT study, reported in May of 2014. The CERENAT study also found higher risk among heavy users, defined as those using their phones at least 896 hours (just 30 minutes a day for five years). "These additional data support

previous findings concerning a possible association between heavy mobile phone use and brain tumors," the study concluded.[37]

Cell phones are not the only wireless suspects. Asked what he would do if he had policy-making authority, Dr. Hardell swiftly replied that he would "ban wireless use in schools and pre-schools. You don't need Wi-Fi," he noted.[38] This is especially interesting in view of the FCC's sharply hiked spending to promote and extend Wi-Fi usage, as well as its consistent refusal to set more stringent standards for children (more on all this later). But for now let's further fill out the roster of the FCC's unnamed "some parties."

Martin Blank is a Special Lecturer in Physiology and Cellular Biophysics at Columbia University. Unlike Dr. Hardell, who looks at broad epidemiological effects over time, Dr. Blank sees cause for concern in research showing there is biological response at the cellular level to the type of radiation emitted by wireless devices. "The biology tells you unequivocally that the cell treats radiation as a potentially damaging influence," Dr. Blank said in a late 2014 interview.[39]

"The biology tells you it's dangerous at a low level," he added. Though some results have been difficult to replicate, researchers have identified a wide range of cellular responses including genetic damage and penetration of the blood brain barrier. Dr. Blank specifically cited the "cellular stress response" in which cells exposed to radiation start to make proteins.

It is still not clear whether biological responses at the cellular level translate into human health effects. But the research seems to invalidate the basic premise of FCC standards that the only biological effect of the type of radiation produced by wireless devices is tissue heating at very high power levels. But the standards-setting agencies "ignore the biology," according to Dr. Blank. He describes the FCC as being "in industry's pocket."[40]

Sweden's Lund University is annually ranked among the top 100 universities in the world. **Leif Salford** has been chairman of the Department of Neurosurgery at Lund since 1996. He is also a former president of the European Association for Neuro-Oncology. In the spring of 2000, Professor Salford told me that wireless usage constituted "the world's largest biological experiment ever."[41]

He has conducted numerous experiments exposing rats to cellular-type radiation. Individual experiments have shown the radiation to penetrate the blood-brain barrier, essential to protecting the brain from bloodstream toxins. Professor Salford also found that rats exposed to radiation suffered loss of brain cells. "A rat's brain is very much the same as a human's. They have the same blood-brain barrier and neurons. We have good reason to believe that what happens in rat's brains also happens in humans," he told the BBC in 2003. Dr. Salford has also speculated that mobile radiation could trigger Alzheimer's disease in some cases but emphasized that much more research would be needed to establish any such causal relationship. Does this man deserve to be dismissed as one of a nameless and discredited group of "some parties?"

And what about the **American Academy of Pediatrics (AAP),** which represents 60,000 American doctors who care for children? In a December 12, 2012 letter to former Ohio Congressman Dennis Kucinich, AAP President Dr. Thomas Mclnerny writes: "Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults."[42]

In a subsequent letter to FCC officials dated August 29, 2013, Dr. Mclnerny points out that "children, however, are not little adults and are disproportionately impacted by all environmental exposures, including cell phone radiation." Current FCC exposure standards, set back in 1996, "do not account for the unique vulnerability and use patterns specific to pregnant women and children," he wrote. (Insert slide: A Plea from Pediatricians). Does an organization representing 60,000 practitioners who care for children deserve to be brushed off along with "some health and safety interest groups?"

So what is the FCC doing in response to what at the very least is a troubling chain of clues to cellular danger? As it has done with wireless infrastructure, the FCC has to this point largely relied on industry "self-regulation." Though it set standards for device radiation emissions back in 1996, the agency doesn't generally test devices itself. Despite its responsibility for the safety of cell phones, the FCC relies on manufacturers' good-faith efforts to test them. Critics contend that this has allowed manufacturers undue latitude in testing their devices.

Critics further contend that current standards, in place since cell phones were barely in use, are far too lax and do not reflect the heavy usage patterns that have evolved. Worse still, industry is allowed to test its own devices using an imprecise system that makes no special provision for protecting children and pregnant women. One 2012 study noted that the procedure widely used by manufacturers to test their phones "substantially underestimates" the amount of RF energy absorbed by 97% of the population, "especially children." A child's head can absorb over two times as much RF energy. Other persons with smaller heads, including women, are also more vulnerable. The authors recommend an alternative computer simulation technique that would provide greater insight into the impact of cellular radiation on children and on to the specific RF absorption rates of different tissues, which vary greatly.[43]

Acting on recommendations of the General Accounting Office, the FCC is now reconsidering its standards for wireless testing and allowed emissions. On the surface, this may seem to represent an effort to tighten standards to promote consumer health and safety. But many believe the FCC's eventual new standard will actually be weaker, intensifying any health risk from industry's self-reported emission levels. "They're under great pressure from industry to loosen the criteria," notes Joel Moskowitz, director of the Center for Family and Community Health at UC Berkeley's School of Public Health.[44] One fear is that the FCC could measure the allowed radiation absorption level (SAR) over a wider sample of tissue, effectively loosening the

standard allowable energy absorption. One FCC official, who asked that his name not be used, contended that a decision had not yet been made to loosen the standard.

But to this point, there is little evidence the FCC is listening to anyone beyond its familiar friends in the wireless industry. Carl Blackman, a scientist at the Environmental Protection agency until retiring in 2014, notes that the FCC does rely to some degree on an inter-agency governmental group for advice on health matters. The group includes, for example, representatives from the EPA and the FDA.

Blackman served on that advisory group and he says that it has been divided. Though some government advisers to the FCC find evidence of wireless health risks convincing, others remain skeptical, said Blackman. Root of the skepticism: even though numerous researchers have found biological and health effects, the mechanism for action by non-ionizing radiation on the human body has still not been identified. "I don't think there's enough of a consensus within the Radio Frequency Inter-agency Working Group for them to come out with stricter standards," he says.[45]

But political pressures also figure mightily in all this. The EPA, notably, was once a hub of research on RF effects, employing as many as 35 scientists. However, the research program was cut off in the late 80s during the Regan presidency. Blackman says he was personally "forbidden" to study health effects by his "supervisory structure."[46] He termed it "a political decision" but recognized that if he wanted to continue to work at the EPA he would have to do research in another area.

Blackman is cautious in imputing motives to the high government officials who wanted his work at EPA stopped. But he does say that political pressure has been a factor at both the EPA and FCC: "The FCC people were quite responsive to the biological point of view. But there are also pressures on the FCC from industry." The FCC, he suggests, may not just be looking at the scientific evidence "The FCC's position—like the EPA's—is influenced by political considerations as well."[47]

Still, the FCC has ultimate regulatory responsibility and cannot indefinitely pass the buck on an issue of fundamental public health. Remarkably, it has not changed course despite the IARC classification of cell phones as possibly carcinogenic, despite the recent studies showing triple the glioma risk for heavy users, despite the floodtide of research showing biological effects, and despite even the recent defection of core industry booster Alex Lerchl. It is the refusal of both industry and the FCC to even acknowledge this cascade of warning signs that seems most incriminating.

Of course, industry behavior goes well beyond pushing for the FCC's willful ignorance and inaction. Industry behavior also includes self-serving public relations and hyper aggressive legal action. It can also involve undermining the credibility of and cutting off the funding for researchers who do not endorse cellular safety. It is these hardball tactics that recall 20th century Big Tobacco tactics. It is these tactics that heighten suspicion that the wireless industry does

indeed have a dirty secret. And it is those tactics that intensify the spotlight on an FCC that so timidly follows the script of the fabulously wealthy, bullying, billion-dollar beneficiaries of wireless.

Chapter Four: You Don't Need Wires To Tie People Up

So let's look a little more deeply at some of the actions of an industry group that boasts of 500 meetings a year with the FCC. Lobbying is one thing. Intimidation is another. CTIA has shown its skill at—and willingness to use—both.

Outright legal bullying is a favored tactic. The City of San Francisco passed an ordinance in 2010 that required cell phone manufacturers to display more prominently information on the emissions from their devices. This information was already disclosed—but often buried—in operator manuals and on manufacturer websites. The idea was to ensure that consumers saw information already mandated and provided.

Seeing this as a threat to its floodtide of business, the industry sued the City of San Francisco. The City, fearing a prolonged legal fight with an industry that generates hundreds of billions of dollars in annual revenue, backed down.

On May 12, 2015, Berkeley, California's City Council unanimously passed a similar ordinance. Joel Moskowitz, director of the Center for Family and Community Health at the University of California-Berkeley's School of Public Health, has been involved in the effort. Berkeley, he says, didn't want to run into the same legal threats that paralyzed San Francisco. So it tried to draft the most inoffensive and mild language possible. The proposed Cell Phone Right to Know ordinance: "To assure safety, the Federal Government requires that cell phones meet radio frequency (RF) exposure guidelines. If you carry or use your phone in a pants or shirt pocket or tucked into a bra when the phone is ON and connected to a wireless network, you may exceed the federal guidelines for exposure to RF radiation. This potential risk is greater for children. Refer to the instructions in your phone or user manual for information about how to use your phone safely."[48]

Sounds pretty inoffensive, no? Not to the CTIA, which indicated that it was prepared to sue, according to Berkeley City Attorney Zach Cowan.[49] (On June 8th, CTIA did indeed sue the City of Berkeley.)

Well, from the industry point of view, why not throw around your weight? Smash mouth legal tactics have been highly successful thus far as industry has managed to throttle several efforts to implicate manufacturers in cases where heavy users suffered brain tumors.

But one current case has advanced in district court in Washington to the point where the judge allowed plaintiffs to present expert witness testimony. The industry response: file a legal action seeking to invalidate long-held court methods for qualifying expert witnesses.

This is a very rich industry that does not hesitate to outspend and bully challengers into submission. Meanwhile, amidst the legal smoke and medical confusion, the industry has

managed to make the entire world dependent on its products. Even tobacco never had so many hooked users.

Such sustained success in the face of medical doubt has required industry to keep a lid on critics and detractors. Many scientists who've found real or potential risk from the sort of microwave radiation emanating from wireless devices have learned there is a price to be paid for standing up to the industry juggernaut. A few prominent examples:

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In 1994, University of Washington researchers Henry Lai and N.P. Singh found that rats exposed to microwave radiation suffered DNA damage to their brain cells. This was a scary finding since DNA damage can lead to mutations and possibly cancer.

The reaction from industry was swift. Motorola was at that time the U.S. market leader in cell phones. In a memorandum obtained by the journal Microwave News, Motorola PR honcho Norm Sandler outlined how the company could "downplay the significance of the Lai study." One step: "We have developed a list of independent experts in this field and are in the process of recruiting individuals willing and able to reassure the public on these matters," Sandler wrote. After outlining such measures, he concluded that Motorola had "sufficiently war-gamed" the issue. The practices of lining up industry-friendly testimony and "war-gaming" researchers who come up with unfavorable results have been persistent themes with this industry.

Motorola "War-Games" Bad News

Motorola, Microwaves and DNA Breaks: "War-Gaming" the Lai-Singh Experiments

"We have developed a list of independent experts in this field and are in the process of recruiting individuals willing and able to reassure the public on these matters."

"I think we have sufficiently war-gamed the Lai-Singh issue..."

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After Lai's results were published, Motorola decided to sponsor further research on microwaves and DNA damage. Oftentimes. lab results cannot be reproduced by other

researchers, particularly if experiments are tweaked and performed a bit differently. Non-confirming studies raise doubt, of course, on the original work.

Motorola lined up Jerry Phillips, a scientist at the Veteran's Administration Medical Center in Loma Linda, California, and Phillips tested the effect of radiation at different frequencies from those tested by Lai and Singh. Nevertheless, Phillips found that at some levels of exposure, DNA damage increased, while at other levels it decreased. Such findings were "consistent" with the sorts of effects produced by chemical agents, Phillips said in an interview.[50] In some cases, the radiation may have activated DNA repair mechanisms, reducing the overall microwave effect. But what was important, Phillips explained, is that there were *any* biological effects at all. The wireless industry has long contended—and the FCC has agreed—that there is no evidence that non-ionizing radiation at the frequencies and power levels used by cell phones is biologically active.

Understanding the potential impact of "biological effect" findings, Motorola again turned to damage control, said Phillips. He recalls receiving a phone call from a Motorola R&D executive. "I don't think you've done enough research,'" Phillips recalls being told. The study wasn't ready for publication, according to the Motorola executive. Phillips was offered more money to do further research without publishing the results of what he'd done.

But Phillips felt he'd done enough. Despite warnings for his own boss to "give Motorola what it wants," Phillips went ahead and published his findings in 1998. Since then, Phillips' industry funding has dried up. Meanwhile, as many other researchers report, government funding to do independent research on microwave radiation has dried up, leaving the field at least in the U.S. to industry-funded scientists. "There is no money to do the research," Said Phillips. "It's not going to come from government because government is controlled by industry."[51]

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Om P. Gandhi is Professor of Electrical and Computer Engineering at the University of Utah and a leading expert in dosimetry—measurement of non-ionizing radiation absorbed by the human body. Even before cell phones were in wide use, Professor Gandhi had concluded that children absorb more emitted microwave radiation. "The concentration of absorbed energy is 50 to 80% greater," he explained.[52]

These conclusions were not acceptable to Professor Gandhi's industrial sponsors. In 1998, he recalls, an executive from a cell phone manufacturer—which he did not want to identify—told him directly that if he did not discontinue his research on children his funding would be cut off. Professor Gandhi recalled replying: "I will not stop. I am a tenured professor at the University of Utah and I will not reject my academic freedom." Professor Gandhi also recalled some of his thought process: "I wasn't going to order my students to alter their results so that I can get funding." His industry sponsors cancelled his contract and asked for a return of funds.

Professor Gandhi believes that some cell phone users require extra protection because their heads are smaller and more absorptive. "Children, as well as women and other individuals with smaller heads absorb more concentrated energy because of the proximity of the radiating antenna to the brain tissue," he said. And yet the FCC has not acted to provide special protection for these groups. Asked why not, Professor Gandhi conceded that he doesn't know. He does note, however, that recent standards-setting has been dominated by industry representatives.[53]

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While the mobile industry refuses to admit to even the possibility that there is danger in RF radiation, giant insurance companies see things differently. Several insurers have in recent years issued reports highlighting product liability risk with cell phones. This is important because it is evidence that where money is on the line professionals outside the industry see the risk of legal liability.

Legal exposure could be one reason—perhaps the central one—the industry continues to stonewall. Should legal liability be established, one key question will be how much wireless executives knew—and at what point in time. Meanwhile, the combination of public relations denials, legal intimidation and the selective application of pressure on research follows a familiar pattern. "The industry is basically using the tobacco industry playbook," UC Berkeley's Moskowitz said in a recent radio interview.[54]

That playbook has thus far been highly successful in warding off attention, regulation and legal incrimination.

Chapter Five: $270 Billion . . . and Looking for Handouts

The FCC's network of corruption doesn't just shield industry from needed scrutiny and regulation on matters of public health and safety. Sometimes it just puts its hand directly into the public pocket and redistributes that cash to industry supplicants.

Such is arguably the case with the Universal Service Fund. Originally established to extend telephone service to rural and urban areas that industry would find difficult or uneconomical to wire, the USF is now shifting from subsidizing landline phone service to subsidizing the extension of broadband Internet. USF monies also support the Lifeline program, which subsidizes cell phone service to low-income consumers, and the E-Rate program, which subsidizes Internet infrastructure and service to schools and libraries.

Since 1998, more than $110 billion has been allocated to Universal Service programs, notes Charles Davidson, director of the Advanced Communications Law & Policy Institute at New York Law School. The FCC has allocated over $40 billion to the E-Rate program alone.

Who pays the freight for these high-cost programs? You do.

Technically, landline and wireless phone companies are assessed for the Universal Service fund's expenditures. But the FCC also allows those companies to pass on such charges to their subscribers, which they do. Both landline and wireless subscribers pay a monthly Universal Service charge that is tacked on to their phone bills. That charge has been rising and recently amounted to a 16% surcharge on interstate calls.

Consumers who pay for these programs might be interested to learn that both the E-Rate and Lifeline programs have been riddled with fraud. Government watchdogs have repeatedly found the programs to be inefficient and prone to inflated and fraudulent claims. But the programs have been a windfall for tech and telecom industry beneficiaries. Wherever the FCC presides, it seems, these industries reap a windfall.

The General Accounting Office (GAO) has issued several reports citing fraud, waste and mismanagement, along with inadequate FCC oversight of the subsidy program. Bribery, kickbacks and false documentation can perhaps be expected in a handout program mandated by Congress and only indirectly supervised by the FCC.

But the scope of fraud has been impressive. The most striking corruption has marred the E-Rate program, which subsidizes Internet hardware, software and service for schools and libraries, and the Lifeline cell phone subsidies.

In recent years, several school districts have paid fines to settle fraud cases involving bribery, kickbacks, non-competitive bidding of contracts and false documentation in the E-Rate

program. More eye opening perhaps are the settlements of fraud claims by tech giants like IBM, Hewlett Packard and AT&T. The HP case, for example, involved some colorful bribery allegations, including gifts of yachts and Super Bowl tickets. HP settled for $16 million. An HP official and a Dallas Independent School District official both received jail sentences.

The Lifeline program has also been riddled with fraud. A Wall Street Journal investigation of the five top corporate beneficiaries of Lifeline showed that 41% of more than 6 million subsidy claimants "couldn't demonstrate their eligibility or didn't respond to requests for certification."[55] AT&T, Verizon, and Sprint Nextel were three of the major Lifeline beneficiaries.

The FCC has initiated several efforts to clean up USF programs and seems honestly determined to bring greater accountability and efficiency to its subsidy efforts. Nevertheless, problems with fraud persist, as reported recently by the FCC's own top investigator.

Congress established the FCC's Office of Inspector General in 1989 to "provide objective and independent investigations, audits and reviews of the FCC's programs and operations." Here's what the FCC's internal investigative unit said in a September 30, 2014 report to Congress about its Office of Investigation (OI): "*The bulk of the work of OI involves investigating and supporting civil and criminal investigations/prosecutions of fraud in the FCC's federal universal service program.*"[56]

Office of Inspector General

OFFICE OF INVESTIGATION

The bulk of the work of OI involves investigating and supporting civil and criminal investigations/prosecutions of fraud in the FCC's federal universal service program.

Fraud—as pervasive and troubling as it has been—is just one of the problems with the programs of universal service. It may not even be the fundamental problem. More fundamental issues concern the very aim, logic and efficiency of programs to extend broadband and wireless technology at public expense. Though the aims of extending service to distant impoverished areas seem worthy on the surface, there are many reasons to think the major beneficiaries of these programs are the technology companies that win the contracts.

Lobbyists have long swarmed over the FCC looking to get an ever-growing piece of the USF honeypot. An FCC report on meetings with registered lobbyists details a 2010 meeting with representatives of the International Society for Technology in Education and other education lobbyists. Topics discussed, according to the FCC report, included "the need to raise the E-Rate's annual cap."[57]

The CTIA, leaving no stone unturned in its efforts to pump up member revenues, last year responded to a House hearing on the USF by grousing that "current USF-supported programs skew heavily toward support of wireline services. . . . The concentration of USF monies to support wireline services is inconsistent with technological neutrality principles and demonstrated consumer preferences," CTIA wrote..[58] An industry that generates hundreds of billions of dollars in equipment and service revenues annually bellies up for a bigger slice of the $8 billion a year USF.

The grousing has paid off. The FCC recently announced that it will raise spending on E-Rate from what had been a cap of $2.4 billion a year to $3.9 billion. A significant portion of new outlays will go to Wi-Fi—yet another wireless industry victory at the FCC. But the CTIA is by no means the only industry group pressing the FCC.

Leading the roster of active lobbyists on E-Rate issues is the Software and Information Industry Association. Beginning in 2006, SIAA led all lobbyists with 54 mentions of E-Rate in its filings, according to the Center for Responsive Politics. SIAA board members include executives from tech heavyweights Google, Oracle and Adobe Systems.

Tech business leaders—many of them direct beneficiaries of FCC programs—made a direct pitch to FCC Chairman Wheeler last year to hike E-Rate funding. "The FCC must act boldly to modernize the E-Rate program to provide the capital needed to upgrade our K-12 broadband connectivity and Wi-Fi infrastructure within the next five years," the executives wrote.[59]

There were dozens of corporate executive signees to this letter, including the CEOs of many Fortune 500 giants. But let's just consider the participation of three: top executives of Microsoft, Google and HP all joined the call to expand E-Rate subsidies. Consider the simple fact that these three tech giants alone had revenues of $270 billion—more than a quarter of a trillion dollars—in a recent four-quarter period. Together, they produced nearly $40 billion in net income. And yet their top executives still thought it necessary to dun the FCC—and really, they were surreptitiously hitting up the public—for ramped-up spending on what was then a $2.4 billion a year program.

Is that greed? Arrogance? Or is it simply behavior conditioned by success in repeatedly getting what they want at the public trough? Almost never mentioned in these pleas for higher subsidies is the fact that ordinary American phone subscribers are the ones footing the bill for the E-Rate program—not the FCC or the telecom industry.

Much of the added spending, as noted, will go towards the installation of wireless networks. And yet Wi-Fi does not have a clean bill of health. When Lennart Hardell, professor of Oncology and Cancer Epidemiology at the University Hospital in Orebro, Sweden, was asked what he would do if given policy authority over wireless health issues, he replied swiftly that he would "ban wireless use in schools and pre-school." Noting that there are wired alternatives, Professor Hardell flatly stated: "You don't need Wi-Fi."[60] And yet the FCC, prodded by an industry ever on the lookout for incremental growth opportunities, is ignoring the health of youngsters to promote expanded Wi-Fi subsidies in schools across the U.S.

And what about the merit of the program itself? Overlooking the fraud and lobbying and Wi-Fi safety issues for a moment, shouldn't schools and libraries across the country be equipped with the best electronic gear, accessing the Internet at the fastest speeds? Doesn't the government owe that to its younger citizens, especially those disadvantaged by the long-referenced digital divide?

Well, maybe. But answers to these questions hinge on even more fundamental question: Do students actually learn more or better with access to the latest high-speed electronic gadgetry?

It would be foolish to argue that nobody benefits from access to high-speed Internet. But the benefits are nowhere near as broad or rich as corporate beneficiaries claim. Some researchers, for example, have concluded that computers don't seem to have positive educational impact—they may even have negative impact—when introduced into the home or freely distributed to kids from low income backgrounds.

Duke University researchers Jacob Vigdor and Helen Ladd studied the introduction of computers into North Carolina homes. They found that the academic performance of youngsters given computers actually declined. "*The introduction of home computer technology is associated with modest but statistically significant and persistent negative impacts on student math and reading test scores.*" the authors wrote in a National Bureau of Economic Research Working Paper.[61] The impact was actually most negative on the poorer students.

A study in the Journal of International Affairs examined the impact of the global One Laptop Per Child Program (OLPC), which has distributed millions of computers to children around the world. Researchers Mark Warschauer and Morgan Ames conclude: "*The analysis reveals that provision of individual laptops is a utopian vision for the children in the poorest countries, whose educational and social futures could be more effectively improved if the same investments were instead made on more proven and sustainable interventions. Middle- and high-income countries may have a stronger rationale for providing individual laptops to children, but will still want to eschew OLPC's technocratic vision. In summary, OLPC represents the latest in a long line of technologically utopian schemes that have unsuccessfully attempted to solve complex social problems with overly simplistic solutions.*"[62]

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Can One Laptop Per Child Save the World's Poor?

"...In summary, One Laptop Per Child represents the latest in a long line of technologically utopian development schemes that have unsuccessfully attempted to solve complex social problems with overly simplistic solutions."

Access to computers in the home may not work educational magic. But what about computers in the classroom? Don't they have educational value there?

The anecdotal evidence is mixed at best. Consider how students in Los Angeles, newly equipped with flashy iPads at a mind-boggling taxpayer cost of more than $1 billion, went about using the new tools to improve their educational performance. "Instead of solving math problems or doing English homework, as administrators envisioned, more than 300 Los Angeles Unified School District students promptly cracked the security setting and started tweeting, posting to Facebook and playing video games."[63]

But let's cut through the self-serving corporate claims and the troubling anecdotes to hear from someone who actually has had extensive and unique field experience. Kentaro Toyama was co-founder of Microsoft's research lab in India. Over more than five years he oversaw at least a dozen projects that sought to address educational problems with the introduction of computer technology. His conclusion: "The value of technology has been over-hyped and over-sold."

The most important factor in improving schools, says Toyama, now the W.K Kellogg Associate Professor of Community Information at the University of Michigan, is good teachers. Without good, well-trained teachers, adequate budgets and solid school administration, technology does little good. "Technology by itself never has any kind of positive impact," he said.[64]

The only schools in his experience that benefited from increased technology investment were those where "the teachers were very good, the budgets adequate." The richer schools, in essence. But as both Vigdor and Warschauer found, the introduction of technology has by itself little if any positive effect. For a public conditioned to believe in the virtues of new technology, such testimony is a bracing dose of cold reality.

But what about cost? Doesn't technology in the schools more efficiently replace alternative investments? Cost reductions are often the most persuasive argument for technology, Toyama agrees. But even these have been overstated. The costs of introducing new technology run far beyond initial hardware and software investments, said Toyama. In reality, the total costs of ownership—including maintenance, training, and repair—typically run to five or ten times the initial cost, according to Toyama. He said of the investment in technology for cost benefits: "I would say that in the long run—and even in the medium run and the short-run—that's probably the worst and most misguided conclusion to come to."[65]

He adds: "The inescapable conclusion is that significant investments in computers, mobile phones and other electronic gadgets in education are neither necessary nor warranted for most school systems. In particular, the attempt to use technology to fix underperforming class rooms . . . is futile. And for all but wealthy, well-run schools, one-to-one computer programs cannot be recommended in good conscience."[66]

But that doesn't keep industry lobbyists from recommending them. And it hasn't kept the FCC for spending scores of billions subsidizing technology to the very groups least likely to benefit from it.

Unmoved by the arguments of researchers and educators like Vigdor, Warschauer, and Toyama, the FCC keeps moving to increase technology subsidies. Ignoring research that disputes the value of technology in closing the so-called "digital divide," the FCC has even pioneered a new slogan: "the Wi-Fi gap."

In announcing that it was lifting E-Rate's annual budget from $2.4 billion to $3.9 billion and stepping up investment in wireless networking, FCC chairman Wheeler exulted that "10 million students are going to experience new and better opportunities."[67] The impact on consumer pocketbooks (and potentially on youngsters' health from daily Wi-Fi exposure) were not mentioned.

The two Republican members of the FCC did at least recognize the pocketbook impact. "It always seems easier for some people to take more money from the American people via higher taxes and fees rather than do the hard work," said Commissioner Michael O'Reilly.[68]

The subsidized provision of high-speed Internet service is yet another pet project of the FCC. Julius Genachowski, chairman from 2009 to 2013, championed the transition of the USF from landline phone service to broadband. Universal broadband Internet connections would begin to absorb the monies collected from consumers to extend basic phone service.

As with government subsidies for cell phone service, classroom technology, and Wi-Fi, there are basic questions about the wisdom of subsidizing broadband. Charles Davidson and Michael Santorelli of the New York Law School found that spending billions to extend broadband is a flawed approach since there are many largely ignored reasons people choose not to adopt

broadband. "Everybody is pushing broadband non-stop," noted Davidson, director of the Law School's Advanced Communications Law and Policy Institute. "I think the FCC is focused on the wrong set of issues," he said.[69]

Already, he explained, over 98% of Americans have access to wired or wireless broadband. The issue is not one of supply. It's one of demand. Many people—for a variety of reasons—don't really care about broadband, he contends. Price is one issue. Also powerful factors—but given almost no attention—are privacy and security concerns. "In our view, they should be focused on barriers to meaningful broadband utilization: privacy and security," said Davidson.[70]

But consumer privacy (more on this subject in Chapter Seven) has no well-funded lobby with limitless access to the FCC.

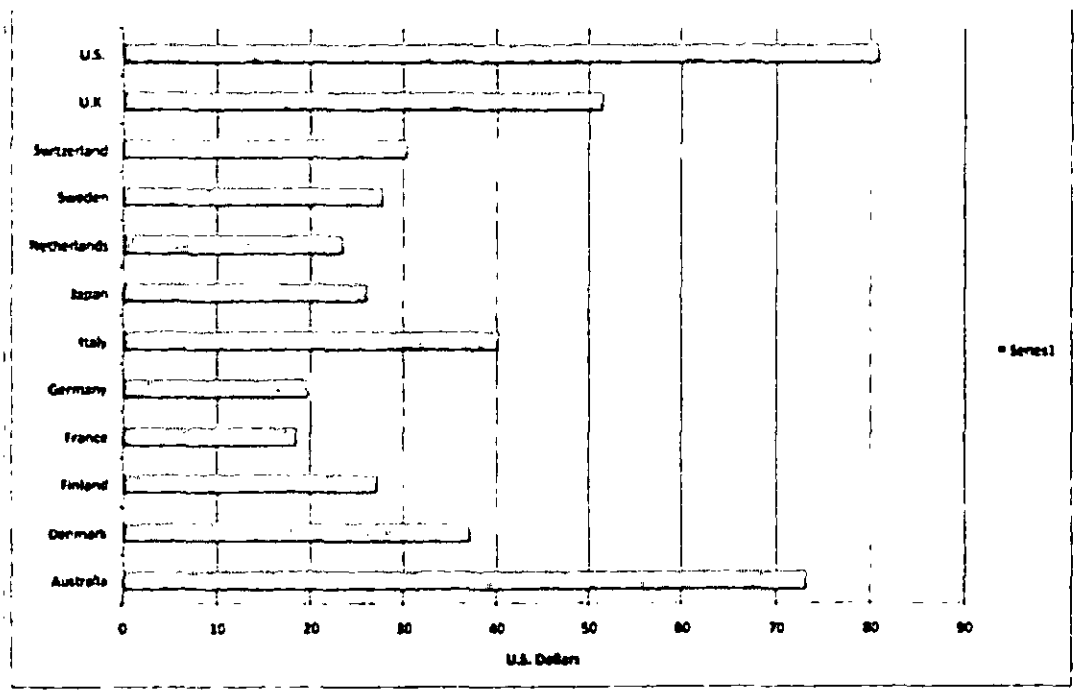
Chapter Six: The Cable Connection

The network has also been active in diluting FCC control of the cable television industry. Over the years, cable has devolved into major de facto local monopolies. Comcast and Time Warner Cable, whose merger proposal was dropped in April, are dominant forces in both cable television and broadband Internet subscriptions. Somehow, though, they have managed to steer clear of one another in specific markets, giving each pricing power where it faces little local competition.

It's interesting that cable companies annually rank in consumer polls among the "most hated" or "most disliked" American corporations. Indeed, Comcast and Time Warner Cable often top the "most hated" list.[71] Why would these companies—providers of the TV programming that has so expanded consumer options in recent decades—be so widely scorned? After all, the U.S. has been a leader in developing both cable technology and diverse television programming.

The problem is that it hasn't been anything close to a leader in bringing down subscriber prices. Industry consultants typically measure pricing by the metric of average revenue per subscriber. Industry trackers at IHS compared the price of U.S. pay television (which includes satellite services) to those in more than 60 other countries. U.S. prices were the highest, with only Australia even coming close. The average revenue per subscriber in the U.S. in 2013 was $81. But in France it was just $18.55. In Germany it was $19.68. In Japan it was just over $26.

Pay TV Monthly Revenue Per Person:



And U.S. cable prices have risen in recent years at rates three or more times the rate of inflation. This has been going on for some time. From 1995 to 2013 cable rates increased at a 6.1% annual clip. The Consumer Price Index, by contrast, rose by just 2.4% annually. Former FCC commissioner Michael Copps says the FCC shares a major part of the blame. "The FCC is as culpable for allowing that as much as the companies for imposing it," he said.[72]

One area where the FCC has contributed to the problem is in its traditional rubber-stamping of merger agreements. The proposed Comcast/Time Warner Cable deal has been shelved, largely because of Justice Department reservations. But a long run of earlier FCC-sanctioned deals allowed Comcast and Time Warner Cable to grow to the market dominance—and attendant pricing power—they currently command.

Lofty monthly cable bills pinch consumers. But it's more than that. Subscribers paying $80 a month are often paying for a lot of channels they don't watch and don't want. The FCC has never required cable operators to charge for what consumers actually want to watch. Kevin Martin, who chaired the FCC from 2005 to 2009, pushed to "debundle" programming in hopes of lowering bills. But the issue was never resolved. Only recently have viable competitive alternatives to cable's "bundled" packages become available. The satellite service Dish, for example, months ago introduced its Sling offering that enables consumers to opt for smaller and cheaper packages.

In fairness to cable operators, it should be pointed that programmers often require operators to take unwanted or fledgling channels along with their stars. New York cable operator Cablevision Systems filed suit against Viacom in 2013, charging that in order to get popular channels like MTV and Nickelodeon it was also forced to take low-rated channels like Nicktoons and VH1 Soul. But the simple truth is that no matter who is to blame, the cable consumer pays high prices, typically for some programming he doesn't want. As it often does when powerful interests pursue dubious practices, the FCC has for the most part idly stood by.

Still, the FCC isn't entirely to blame. Some factors in the growth of the cable giants cannot be laid at its doorstep. Local municipalities often granted monopoly or duopoly status in granting franchises to cable network builders. With the huge capital investments required to cable metropolitan areas, this once seemed to make sense.

And over the years, the cable giants have used a variety of tactics to weaken what little local competition they may have had. Active lobbyists on the local level, the cable giants have managed to convince a growing number of states to outlaw municipal systems that could threaten private corporate incumbents. The FCC for many years declined to tangle with the states in this matter, partly due to the opposition of Republican commissioners. But the Wheeler-led Commission did vote recently to override state laws that limit the build-out of municipal cable systems.

Still, many years of industry subservience will be difficult to swiftly undo. One linchpin merger shows how FCC decision-making has been thoroughly undermined by the revolving door, lobbying, and carefully targeted campaign contributions. All conspired in Comcast's pivotal 2011 buyout of NBC Universal, a deal which reinforced Comcast's domination of both cable and broadband access. This deal also set the stage for the recent headline-grabbing acrimony over the issue of net neutrality.

In 2011, mighty Comcast proposed to acquire NBC Universal. A series of mergers including the 1986 acquisition of Group W assets and the 2002 acquisition of AT&T's cable assets had already vaulted Comcast into cable market leadership. In bidding for NBC Universal, a huge step towards vertical integration, Comcast was once again raising the stakes. NBC Universal would give Comcast a treasure trove of programming, including valued sports content like NFL football and the Olympics.

Suddenly, the issue was not just cable subscriber base size—where Comcast had already bought its way to dominance. NBC Universal would also allow Comcast to consolidate its growing power as a broadband Internet provider. And with NBC Universal's programming assets, Comcast would gain new leverage when negotiating prices to carry the competing programming content of rivals. This would prompt a new round of debate over net neutrality. Couldn't a programming-rich Comcast slow down rival services—or charge them more to carry their programming?

To short-circuit any potential opposition to the merger, Comcast assembled a superstar cast of lobbyists. As Susan Crawford reports in her 2013 book, "Comcast hired almost eighty former government employees to help lobby for approval of the merger, including several former chiefs of staff for key legislators on congressional antitrust committees, former FCC staffers and Antitrust Division lawyers, and at least four former members of Congress.[73] Such "profligate hiring," Crawford observes, pretty much silenced the opposition to the deal. If Comcast had already retained one member of a lobbying firm, the firm could not under conflict of interest rules object to the deal. And Comcast had locked up key lobbying shops. Money was both weapon and silencer.

Of course, Comcast had always been a big spender on lobbying, with outlays exceeding $12 million every year since 2008. Lobbying costs peaked in 2011 at $19.6 million, according to the Center for Responsive Politics.

For its part, the FCC had a long history of approving most media mergers. So it was hardly a great surprise when the agency, after exacting some relatively minor concessions from Comcast, rubber-stamped the deal. Comcast would thus broaden its footprint as local monopoly distributor of cable. And with its new programming assets, it would enhance its leverage in negotiating deals to carry its rivals' programming. It would also fortify its position of growing strength as broadband Internet gatekeeper.

The most telling footnote to the deal would come just four months later. FCC Commissioner Meredith Atwell Baker, who voted to approve the merger in January 2011, left the FCC to become a top-tier Comcast lobbyist in May. It was the ultimate—and perhaps most telling—glide of the revolving door.

Baker's was a high-profile defection. But it was neither the first nor the last. Comcast had successfully convinced other FCC officials to take their expertise and government contacts to the cable giant. Comcast has long been a master at spinning the revolving door to its own advantage. "Comcast has been very good at hiring everyone who is very smart," said Crawford.[74]

Approval of the NBC Universal deal was another in the long string of FCC merger approvals that made Comcast a nationwide monopolist that could dictate both pricing and viewer programming choice.

But the deal may have had another unintended consequence. It set the stage for Comcast's subsequent battles on net neutrality. "Those mergers gave additional oomph to the issue of net neutrality," noted former commissioner Copps. Speaking specifically of Comcast's buyout of NBC Universal, IHS senior analyst Eric Brannon agreed. "That merger laid the grounds for net neutrality."

In allowing Comcast to acquire major programming assets, the deal would sharpen questions about the power of gatekeepers like Comcast to control the flow of traffic from rival Web services. So in bowing to lobbyist pressure, the FCC would bring on itself a whole new set of pressures by focusing public attention on the issue of net neutrality.

With activists rounding up comments from the public and hip TV personalities like HBO's John Oliver also beating the drums, net neutrality quickly grew into a popular issue that won the support of President Obama, and by proxy, his hand-picked appointee Tom Wheeler. When the FCC ruled in February of 2015 that it would seek Title II authority to regulate the Internet and presumably block any favoritism by broadband gatekeepers, it seemed to finally cast its lot with the public against steamrolling corporate interests

The issue had simmered for years but reached full boil when movie purveyor Netflix, which had argued that its service was slowed down by Comcast, signed a side deal ensuring better download speeds for its wares. This triggered an outburst of public concern that Comcast was now in position to operate "fast" and "slow" lanes, depending on whether a rival programmer could afford to ensure that Comcast provide adequate download speed.

With nearly 4 million comments—many supplied or encouraged by public interest groups—filed to the FCC, net neutrality was a bankable political issue. And there's no question, net neutrality attracted public interest because it gave cable viewers—long furious at the treatment by the monopolists who send them monthly bills—issues of both viewing pleasure and economics.

But it also fed into the longstanding sentimental but increasingly unrealistic view of the Internet as the last bastion of intellectual freedom. Internet romanticists have long seen the Web as a place that somehow deserves special rules for breaking the stranglehold of traditional media and offering exciting new communications, information retrieval and shopping efficiencies.

Yes, the Internet is a modern marvel. This is beyond dispute. But some of the favors it has won from government over the years have had unfortunate unintended consequences.

In the 1990s, for example, net access providers were repeatedly exempted as an "infant industry" from paying access charges to the Baby Bells even though they had to connect users through local phone networks. The long distance companies were then paying as much as $30 billion a year for the privilege. But the Internet was exempted.

As the late 90s approached, the Internet was no longer an infant industry. Still, the exemption from access charges was extended. That exemption essentially allowed AOL in the late 90s to offer unlimited unmetered online time, a key factor in boosting usage and siphoning advertisers from print media. Why buy an ad in print that might get viewed with the transitory flip of a page when you can get round-the-clock attention online?[75] FCC decisions to grant the Internet access-charge exemptions arguably accelerated the decline of print media and much of the quality journalism print advertising could once support.

Meanwhile, retailers on the Internet were making inroads into brick and mortar retail business with the help of a Supreme Court-sanctioned exemption from collecting sales tax.[76] This judicial coddling of the Internet was the death knell for many smaller mom and pop local businesses, already challenged to match online pricing. And that's not all. The special favors continue virtually every year, as Congress proposes and/or passes legislation to extend special tax exemptions to Internet services.

Well, maybe tax breaks aren't such a bad idea for such an innovative and transformational emerging technology. For all its faults, the Internet—gateway to all goods, repository of all things, wizardly guide to all knowledge, enabler of universal self-expression—is undeniably cool.

But let's not deny that the combination of tax advantages and deregulation was toxic. Allow an industry to emerge with advantages over useful existing industries that largely play by the rules—well, maybe that can be rationalized. But then fail to hold the upstart industry to the same rules, allowing it more leeway to trample fundamental rights because it has the technical capacity to do so. Well, then you have a cruel Faustian bargain.

With the see-no-evil deregulatory gospel loosing all constraints, the Web would devolve into a playground for corporate snoops and criminals. For all its wonders, the Internet comes at a cost: the loss of control over personal data, the surrender of personal privacy, sometimes even the confiscation of identity.

Perhaps the most favorable consequence of net neutrality—and one that has gotten surprisingly little attention—is that it could set the stage for privacy reform. (More on this in Chapter Seven). The FCC can now choose to exercise its Title II powers to enforce privacy standards over broadband Internet. Privacy is one area where the FCC has done a pretty good job in the past.

Worth remembering, though, is that the hard-fought public victory over Net Neutrality may be transitory. AT&T and others have threatened to go to court to upend the FCC rules. And there's a fair chance a Republican Congress will legislate against Title II.

Meanwhile, though, one supreme irony has begun to unfold in the marketplace.

Modern-day laissez fair ideologues love to invoke the wisdom of markets as represented by the "mysterious hand" of Adam Smith. Unfortunately, in the absence of effective regulation, the putatively wise "mysterious hand" generally seems to work its magic for those with huge financial resources and the political access it buys.

In the current cable situation, however, the mysterious hand may actually be working in consumer-friendly ways. Years of regulation that favored the cable companies have now backfired as the market reacts to monopolistic pricing and content control.

Whereas cable giants have commanded premium monthly subscriber prices to deliver packages of largely unwatched channels, the market is now beginning to burst with new "debundled" options that are whittling away at cable's vast subscriber base.

Satellite service Direct TV, as noted, now offers its streaming video Sling TV package of popular networks that includes live sports and news. Amazon, Apple, CBS, HBO, Netflix, Sony, and others offer a variety of streaming video options that allow viewers to cut the cable cord. Suddenly, consumers have the cherry-picking capability that bundled—and expensive—cable packages have never allowed.

In this case, at least, the unintended consequences of the FCC's pro-industry policies may be producing an unexpected pro-consumer twist.

Chapter Seven: What about Privacy?

Has any issue gotten as much lip service—and as little meaningful action?

For all the various congressional bills, corporate self-regulatory schemes and presidential Privacy Bill of Rights proposals, the simple truth remains that no personal information is safe on the Internet. Data brokers have built a multi-billion dollar business exchanging information used to build profiles of Net users. Your shopping and surfing habits, your health history, your banking data, your network of social ties, perhaps even your tax filings are all potentially exposed online. Both legal and criminal enterprises amass this information. And it doesn't go away.

At any given moment people you don't know somehow know where you are. They may very well know when you made your last bank deposit, when you had your last asthma attack or menstrual period. Corporations encourage and pay for every bit of information they can use or sell. Creepy? Perhaps, but as Jeff Chester, president of the Center for Digital Democracy points out: "The basic business model that drives online is advertising."[77]

The FCC largely escapes blame on this one. It is the Federal Trade Commission that has had primary responsibility for protecting Internet privacy. The FCC does have some limited authority, which, some critics say, could have been exercised more vigorously. But for the most part the FCC is not to blame for the rampant online abuse of personal privacy and identity.

The FCC does however have privacy authority over the phone, cable and satellite industries. Until recently, at least, the FCC has kept privacy issues at bay among the companies in these industries. "The FCC has generally taken privacy very seriously," noted Harold Feld, a senior vice president at the non-profit Public Knowledge.[78]

But dynamics now in place suggest that privacy may be the next great testing ground for the FCC. A new chance, perhaps, to champion public interest. Even before the opportunity for privacy enforcement under Title II regulatory powers, the FCC faces new challenges from phone companies, now itching to monetize their vast consumer data stashes the way Net companies have. The commonly used term is "Google envy."

"Until now, ISPs (Internet Service Providers) have mostly not gotten into hot water on privacy—but that's changing," observed Jonathan Mayer, a fellow at the Center for Internet and Society.[79] Verizon and AT&T, major providers of mobile Internet access, have each introduced "super cookies" that track consumer behavior even if they try to delete older, less powerful, forms of cookies. AT&T is actually charging its customers an extra $30 a month *not* to be tracked.

Showdowns loom.

In adopting Title II to enforce net neutrality, the FCC has made broadband Internet access a telecom service subject to regulation as a "common carrier." This reclassification means that the FCC could choose to invoke privacy authority under Title II's Section 222. That section, previously applied to phone and cable companies, mandates the protection of consumer information. Such information—called CPNI for Customer Proprietary Network Information—has kept phone companies from selling data on whom you call, from where you call and how long you spend on the phone. Consumers may have taken such protection for granted on their phone calls. But they have no such protection on their Internet activity—which, as noted, has been a multi-billion dollar safe house hideaway for corporate and criminal abusers of personal privacy.

Now, though, the FCC could put broadband Internet communications under Section 222 protection. To Scott Cleland, a telecom industry consultant who has often been ahead of the analytic pack, this would be a momentous decision.

When the smoke clears—and it hasn't yet—the FCC could make consumer identifiers like IP addresses the equivalent of phone numbers. Suddenly, the Internet companies that have trafficked in all that personal data would be subject to the same controls as the phone and cable companies.

Cleland argues that the risk for privacy abuses extends beyond broadband access providers like Comcast and Verizon to Internet giants like Google and Facebook that have until now flourished with all that personal data. "They are at risk and they are going to live under the uncertainty their business model could be ruled illegal by the FCC," Cleland said.[80]

Much has been written about the legal challenges broadband access providers intend to mount against the FCC's new rules. But Cleland argues that a very different type of legal action could engulf companies that have benefited from the use and sale of private data. Trial lawyers, he argues, will see opportunity in rounding up massive class action suits of Internet users whose privacy has been violated. What sorts of privacy abusers face legal action? Anyone who has "collected CPNI via some type of cookie," according to Cleland.

"Right now, edge providers like Google, Facebook and Twitter are at risk of being sued by trial lawyers," he said.[81]

Sounds great for consumers who care about privacy on the Internet and how it has been abused. But the FCC, Cleland was reminded, has never been a consumer advocate. "Bingo," replied Cleland. That's what makes the FCC's potential move into privacy protection so important and so surprising, he suggests.

There are other signs that the FCC under Tom Wheeler might actually become more consumer-friendly on the issue of data privacy. While Wheeler has brought some former associates from lobbying groups to the FCC, he has also peppered his staff with respected

privacy advocates. Indeed, he named Gigi Sohn, longtime president of the non-profit Public Knowledge, as Counsellor to the Chairman in April.

Another appointee with a privacy background is Travis LeBlanc, head of the FCC's Enforcement Bureau. In previous employment in California's Office of the Attorney General, LeBlanc was active in enforcing online privacy. LeBlanc has stated an interest in privacy and has already taken action against two firms that exposed personal information—including social security numbers—on unprotected Internet servers.

But many aspects of LeBlanc's approach to regulating Internet privacy under Title II remain unclear. Unfortunately, the FCC declined repeated requests to make LeBlanc available for an interview. (It also declined to answer written questions on its enforcement intentions in both privacy and cell tower infrastructure emissions.)

It remains to be seen if LeBlanc and his superiors at the FCC are really willing to take on privacy enforcement. Such a stance would require great courage as the entire Internet infrastructure is built around privacy abuse. It is also questionable whether the FCC would have the courage to challenge Google—a rare corporate ally in the battles over Net Neutrality.

Chapter Eight: Dependencies Power the Network of Corruption

As a captured agency, the FCC is a prime example of institutional corruption. Officials in such institutions do not need to receive envelopes bulging with cash. But even their most well-intentioned efforts are often overwhelmed by a system that favors powerful private influences, typically at the expense of public interest.

Where there is institutional corruption, there are often underlying dependencies that undermine the autonomy and integrity of that institution. Such is the case with the FCC and its broader network of institutional corruption.

As noted earlier, the FCC is a single node on a corrupt network that embraces Congress, congressional oversight committees and Washington social life. The network ties the public sector to the private through a frictionless revolving door—really no door at all.

Temptation is everywhere in Washington, where moneyed lobbyists and industry representatives throw the best parties and dinners. Money also allows industry to control other important factors, like the research agenda. All of this works together to industry's advantage because—as with other instances of institutional corruption—there are compromising dependencies. Policy makers, political candidates and legislators, as well as scientific researchers *are all compromised by their dependence on industry money.*

Dependency #1 – So much of the trouble here comes back to the core issue of campaign finance. Cable, cellular and educational tech interests know where to target their funds for maximum policy impact. And the contributions work, seemingly buying the silence of key committee congressmen—even those with past records as progressives. Key recipients of industry dollars include Massachusetts Senator Ed Markey and, until he retired, California Democrat Henry Waxman. Though they have intermittently raised their voices on such issues as data privacy and cellular health and safety, neither has shown any great inclination to follow through and take up what would have to be a long and tough fight on these issues.

Dependency #2 – Democrats might be expected to challenge industry now and then. They traditionally have done so, after all. But this is the post-*Citizens United* era where the Supreme Court has turned government into a giant auction house.

Bid the highest price and you walk home with the prize—your personal congressman, legislative loophole, even an entire political party.

Such is the case with technology industries and the Democrats. The communications/electronics industry is the third largest industry group in both lobbying and campaign contributions, according to the Center for Responsive Politics. In just 2013 and 2014, this industry sector spent well over $750 million on lobbying.[82]

Only the finance/insurance/real estate and health industries outspend the tech sector on lobbying. But those industry groups lean Republican. Over 62% of the finance/insurance/real estate campaign contributions go to the GOP. Health contributions lean Republican 57% to 43%. But the technology group leans sharply to Democrats, who got 60% of contributions in the 2013-2014 election cycle.[83] The two next largest industry groups—energy/natural resources and agribusiness—also lean heavily Republican. So of the top five industry groups whose money fuels and often tilts elections four are strongly Republican. The Democrats need the tech industry—and they show that dependence with consistent support, rarely raising such public interest issues as wireless health and safety and Internet privacy.

Dependency #3 – Spectrum auctions give the wireless industry a money-making aura. In recent Congressional testimony, an FCC official reminded legislators that the FCC has over the years been a budget-balancing revenue-making force.[84] Indeed, the auctions of electromagnetic spectrum, used by all wireless communications companies to send their signals, have yielded nearly $100 billion in recent years. The most recent auction to wireless providers produced the unexpectedly high total of $43 billion. No matter that the sale of spectrum is contributing to a pea soup of electromagnetic "smog" whose health consequences are largely unknown. The government needs money and Congress shows its appreciation with consistently pro-wireless policies.

Dependency #4 – Science is often the catalyst for meaningful regulation. But what happens when scientists are dependent on industry for research funding? Under pressure from budget cutters and deregulators, government funding for research on RF health effects has dried up. The EPA, which once had 35 investigators in the area, has long since abandoned its efforts.[85] Numerous scientists have told me there's simply no independent research funding in the U.S. They are left with a simple choice: work on industry-sponsored research or abandon the field.

Chapter Nine: A Modest Agenda for the FCC

Nobody is proposing that cell phones be banned. Nor does anyone propose the elimination of the Universal Service program or other radical reforms. But there are some steps—and most are modest—that the FCC can take now to right some of the wrongs that result from long years of inordinate industry access and influence:

1. Acknowledge that there may be health risks in wireless communications. Take down the dismissive language. Maturely and independently discuss the research and ongoing debate on the safety of this technology.

2. In recognition of this scientific uncertainty, adopt a precautionary view on use of wireless technology. Require prominent point-of-sale notices suggesting that users who want to reduce health risks can adopt a variety of measures, including headphones, more limited usage and storage away from at-risk body parts.

3. Back off the promotion of Wi-Fi. As Professor Lennart Hardell has noted, there are wired alternatives that do not expose children to wireless risk.

4. Petition Congress for the budgetary additions needed to expand testing of emissions on antenna sites. It was Congress after all that gave industry carte blanche for tower expansion so long as they comply with FCC standards. But there is evidence of vast non-compliance and Congress needs to ensure that tower infrastructure is operating within the law.

5. Acknowledge that children and pregnant women may be more vulnerable to the effects of RF emissions and require special protection.

6. Promote cable debundling as a way to lighten consumer cable bills, especially for those customers who don't care about high-cost sports programming.

7. Apply more rigorous analysis to properly assess the value of technology in education. Evidence continues to pile up that technology in education is not as valuable as tech companies claim. Pay less attention to tech CEOs—pay more attention to the researchers who've actually studied the impact of trendy technology fixes on learning

8. Take over enforcement of personal privacy rights on the Internet. Of all the basic suggestions here, this would require the most courage as it would involve challenging many of the entrenched powers of the Internet.

Chapter Ten: Stray Thoughts

Some concluding thoughts:

Why do so many of the most dubious FCC policies involve technology?

In large part, of course, because the FCC has authority over communications and that is a sector that has been radically transformed—along with so many others—by technology.

Let's be clear, though. The problem is not technology, which unarguably brings countless benefits to modern life. The problem is with the over-extension of claims for technology's usefulness and the worshipful adulation of technology even where it has fearful consequences. Most fundamentally, the problem is the willingness in Washington—for reasons of both venality and naïveté—to give technology a free pass.

Personally, I don't believe that just because something can be done it should heedlessly be allowed. Murder, rape and Ponzi schemes are all doable—but subject to prohibition and regulation. Government regulators have the responsibility to examine the consequences of new technologies and act to at least contain some of the worst. Beyond legislators and regulators, public outrage and the courts can also play a role—but these can be muffled indefinitely by misinformation and bullying.

There are precedents for industries (belatedly perhaps) acting to offset the most onerous consequences of their products. In responding to a mix of litigation, public demand and regulatory requirement, the auto industry, for example, has in the last 50 years substantially improved the safety and environmental footprint of its products.

Padded instrument panels, seat belts, air bags, and crumple zones have all addressed safety issues. Environmental concerns have been addressed with tightened emissions and fuel consumption standards. The response to new safety challenges is ongoing. Before side air bags were widely deployed, sedan drivers side-swiped by much larger SUVs were at vastly disproportionate risk of death and dismemberment.[86] But the deployment of side air bags has "substantially" reduced the risk of collision deaths.[87] Overall, auto fatality rates per 100,000 persons have dropped by nearly 60% in the U.S. since 1966.[88] Today, automakers continue to work on advanced safety features like collision avoidance.

It can be argued that most of these safety improvements came decades after autos were in wide usage and only in response to outrage at Ralph Nader's 1965 revelations on the auto industry.[89] No matter the catalysts. The simple truth remains that the auto industry—and its regulators—have for the last half-century been addressing safety and environmental issues.

But with the overwhelming application of money and influence, information and communications technologies have almost totally escaped political scrutiny, regulatory control, and legal discipline.

Should the Internet have been allowed to develop into an ultra-efficient tool for lifting personal information that includes financial records, health histories and social security numbers? Should wireless communications be blindly promoted even as new clues keep suggesting there may be toxic effects? Should local zoning authorities and American citizens be stripped of the right to protect their own health? Should education be digitized and imposed just because technology companies want to develop a new market and lock in a younger customer base?

All these questions can perhaps be rolled up in one: do we all just play dead for the corporate lobbyists and spinners who promote the unexamined and unregulated application of their products?

Finally, a word about the structure of the FCC. With five commissioners—no more than three from the same party—the structure seems to make some kind of sense.

But in practice, it works out poorly. The identification of commissioners by party tends to bring out the worst in both Republicans and Democrats. Instead of examining issues with clear-sighted independence, the commissioners seem to retreat into the worst caricatures of their parties. The Republicans spout free market and deregulatory ideology that is most often a transparent cover for support of business interests. The Democrats seems satisfied if they can implement their pet spending programs—extension of broadband wireless to depressed urban and rural schools, cell phone subsidies for low income clients. The result is a Commission that fulminates about ideology and spends heavily to subsidize powerful interests.

Perhaps one solution would be to expand the Commission to seven by adding two public interest Commissioners. The public interest only rarely prevails at the FCC. So it would represent vast improvement if both Republican and Democrat commissioners had to vie for support of public interest representatives in order to forge a majority. The public interest, in other words, would sometimes carry the swing votes.

It's very hard to believe, though, that Congress would ever approve such a plan. It simply represents too much of a threat to the entrenched political power of the two parties. Why would they ever agree to a plan that dilutes that power?

It's also worth noting that the public interest is not always easy to define. Sometimes there are arguably conflicting definitions. Still, an FCC with public interest commissioners is an idea worth consideration. It would at least require party apologists to defend how they so consistently champion the moneyed interests that have purchased disproportionate access and power in Washington.

Appendix—Survey of Consumer Attitudes

What does the public believe about the science and politics of wireless health research? Under what conditions would people change wireless usage patterns? Is the FCC currently trusted to protect public health? How would confirmation of health risks affect trust in the FCC?

These are some of the questions Ann-Christin Posten[90] and Norm Alster[91] hoped to answer with an April 2015 online survey of 202 respondents. Participants were recruited through Amazon's Mechanical Turk online platform. All were U.S. residents and had achieved qualifying approval rates in prior Mechanical Turk surveys.

Participants were asked how likely they believed the following statements to be true:

Statement 1. Prolonged and heavy cell phone use can have a variety of damaging effects on health.

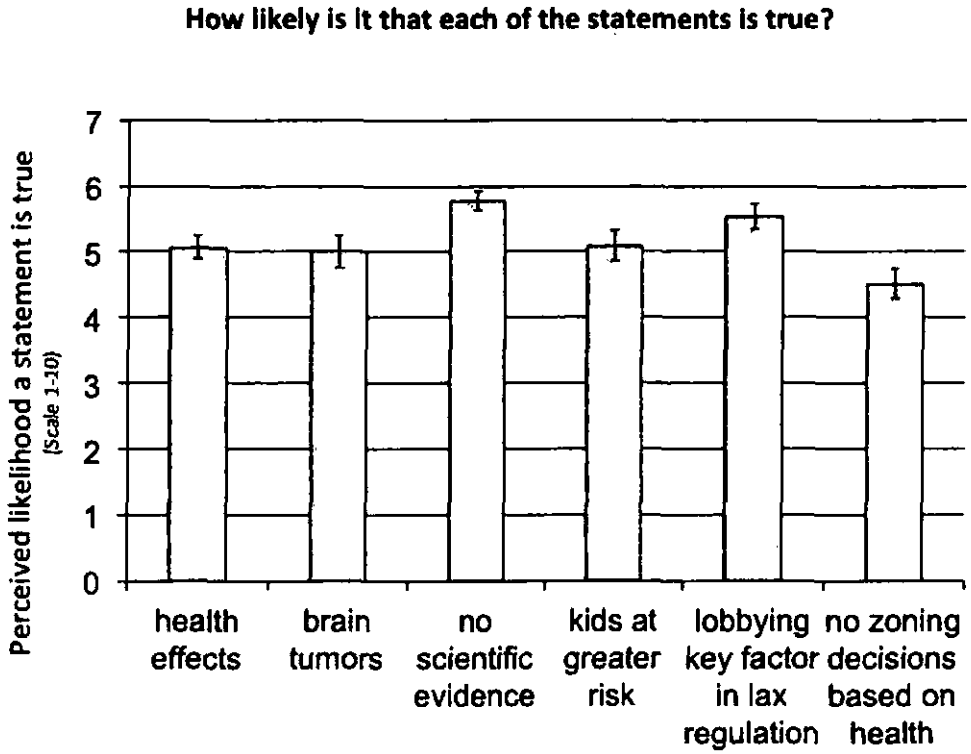
Statement 2. Prolonged and heavy cell phone use triples the risk of brain tumors.

Statement 3. There is no scientific evidence that proves that wireless phone usage can lead to cancer or a variety of other problems.

Statement 4. Children and pregnant women are especially vulnerable to radiation from wireless phones, cell towers and Wi-Fi

Statement 5. Lobbying and campaign contributions have been key factors in keeping the government from acknowledging wireless hazards and adopting more stringent regulation.

Statement 6. The U.S. Congress forbids local communities from considering health concerns when deciding whether to issue zoning permits for wireless antennae.

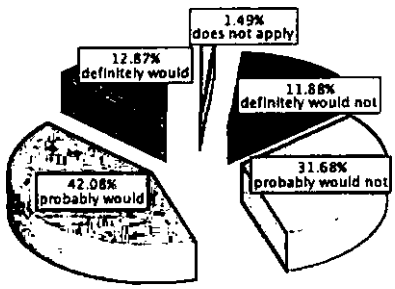


Two findings seem especially interesting:

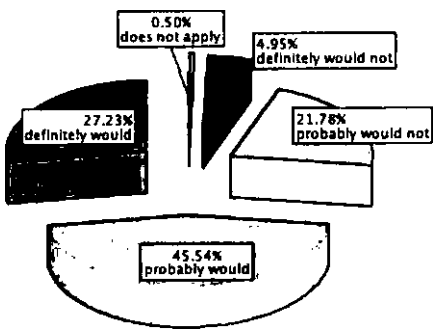
1. Statement 3 received a higher credibility rating than Statements 1 and 2. The different credibility levels are statistically significant. Respondents are more likely to trust in wireless safety than to believe there are general or specific health risks.

2. The only statement that is a matter of uncontested fact is Statement 6 on the outlawing of opposition to antenna sites on health grounds. (All other statements have been both proclaimed and denied.) And yet Statement 6 was least likely to be believed. Just 1.5% of respondents recognized this as an "absolutely true" statement. Over 14% thought this statement was "not true at all." Answers to this question would seem to reflect public ignorance on the political background to wireless health issues.

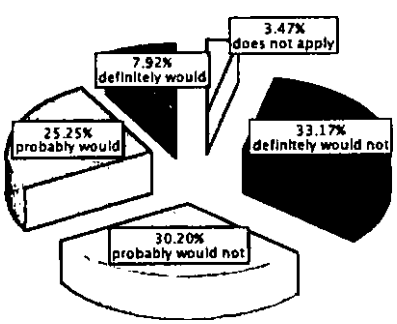
Participants were also asked how they would change behavior if claims of wireless health risks were established as true:



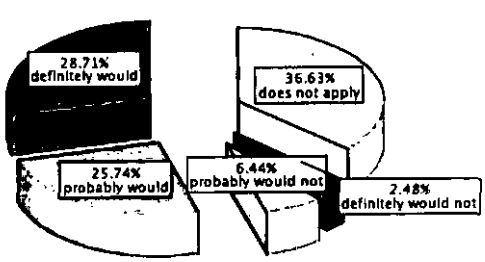
If statement 1 was true,
I would start using headphones.



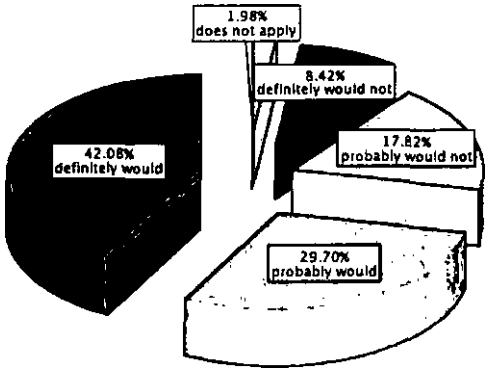
If statement 1 was true,
I would restrict the amount of time
I spend on the phone.



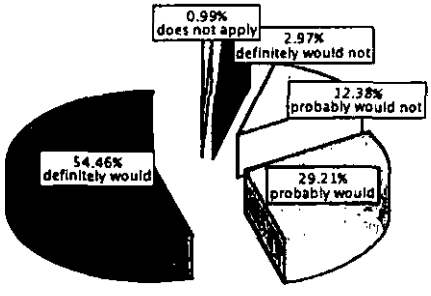
If statement 1 was true,
I would start up a new land line
account for home use.



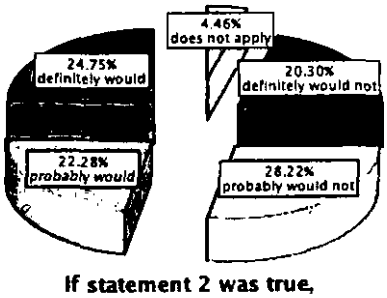
If statement 1 was true,
I would restrict my children's cell phone use.



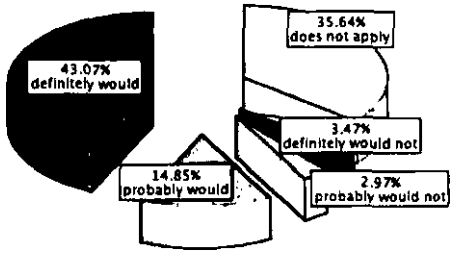
If statement 2 was true,
I would start using headphones.



If statement 2 was true,
I would restrict the amount of time
I spend on the phone.



If statement 2 was true,
I would start up a new land line
account for home use.



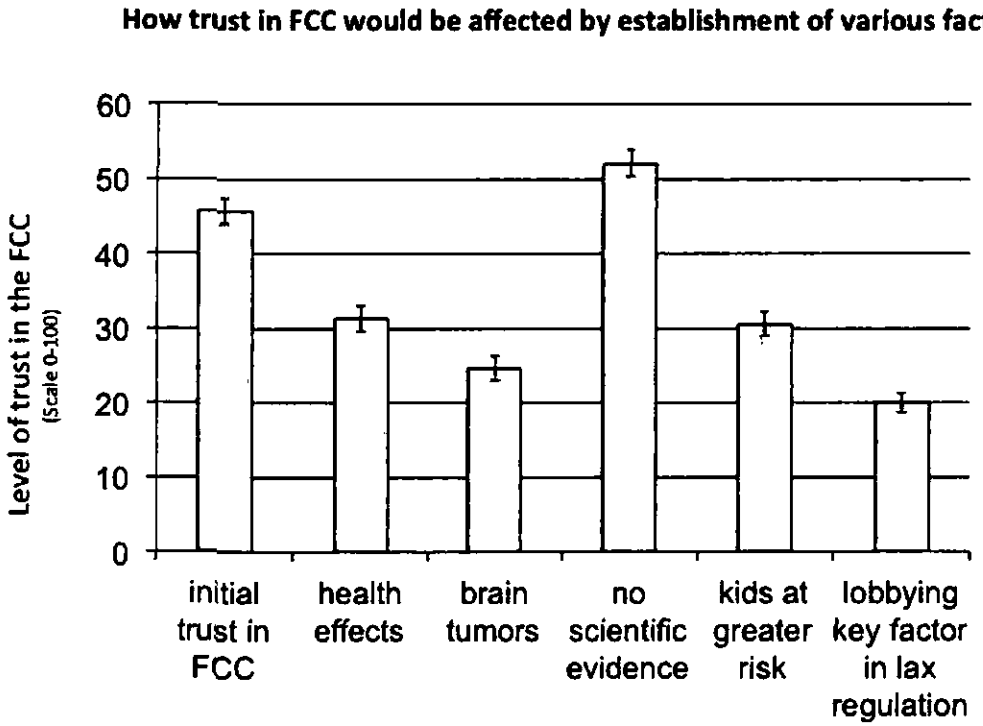
If statement 2 was true,
I would restrict my children's cell phone use.

The greatest impact on behavior came when respondents were asked to assume it is true that prolonged and heavy cell phone use triples the risk of brain tumors. More than half said they would "definitely" restrict the amount of time spent on the phone. Just over 43% would "definitely" restrict their children's phone use. Perhaps most surprisingly, close to 25% would "definitely" start up a new landline phone account. (This last response suggests it may be foolishly premature for the phone giants to exit the landline business just yet.)

The inclination of consumers to change behavior should negative health effects be confirmed suggests the stakes are enormous for all companies that derive revenue from wireless usage.

This survey points to—but cannot answer—some critical questions: Do wireless companies better protect themselves legally by continuing to deny the validity of all troublesome research? Or should they instead be positioning themselves to maintain consumer trust? Perhaps there is greater financial wisdom in listening to the lawyers right now and denying all chance of harm. If so, however, why would anyone seriously concerned about health listen to the industry—or to its captured agency? That's a question the FCC will eventually need to answer.

Trust could eventually become a central issue. Respondents were initially asked to describe their level of trust in the wireless industry and in the FCC as its regulator. Not surprisingly, establishment of any of the presumed health risks—or confirmation of inordinate industry pressure—resulted in statistically significant diminution of trust in both the industry and the FCC.



On a scale of 1 to 100, the FCC had a mean baseline trust level of 45.66. But if the tripling of brain tumor risk is established as definitely true, that number falls all the way to 24.68. If "lobbying and campaign contributions" have been "key factors" in keeping the government from acknowledging wireless hazards, the trust level in the FCC plummets to 20.02. All results were statistically significant.

It's clear that at this point confirmation of health dangers—or even of behind-the-scenes political pressures—from wireless will substantially diminish public trust in the FCC. Skeptics might argue that this gives the FCC motive to continue to downplay and dismiss further evidence of biological and human health effects. Those of a more optimistic bent might see in these findings reason to encourage an FCC concerned about public trust to shake itself loose from special interests.

Endnotes

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[3] December 2014 interview with Twaun Samuel.

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[45] February 2015 interview with Carl Blackman.

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[47] Id.

[48] Lawrence Lessig, Roy L. Furman Professor of Law and Leadership at Harvard Law School, helped to draft the Right to Know ordinance and has offered pro bono legal representation to the city of Berkeley. Professor Lessig was director of the Lab at Harvard's Safra Center for Ethics, from which the Project on Public Narrative was spun off in November of 2014.

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[50] December 2014 interview with Jerry Phillips.

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[52] February 2015 interview with Om P. Gandhi.

[53] Id.

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APPENDIX F

Open Access

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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/cm², limited to 6 min exposure) in contrast to those for continuous, that is non-pulsed exposures

(10 mW/cm², 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).

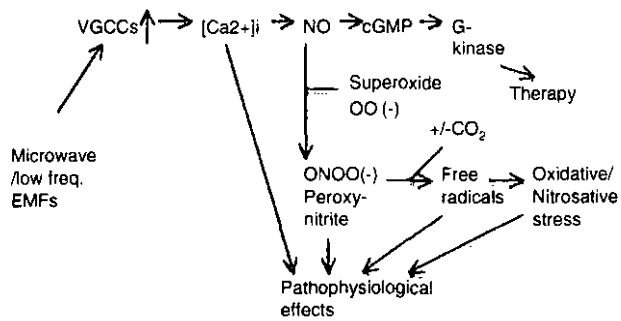

Figure 1: Mechanisms of action for microwave EMFs leading to diverse pathophysiological responses and therapeutic responses. Microwave/lower frequency electromagnetic fields (EMFs) act to stimulate voltage-gated calcium channels (VGCCs), increasing levels of intracellular calcium [Ca2+]i. Elevated [Ca2+]i 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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APPENDIX G

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Electromagnetic fields act *via* activation of voltage-gated calcium channels to produce beneficial or adverse effects

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Abstract

The direct targets of extremely low and microwave frequency range electromagnetic fields (EMFs) in producing non-thermal effects have not been clearly established. However, studies in the literature, reviewed here, provide substantial support for such direct targets. Twenty-three studies have shown that voltage-gated calcium channels (VGCCs) produce these and other EMF effects, such that the L-type or other VGCC blockers block or greatly lower diverse EMF effects. Furthermore, the voltage-gated properties of these channels may provide biophysically plausible mechanisms for EMF biological effects. Downstream responses of such EMF exposures may be mediated through Ca^{2+}/calmodulin stimulation of nitric oxide synthesis. Potentially, physiological/therapeutic responses may be largely as a result of nitric oxide-cGMP-protein kinase G pathway stimulation. A well-studied example of such an apparent therapeutic response, EMF stimulation of bone growth, appears to work along this pathway. However, pathophysiological responses to EMFs may be as a result of nitric oxide-peroxynitrite-oxidative stress pathway of action. A single such well-documented example, EMF induction of DNA single-strand breaks in cells, as measured by alkaline comet assays, is reviewed here. Such single-strand breaks are known to be produced through the action of this pathway. Data on the mechanism of EMF induction of such breaks are limited; what data are available support this proposed mechanism. Other Ca^{2+}-mediated regulatory changes, independent of nitric oxide, may also have roles. This article reviews, then, a substantially supported set of targets, VGCCs, whose stimulation produces non-thermal EMF responses by humans/higher animals with downstream effects involving Ca^{2+}/calmodulin-dependent nitric oxide increases, which may explain therapeutic and pathophysiological effects.

Keywords: intracellular Ca^{2+} • voltage-gated calcium channels • low frequency electromagnetic field exposure • nitric oxide • oxidative stress • calcium channel blockers

Introduction

An understanding of the complex biology of the effects of electromagnetic fields (EMFs) on human/higher animal biology inevitably must be derived from an understanding of the target or targets of such fields in the impacted cells and tissues. Despite this, no understanding has been forthcoming on what those targets are and how they may lead to the complex biological responses to EMFs composed of low-energy photons. The great puzzle, here, is that these EMFs are comprised of low-energy photons, those with insufficient energy to individually influence the chemistry of the cell, raising the question of how non-thermal effects of such EMFs can possibly occur. The author

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has found that there is a substantial literature possibly pointing to the direct targets of such EMFs and it is the goal of this study to review that evidence as well as review how those targets may lead to the complex biology of EMF exposure.

The role of increased intracellular Ca^{2+} following EMF exposure was already well documented more than 20 years ago, when Wallec-zek [1] reviewed the role of changes in calcium signalling that were produced in response EMF exposures. Other, more recent studies have confirmed the role of increased intracellular Ca^{2+} following EMF exposure, a few of which are discussed below. His review [1] included two studies [2, 3] that showed that the L-type voltage-gated channel blocker, verapamil could lower or block changes in response to EMFs. The properties of voltage-gated calcium channels (VGCCs) have been reviewed elsewhere [4]. Subsequently, extensive evidence has been published clearly showing that the EMF exposure can act to produce excessive activity of the VGCCs in many cell types [5–26] suggesting that these may be direct targets of EMF exposure. Many of these studies implicate specifically the L-type VGCCs such that various L-type calcium channel blockers can block responses to EMF exposure (Table 1). However, other studies have shown lowered responses produced by other types of calcium channel blockers including N-type, P/Q-type, and T-type blockers (Table 1), showing that other VGCCs may have important roles. Diverse responses to EMFs are reported to be blocked by such calcium channel blockers (Table 1), suggesting that most if not all EMF-mediated responses may be produced through VGCC stimulation. Voltage-gated calcium channels are essential to the responses produced by extremely low frequency (including 50/60 Hz) EMFs and also to microwave frequency range EMFs, nanosecond EMF pulses, and static electrical and magnetic fields (Table 1).

In a recent study, Pilla [27] showed that an increase in intracellular Ca^{2+} must have occurred almost immediately after EMF exposure, producing a Ca^{2+}/calmodulin-dependent increase in nitric oxide occurring in less than 5 sec. Although Pilla [27] did not test whether VGCC stimulation was involved in his study, there are few alternatives that can produce such a rapid Ca^{2+} response, none of which has been implicated in EMF responses. Other studies, each involving VGCCs, summarized in Table 1, also showed rapid Ca^{2+} increases following EMF exposure [8, 16, 17, 19, 21]. The rapidity of these responses rule out many types of regulatory interactions as being involved in producing the increased VGCC activity following EMF exposure and suggests, therefore, that VGCC stimulation in the plasma membrane is directly produced by EMF exposure.

Possible modes of action following VGCC stimulation

The increased intracellular Ca^{2+} produced by such VGCC activation may lead to multiple regulatory responses, including the increased nitric oxide levels produced through the action of the two Ca^{2+}/calmodulin-dependent nitric oxide synthases, nNOS and eNOS. Increased nitric oxide levels typically act in a physiological context through increased synthesis of cGMP and subsequent activation of protein kinase G [28, 29]. In contrast, in most pathophysiological contexts, nitric oxide reacts with superoxide to form peroxynitrite, a potent non-radical oxidant [30, 31], which can produce radical products, including hydroxyl radical and NO_2 radical [32].

Therapeutic bone-growth stimulation *via* Ca^{2+}/nitric oxide/cGMP/protein kinase G

An example of a therapeutic effect for bone repair of EMF exposure in various medical situations includes increasing osteoblast differentiation and maturation and has been reviewed repeatedly [33–44]. The effects of EMF exposure on bone cannot be challenged, although there is still considerable question about the best ways to apply this clinically [33–44]. Our focus, here, is to consider possible mechanisms of action. Multiple studies have implicated increased Ca^{2+} and nitric oxide in the EMF stimulation of bone growth [44–49]; three have also implicated increased cGMP and protein kinase G activity [46, 48, 49]. In addition, studies on other regulatory stimuli leading to increased bone growth have also implicated increased cGMP levels and protein kinase G in this response [50–56]. In summary, then, it can be seen from the above that there is a very well-documented action of EMFs in stimulating osteoblasts and bone growth. The available data, although limited, support the action of the main pathway involved in physiological responses to Ca^{2+} and nitric oxide, namely Ca^{2+}/nitric oxide/cGMP/protein kinase G in producing such stimulation.

Ca^{2+}/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks

As was noted above, most of the pathophysiological effects of nitric oxide are mediated through peroxynitrite elevation and consequent oxidative stress. There are many reviews and other studies, implicating oxidative stress in generating pathophysiological effects of EMF exposure [see for example 57–64]. In some of these studies, the rise in oxidative stress markers parallels the rise in nitric oxide, suggesting a peroxynitrite-mediated mechanism [64–67].

Peroxynitrite elevation is usually measured through a marker of peroxynitrite-mediated protein nitration, 3-nitrotyrosine (3-NT). There are four studies where 3-NT levels were measured before and after EMF exposure [66, 68–70]. Each of these studies provides some evidence supporting the view that EMF exposure increases levels of peroxynitrite and therefore 3-NT levels [66, 68–70]. Although these cannot be taken as definitive, when considered along with the evidence on oxidative stress and elevated nitric oxide production in response to EMF exposure, they strongly suggest a peroxynitrite-mediated mechanism of oxidative stress in response to EMFs.

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Table 1 EMF responses blocked or lowered by calcium channel blockers

Ref. no.	EMF type	Calcium channel	Cell type or organism	Response measured
2	Pulsed magnetic fields	L-type	Human lymphocytes	Cell proliferation; cytokine production
3	Static magnetic field (0.1 T)	L-type	Human polymorphonuclear leucocytes	Cell migration; degranulation
5	ELF	L-type	Rat chromaffin cells	Differentiation; catecholamine release
6	Electric field	L-type	Rat and mouse bone cells	Increased Ca^{2+}, phospholipase A2, PGE2
7	50 Hz	L-type	Mytilus (mussel) immunocytes	Reduced shape change, cytotoxicity
8	50 Hz	L-type	AtT20 D16V, mouse pituitary corticotrope-derived	Ca^{2+} increase; cell morphology, premature differentiation
9	50 Hz	L-type	Neural stem/progenitor cells	*In vitro* differentiation, neurogenesis
10	Static magnetic field	L-type	Rat	Reduction in oedema formation
11	NMR	L-type	Tumour cells	Synergistic effect of EMF on anti-tumour drug toxicity
12	Static magnetic field	L-type	Myelomonocytic U937 cells	Ca^{2+} influx into cells and anti-apoptotic effects
13	60 Hz	L-type	Mouse	Hyperalgesic response to exposure
14	Single nanosecond electric pulse	L-type	Bovine chromaffin cells	Very rapid increase in intracellular Ca^{2+}
15	Biphasic electric current	L-type	Human mesenchymal stromal cells	Osteoblast differentiation and cytokine production
16	DC & AC magnetic fields	L-type	β-cells of pancreas, patch clamped	Ca^{2+} flux into cells
17	50 Hz	L-type	Rat pituitary cells	Ca^{2+} flux into cells
18	50 Hz	L-type, N-type	Human neuroblastoma IMR32 and rat pituitary GH3 cells	Anti-apoptotic activity
19	Nanosecond pulse	L-type, N-type, P/Q-type	Bovine chromaffin cells	Ca^{2+} dynamics of cells
20	50 Hz	Not determined	Rat dorsal root ganglion cells	Firing frequency of cells
21	700–1100 MHz	N-type	Stem cell–derived neuronal cells	Ca^{2+} dynamics of cells
22	Very weak electrical fields	T-type	Sharks	Detection of very weak magnetic fields in the ocean
23	Short electric pulses	L-type	Human eye	Effect on electro-oculogram
24	Weak static magnetic field	L-type	Rabbit	Baroreflex sensitivity
25	Weak electric fields	T-type	Neutrophils	Electrical and ion dynamics
26	Static electric fields, 'capacitive'	L-type	Bovine articular chondrocytes	Agrican & type II collagen expression; calcineurin and other Ca^{2+}/calmodulin responses

EMF: electromagnetic field; ELF: extremely low frequency.

Such a peroxynitrite-mediated mechanism may explain the many studies showing the single-stranded breaks in DNA, as shown by alkaline comet assays or the similar microgel electrophoresis assay, following EMF exposures in most such studies [71–89], but not in all [90–97]. Some of the factors that are reported to influence whether such DNA single-strand breaks are detected after EMF exposure include the type of cell studied [79, 86], dosage of EMF exposure [78] and the type of EMF exposure studied [73, 77]. Oxidative stress and free radicals have roles, both because there is a concomitant increase in oxidative stress and because antioxidants have been shown to greatly lower the generation of DNA single-strand breaks following EMF exposure [72, 75, 81, 82] as has also been shown for peroxynitrite-mediated DNA breaks produced under other conditions. It has also been shown that one can block the generation of DNA single-strand breaks with a nitric oxide synthase inhibitors [82].

Peroxynitrite has been shown to produce single-strand DNA breaks [98–100], a process that is inhibited by many but not all antioxidants [99, 100]. It can be seen from this that the data on generation of single-strand DNA breaks, although quite limited, support a mechanism involving nitric oxide/peroxynitrite/free radical (oxidative stress). Although the data on the possible role of peroxynitrite in EMF-induced DNA single-strand breaks are limited, what data are available supports such a peroxynitrite role.

Discussion and conclusions

How do EMFs composed of low-energy photons produce non-thermal biological changes, both pathophysiological and, in some cases, potentially therapeutic, in humans and higher animals? It may be surprising that the answer to this question has been hiding in plain sight in the scientific literature. However, in this era of highly focused and highly specialized science, few of us have the time to read the relevant literature, let alone organize the information found within it in useful and critical ways.

This study shows that:

1 Twenty-three different studies have found that such EMF exposures act *via* activation of VGCCs, such that VGCC channel blockers can prevent responses to such exposures (Table 1). Most of the studies implicate L-type VGCCs in these responses, but there are also other studies implicating three other classes of VGCCs.

2 Both extremely low frequency fields, including 50/60 cycle exposures, and microwave EMF range exposures act *via* activation of VGCCs. So do static electric fields, static magnetic fields and nanosecond pulses.

3 Voltage-gated calcium channel stimulation leads to increased intracellular Ca^{2+}, which can act in turn to stimulate the two calcium/calmodulin-dependent nitric oxide synthases and increase nitric oxide. It is suggested here that nitric oxide may act in therapeutic/potentially therapeutic EMF responses *via* its main physiological pathway, stimulating cGMP and protein kinase G. It is also suggested that nitric oxide may act in pathophysiological responses to EMF exposure, by acting as a precursor of peroxynitrite, producing both oxidative stress and free radical breakdown products.

4 The interpretation in three above is supported by two specific well-documented examples of EMF effects. Electromagnetic fields stimulation of bone growth, modulated through EMF stimulation of osteoblasts, appears to involve an elevation/nitric oxide/protein kinase G pathway. In contrast to that, it seems likely that the EMF induction of single-stranded DNA breaks involves a Ca^{2+}/elevation/nitric oxide/peroxynitrite/free radical (oxidative stress) pathway.

It may be asked why we have evidence for involvement of VGCCs in response to EMF exposure, but no similar evidence for involvement of voltage-gated sodium channels? Perhaps, the reason is that there are many important biological effects produced in increased intracellular Ca^{2+}, including but not limited to nitric oxide elevation, but much fewer are produced by elevated Na^{+}.

The possible role of peroxynitrite as opposed to protein kinase G in producing pathophysiological responses to EMF exposure raises the question of whether there are practical approaches to avoiding such responses? Typically peroxynitrite levels can be highly elevated when both of its precursors, nitric oxide and superoxide, are high. Consequently, agents that lower nitric oxide synthase activity and agents that raise superoxide dismutases (SODs, the enzymes that degrade superoxide) such as phenolics and other Nrf2 activators that induce SOD activity [101], as well as calcium channel blockers may be useful. Having said that, this is a complex area, where other approaches should be considered, as well.

Although the various EMF exposures as well as static electrical field exposures can act to change the electrical voltage-gradient across the plasma membrane and may, therefore, be expected to stimulate VGCCs through their voltage-gated properties, it may be surprising that static magnetic fields also act to activate VGCCs because static magnetic fields do not induce electrical changes on static objects. However, cells are far from static. Such phenomena as cell ruffling [102,103] may be relevant, where thin cytoplasmic sheets bounded on both sides by plasma membrane move rapidly. Such rapid movement of the electrically conducting cytoplasm, may be expected to influence the electrical charge across the plasma membrane, thus potentially stimulating the VGCCs.

Earlier modelling of electrical effects across plasma membranes of EMF exposures suggested that such electrical effects were likely to be too small to explain EMF effects at levels reported to produce biological changes (see, for example [22]). However, more recent and presumably more biologically plausible modelling have suggested that such electrical effects may be much more substantial [104–109] and may, therefore, act to directly stimulate VGCCs.

Direct stimulation of VGCCs by partial depolarization across the plasma membrane is suggested by the following observations discussed in this review:

1 The very rapid, almost instantaneous increase in intracellular Ca^{2+} found in some studies following EMF exposure [8, 16, 17, 19, 21, 27]. The rapidity here means that most, if not all indirect, regulatory effects can be ruled out.

2 The fact that not just L-type, but three additional classes of VGCCs are implicated in generating biological responses to EMF

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exposure (Table 1), suggesting that their voltage-gated properties may be a key feature in their ability to respond to EMFs.

3 Most, if not all, EMF effects are blocked by VGCC channel blockers (Table 1).

4 Modelling of EMF effects on living cells suggests that plasma membrane voltage changes may have key roles in such effects [104–109]. Saunders and Jefferys stated [110] that 'It is well established that electric fields ... or exposure to low frequency magnetic fields, will, if of sufficient magnitude, excite nerve tissue through their interactions with ... voltage gated ion channels'. They further state [110] that this is achieved by direct effects on the electric dipole voltage sensor within the ion channel.

One question that is not answered by any of the available data is whether what is known as 'dirty electricity' [111–113], generated by rapid, in many cases, square wave transients in EMF exposure, also acts by stimulating VGCCs. Such dirty electricity is inherent in any digital technology because digital technology is based on the use of such square wave transients and it may, therefore, be of special concern in this digital era, but there have been no tests of such dirty electricity that determine whether VGCCs have roles in response to such fields, to my knowledge. The nanosecond pulses, which are essentially very brief, but high-intensity dirty electricity do act, at least in part, *via* VGCC stimulation (Table 1), suggesting that dirty electricity may do likewise. Clearly, we need direct study of this question.

The only detailed alternative to the mechanism of non-thermal EMF effects discussed here, to my knowledge, is the hypothesis of Friedman *et al.* [114] and supported by Desai *et al.* [115] where the apparent initial response to EMF exposure was proposed to be NADH oxidase activation, leading to oxidative stress and downstream regulatory effects. Although they provide some correlative evidence for a possible role of NADH oxidase [114], the only causal evidence is based on a presumed specific inhibitor of NADH oxidase, diphenyleneiodonium (DPI). However, DPI has been shown to be a non-specific cation channel blocker [116], clearly showing a lack of such specificity and suggesting that it may act, in part, as a VGCC blocker. Consequently, a causal role for NADH oxidase in responses to EMF exposure must be considered to be undocumented.

In summary, the non-thermal actions of EMFs composed of low-energy photons have been a great puzzle, because such photons are insufficiently energetic to directly influence the chemistry of cells. The current review provides support for a pathway of the biological action of ultralow frequency and microwave EMFs, nanosecond pulses and static electrical or magnetic fields: EMF activation of VGCCs leads to rapid elevation of intracellular Ca^{2+}, nitric oxide and in some cases at least, peroxynitrite. Potentially therapeutic effects may be mediated through the Ca^{2+}/nitric oxide/cGMP/protein kinase G pathway. Pathophysiological effects may be mediated through the Ca^{2+}/nitric oxide/peroxynitrite pathway. Other Ca^{2+}-mediated effects may have roles as well, as suggested by Xu *et al.* [26].

Conflicts of interest

The author confirms that there are no conflicts of interest.

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APPENDIX H

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LETTER TO THE EDITOR

Electromagnetic field activation of voltage-gated calcium channels: role in therapeutic effects

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Prof. Pilla (2013) presents a well-documented and highly integrated model of non-thermal therapeutic effects of pulsed/modulated electromagnetic fields (EMFs). The model involves increased intracellular Ca^{2+}, stimulation of calmodulin-dependent signaling both via Ca^{2+} elevation and via direct EMF effects on calmodulin, Ca^{2+}/calmodulin stimulation of cNOS activity/nitric oxide (NO) elevation/stimulation of the cGMP signaling pathway. Increased intracellular Ca^{2+} produced by EMF exposure was already well documented over 20 years ago (Walleczek, 1992) and the only concern of this letter is the origin of such increased intracellular Ca^{2+} in Prof. Pilla's model. It has been shown in two dozen studies of EMF effects mostly at the cellular level, that effects of EMF exposure can be blocked by calcium channel blockers, demonstrating that activation of voltage-gated calcium channels (VGCCs) appears to be essential for many and perhaps all EMF responses (Pall, 2013). It may be argued, therefore, that the increased intracellular Ca^{2+} in Prof. Pilla's model is likely to come from such VGCC activation. While it was proposed that EMF-mediated VGCC activation may be due to partial depolarization of the plasma membrane (Pall, 2013), it is equally plausible that the direct influence of EMFs on the charged residues that regulate VGCC channel opening (Catterall, 2000), may be an alternative explanation. There is one other possible implication of this EMF-VGCC study. While therapeutic effects were proposed to occur via a very similar pathway of action to that proposed by Prof. Pilla (2013), it was also proposed that pathophysiological effects of EMFs may be produced via reaction of NO with superoxide to form peroxynitrite, a potent oxidant (Pall, 2013). If this proposal is correct, it may be useful in therapy to use agents that lower superoxide, such as by Nrf2 induction, and perhaps other agents that lower peroxynitrite, to avoid pathophysiological responses to EMF exposure during such therapy.

Declaration of interest

The author reports no conflicts of interest and is solely responsible for the writing and content of the article.

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APPENDIX I

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Review

Microwave frequency electromagnetic fields (EMFs) produce widespread neuropsychiatric effects including depression

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Low-intensity microwave electromagnetic fields

ABSTRACT

Non-thermal microwave/lower frequency electromagnetic fields (EMFs) act via voltage-gated calcium channel (VGCC) activation. Calcium channel blockers block EMF effects and several types of additional evidence confirm this mechanism. Low intensity microwave EMFs have been proposed to produce neuropsychiatric effects, sometimes called microwave syndrome, and the focus of this review is whether *these are indeed well documented and consistent with the known mechanism(s) of action of such EMFs.* VGCCs occur in very high densities throughout the nervous system and have near universal roles in release of neurotransmitters and neuroendocrine hormones. Soviet and Western literature shows that much of the impact of non-thermal microwave exposures in experimental animals occurs in the brain and peripheral nervous system, such that nervous system histology and function show diverse and substantial changes. These may be generated through roles of VGCC activation, producing excessive neurotransmitter/neuroendocrine release as well as oxidative/nitrosative stress and other responses. Excessive VGCC activity has been shown from genetic polymorphism studies to have roles in producing neuropsychiatric changes in humans. Two U.S. government reports from the 1970s to 1980s provide evidence for many neuropsychiatric effects of non-thermal microwave EMFs, based on occupational exposure studies. 18 more recent epidemiological studies, provide substantial evidence that microwave EMFs from cell/mobile phone base stations, excessive cell/mobile phone usage and from wireless smart meters can each produce similar patterns of neuropsychiatric effects, with several of these studies showing clear dose–response relationships. Lesser evidence from 6 additional studies suggests that short wave, radio station, occupational and digital TV antenna exposures may produce similar neuropsychiatric effects. Among the more commonly reported changes are sleep disturbance/insomnia, headache, depression/depressive symptoms, fatigue/tiredness, dysesthesia, concentration/attention dysfunction, memory changes, dizziness, irritability, loss of appetite/body weight, restlessness/anxiety, nausea, skin burning/tingling/dermographism and EEG changes. In summary, then, the mechanism of action of microwave EMFs, the role of the VGCCs in the brain, the impact of non-thermal EMFs on the brain, extensive epidemiological studies performed over the past 50 years, and five criteria testing for causality, all collectively show that various non-thermal microwave EMF exposures produce diverse neuropsychiatric effects.

Contents

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Chemicals having roles:

Calcium(2+)
Nitric oxide (NO)
Oxido nitrite (peroxynitrite)

1. Introduction

Microwave syndrome (Hocking, 2001; Johnson Liakouris, 1998), a combination of various neuropsychiatric symptoms originally described in persons with occupational exposures to microwave frequency EMFs, has been disputed largely because of the lack of an apparent mechanism for generating these symptoms. It is reported to often include such symptoms as fatigue, headache, insomnia, dysesthesia (impaired sensation), irritability, lack of concentration and other symptoms (Hocking, 2001; Johnson Liakouris, 1998). Similar but more extensive combinations of symptoms have been reported following occupational exposures in two U.S. government reports from the 1970s/1980s (Naval Medical Research Institute Research Report, 1971; Raines, 1981) and following environmental exposures as described in two more recent reviews (Khurana et al., 2010; Levitt and Lai, 2010).

The goal here is not just to review the epidemiology, however, but more importantly to consider the issue of possible physiological mechanism(s). Hennekens and Buring (1989), 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." It is of critical importance therefore to assess possible biological mechanism before considering the epidemiological evidence.

Accordingly, this paper considers the mechanism by which low intensity microwave EMFs impact the cells of our bodies, how that mechanism may be predicted to impact the nervous system, evidence for such impact from experimental animal studies, genetic polymorphism evidence for that mechanism acting in humans to produce neuropsychiatric effects and finally, the epidemiological evidence for such effects in human populations with repeated low level microwave EMF exposure. Consideration of each of these types of evidence influences the overall interpretation presented in this paper.

2. Microwave/lower frequency EMFs act to activate voltage-gated calcium channels

In 24 different studies reviewed earlier (Pall, 2013) and two additional studies (Li et al., 2014; Lisi et al., 2006), microwave and lower frequency low intensity EMF effects were blocked or greatly lowered by calcium channel blockers, agents thought to be specific for blocking voltage-gated calcium channels (VGCCs). In these 26 studies, a total of 5 distinct types of channel blockers were used, with each type having a distinct structure and binding to a distinct site, such that it is essentially certain that these must be acting by blocking VGCCs, which is their only known common property. In each of these 26 studies, each of the responses studied, were blocked or greatly lowered by calcium channel blockers, showing that VGCC activation has roles in producing a wide variety of EMF effects. There is a large literature on changes in calcium fluxes and in calcium signaling following microwave EMF exposure (partially reviewed in Walleczek, 1992; Adey, 1993); each of these, including calcium efflux changes, can be explained as being due to VGCC activation, again suggesting a widespread role of VGCC activation in producing biological responses to EMFs. Pilla (2012) showed that pulsed microwave field exposure, produced an almost instantaneous increase in calcium/calmodulin-dependent nitric oxide (NO) signaling, providing strong evidence that these fields can produce an almost instantaneous VGCC activation. It is likely, that these EMFs act directly on the voltage sensor of the VGCCs to produce VGCC activation (Pall, 2015) with the voltage sensor being exquisitely sensitive to these EMFs because of its physical properties and location in the plasma membrane.

EMFs have been proposed to act to produce a wide variety of responses in the cell, via downstream effects of VGCC activation (Pall, 2013, 2014, 2015), including elevated intracellular calcium [Ca2+]i, excessive calcium and nitric oxide signaling and also excessive peroxynitrite, free radicals and oxidative stress.

VGCC activation has been shown to have a universal or near-universal role in the release of neurotransmitters in the brain and also in the release of hormones by neuroendocrine cells (Berridge, 1998; Dunlap et al., 1995; Wheeler et al., 1994), with such release being produced by calcium signaling. There are high densities of diverse VGCCs occurring in neurons throughout the nervous system. Both the high VGCC density and their function in neurotransmitter and neuroendocrine release throughout the nervous system suggests that the nervous system is likely to be highly sensitive to low intensity EMFs.

3. Genetic polymorphism studies

Genetic polymorphism studies are powerful tools for looking at the roles of specific proteins in human populations. In Table 1, a series of genetic polymorphism studies have been performed that show that an allele producing increased expression of the gene encoding the channel of the main L-type VGCC in the brain, produces diverse neuropsychiatric effects. These studies clearly show that excess L-type VGCC activity can cause neuropsychiatric effects. They also predict, therefore, that increased VGCC activity produced by microwave EMFs may be able to also produce widespread neuropsychiatric effects.

4. Histological and functional changes in central nervous system (CNS) and peripheral nervous system (PNS) in animals exposed to microwave EMFs

The most extensive literature on histological and functional changes in animals is from the Soviet literature from the 1950s/1960s with additional Western literature from the same time period. Both Soviet and non-Soviet literature were reviewed in an English language Publication by Tolgskaya and Gordon (1973). This publication is, therefore, the main focus of this section. That publication was divided into thermal and non-thermal exposure studies, with the non-thermal studies which occupy the majority of the text (pp. 53–137) being of sole interest here.

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Table 1
Influence of genetic polymorphism of the CACNA1C in producing diverse neuropsychiatric effects.

Citation	Genetic polymorphism	Changes produced by allele of gene
Bhat et al. (2012)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Review: The polymorphism is associated with increased susceptibility to bipolar disorder, "depression, schizophrenia, autism spectrum disorders, as well as changes in brain function and structure in control subjects who have no diagnosable psychiatric illness."
Bigos et al. (2010)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Associated with increases in both bipolar disorder and schizophrenia
Krug et al. (2010)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Negatively influences language production on a semantic level
Krug et al. (2014)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Influences episodic memory and retrieval
Soeiro-de-Souza et al. (2012)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Produces impaired facial emotion recognition
Tesli et al. (2013)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Produces increased activation of the amygdala during emotional processing
Thimm et al. (2011)	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Associated with attention deficits including alerting, orienting and executive control of attention

These were all derived from the Tolgskaya and Gordon (1973) review and page numbers listed are page numbers from that document. All refer to changes produced by non-thermal exposures in the nervous system of experimental animals, with most being in rats.

This discussion scrolls down through Table 2.

The majority of the histological changes seen in these mostly rodent studies, are seen in the nervous system, despite its being less than 2% of the rodent cell mass. There are statements made that the nervous system, both central and peripheral, is the most highly sensitive tissue to these non-thermal microwave and lower frequency EMFs. Following the nervous system in sensitivity are *the myocardium and the testis; myocardial cells are known to have* very high densities of VGCCs with especially high densities in the pacemaker cells and the testis is known to have high densities specifically of the T-type VGCCs. Pulsed EMFs are more active in producing histological changes in the brain than are non-pulsed fields, in two studies reviewed; there is a much larger literature showing that in most cases pulsed fields are more biologically active (Pall, 2015; Pangopoulos et al., 2013; Belyaev, 2015).

A wide variety of brain and peripheral nervous system tissues show histological changes following non-thermal exposures. Among the important tissues impacted are the hypothalamus and pituitary gland, where both show similar patterns of changes in neuroendocrine activities. There is an initial increase in neuroendocrine activity (this may be produced directly by VGCC stimulation of secretion), followed over time by "exhaustion" of neuroendocrine activity (this may be produced by tissue damage produced from long term intracellular calcium [Ca2+]i elevation).

There are widespread histological changes produced in neuronal and neuroendocrine tissues. These were repeatedly reported to be largely reversible on cessation of EMF exposure. They become, however, irreversible when exposure is extended in time. There are changes in EEG activity, which may be an easily measurable monitor of neurological damage.

In a summary statement, Tolgskaya and Gordon (1973) state, "This does not confirm the view, so widely held in the past among Soviet investigators and still maintained to a large extent even at the present time in the West, that the action of microwaves is entirely thermal."

While there were many studies of brain impact of non-thermal EMFs performed in the 1950s/60s that make the information content of Tolgskaya and Gordon (1973) quite high, there is also a substantial recent literature on brain effects of non-thermal microwave EMF exposures (see, for example: Ammari et al., 2008a,b; Bas et al., 2009; Brillaud et al., 2007; Carballo-Quintás et al., 2011; Eberhardt et al., 2008; Dasdag et al., 2009, 2012; Grafström et al., 2008; Kumlin et al., 2007; López-Martín et al., 2006; Mausset-Bonnefont et al., 2004; Odaci et al., 2008; Rağbetli et al., 2010; Salford et al., 2003; Sonmez et al., 2010).

5. Older epidemiological reviews and other related studies

Two U.S. Government reports each listed many apparent neuropsychiatric effects of microwave/radiofrequency EMFs and a third recognized the role of non-thermal effects on our bodies, but had only a little consideration of neuropsychiatric effects.

The earliest to these was a Naval Medical Research Institute (NMRI) Research Report (1971) which listed 40 apparent neuro*psychiatric changes produced by non-thermal exposures includ*ing: 5 central/peripheral nervous system (NS) changes, 9 CNS effects, 4 autonomic system effects, 17 psychological disorders, 4 behavioral changes and 2 misc. effects. This NMRI report also provided a supplementary document listing over 2300 citations documenting these and other effects of microwave exposures in humans and in animals.

The Raines (1981) NASA report reviewed extensive literature based on occupational exposures to non-thermal microwave EMFs, with that literature coming from U.S., Western European and Eastern European studies. There are no obvious differences in the literature coming from these different regions. Based on multiple studies, Raines (1981) reports 19 neuropsychiatric effects to be associated with occupational microwave/radiofrequency EMFs.

The Bolen (1994) report put out by the Rome Laboratory of the U.S. Air Force, acknowledged the role of non-thermal effects of microwave EMFs on humans. This report states in the Conclusion section that "Experimental evidence has shown that exposure to low intensity radiation can have a profound effect on biological processes. The nonthermal effects of RF/MW radiation exposure are becoming important measures of biological interaction of EM fields." Clearly Bolen (1994) rejects the claim that only thermal effects occur. Bolen (1994) discusses a specific non-thermal neuropsychiatric effect, where anesthetized animals are awakened when the head is irradiated with microwave EMFs. This suggests a similar mechanism to that acting in humans where such EMFs produce insomnia (see below).

6. Specific epidemiological studies on neuropsychiatric effects of microwave EMFs

There are 26 different epidemiological studies described in Table 3. Although 4 of these only studied a single neuropsychiatric effect, 22 of these each provide substantial evidence for the pattern described in the earlier U.S. reports, that a wide range of

Table 2
Histological and functional changes in brain function in animals following exposure to non-thermal microwave EMFs.

Observations including page numbers	Comment from Author
The majority of the histological changes seen following non-thermal exposures, occurred in the nervous system, despite its being only about 2% of the tissue mass in rodents; this suggests that the nervous system is highly sensitive to such exposures. Elsewhere (pp. 129, 136), it is suggested that the nervous system is the most sensitive tissue, followed by the heart and the testis, among all of the tissues of the body. The most severe histological changes produced by these non-thermal EMF exposures occur in the nervous system (pp. 136).	High CNS sensitivity to EMFs is predicted by the high density of VGCCs that occur in neurons throughout the nervous system, plus the VGCC role in neurotransmitter and neuroendocrine release.
Pulsed fields were more active than non-pulsed fields in producing histological changes (pp. 71, 97).	Pulsed fields have often been found to be more biologically active than are non-pulsed fields in many different studies from many countries (Pall, 2015; Pangopoulos et al., 2013; Belyaev, 2015).
Nervous system regions impacted by non-thermal microwave and lower frequency fields include: cortex, diencephalon including the hypothalamus and thalamus, hippocampus, autonomic ganglia, sensory fibers, pituitary gland including neurohypophysis.	
Neuroendocrine changes seem to undergo change over increased time of exposure. Neurosecretion in the hypothalamus and in the pituitary each go through a complex sequence over time, where EMF exposure initially produces increased hormone secretion but where over time, the neurosecretory cells become "exhausted", leading to lowered secretion and in some cases cell death (pp. 77–96).	Elevated [Ca2+]i stimulates hormone secretion. However when such elevated [Ca2+]i occurs over extended time periods it is highly damaging to the cell, leading in some cases to apoptosis; thus this time course of action should not be surprising.
Histological changes include boutons/argyrophilia, smaller neurons, vacuole formation in neuroendocrine cells, bead-like thickening along dendrites (pp. 66, 70, 71, 73, 97, 98, 100, 111, 115–117, 121–125). Spines near the ends of dendrites become deformed and with still more sessions of irradiation, disappeared entirely (p. 70). Sensory neurons, following exposures, developed changes characteristic of irritation, with "marked tortuosity of the nerve fibers." Many histological changes are seen in the hypothalamic cells (pp. 87–92) as their neuroendocrine function becomes impacted. Histological changes were found even with exposures that produced no apparent functional changes.	
Many histological and functional changes are reported to initially be reversible, following cessation of exposure, but progressively become irreversible with longer exposure. (pp. 64, 72, 74). Paralleling the development of irreversibility, it is found that "Repeated exposure leads to gradual increase in severity of observed changes." ... including "increasingly severe disturbance of conditioned reflex activity in the animals, changes in responses of animals particularly sensitive to acoustic stimulation. ..." (p. 104).	If this is also true in humans, then claims that there cannot be non-thermal effects, claims which act to prolong exposures, may be causing irreversible damage to many humans.
EEG changes (pp. 55, 60, 102), including seizure activity following sensory provocation.	Lai (1997) has an extensive review of EEG changes in animals following non-thermal microwave EMF exposures
Neurodegeneration is reported in a number of places in this review (pp. 72, 83, 117).	
Synaptic connections in regions of the brain are disrupted (pp. 65–74, 97, 113, 121, 136), and at the extreme, some neurons are completely asynaptic (p. 73).	Synaptic connections are known to be disrupted in autism; could this suggest that autism may be generated by EMF exposure? No doubt, we need much more evidence on this. One wonders whether almost 60 years ago, the Soviet literature may have already described a possible animal model for EHS. None is known to exist today, and because of that, EHS studies are severely constrained. Clearly one needs to be skeptical about this interpretation, but it is of great importance that this be further studied.
"after prolonged and repeated irradiation with low-intensity centimeter waves, with no elevation of the body temperature and when the animal's condition remained satisfactory, changes were nevertheless found in the sensory fibers of the skin and viscera in the form of irritation phenomena. These findings concur with the view in the literature that the receptor system as a whole and, in particular its preterminal portions are highly sensitive." p. 76. This description is similar to what is reported to occur in electromagnetic hypersensitivity (EHS). Other such studies are described and include cumulative changes over time, that may also explain changes reported in EHS (pp. 75, 99, 100, 104).	

neuropsychiatric effects are produced by exposure to various non-thermal microwave frequency EMFs. Perhaps the most important of these 26 is the Santini et al. (2003) study of people living near cell phone base stations.

There are three recent studies on the generation of headache during or shortly following long mobile phone calls (listed under Chu et al., 2011 in Table 3). The timing of development of these headaches and the finding that they occur on the ipsilateral side of the head, the side receiving much higher EMF exposure during the call, both argue strongly that these headaches are caused by the long mobile phone calls. Such causality was concluded earlier by Frey (1998) based on earlier studies and is now still more strongly documented.

7. Criteria for assessing causality in epidemiological studies

It is important to consider the different criteria that allow one to judge whether a cause and effect relationship is justified by the studies listed in Table 3 and the individual studies cited in Raines (1981). There are five such criteria that should be considered in making that judgment (see pp. 39–43 in Hennekens and Buring, 1989):

Strength of Association: Is there a strong correlation between exposure and the neuropsychiatric symptoms? There clearly is for several studies cited in Raines (1981). One example is the Dwyer and Leeper (1978) study (see Table 3) where there is a large increase in symptoms and where that increase is greater with longer occupational exposure. Another example is the Lerner (1980) study of 1300 microwave workers, where workers with relatively low exposure levels had an approximate doubling of neurological complaints and where those with substantially higher exposure levels had an approximate tripling of neurological complaints over controls. Sadcikova (1974) found that 7 of 8 neuropsychiatric symptoms studied, showed a statistically significant rise in prevalence with longer occupational exposure (see Table 3). Sadcikova (1974), also found that microwave workers had increases of 3 to over 10-fold in: feeling of heaviness in the head; tiredness; irritability; sleepiness; partial loss of memory; and skin sensitivity. There is also a strong association where important new exposures occur – this is clearly the case with all of the studies of people living near cell/mobile phone base

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Table 3
Neuropsychiatric symptoms apparently produced by exposure to various electromagnetic fields.

Citation	EMF exposure	Apparent neuropsychiatric symptoms
Abdel-Rassoul et al. (2007)	Living near mobile phone base station	Significant increases in neuropsychiatric complaints included: headache, memory changes, dizziness, tremors, depressive symptoms, sleep disturbance; attributed to effects of EMFs on the human nervous system.
Al-Khlaiwi and Meo (2004)	Mobile phone use	Higher prevalence of fatigue, headache, dizziness, tension and sleep disturbance; the authors conclude that mobile phone use is a risk factor for developing these symptoms.
Altpeter et al. (2000)	Short-wave broadcasting tower, ranging from 6.1 to 21.8 MHz	Sleep disruption shown to occur, correlated with exposures and apparent increase over time; short term suppression of melatonin shown, based on melatonin increases during a 3 day period when the tower was turned off.
Bortkiewicz et al. (2004)	Living near cell phone base station EMFs	Sleep disturbance, irritability, depression, blurred vision, concentration difficulties, nausea, lack of appetite, headache, vertigo.
Bortkiewicz et al. (2012)	Living near mobile phone base stations	Dose response relationships for sleep disturbance, irritability, depression, blurred vision, concentration difficulties, nausea, lack of appetite.
Chu et al. (2011), also Chia et al. (2000), Oftedal et al. (2000)	Mobile phone use	Headache during prolonged mobile phone use or within an hour following such use, with pain occurring on the ipsilateral side of the head; similar observations obtained in each of the 3 studies in column 1; see also Frey (1998).
Conrad (2013)	Smart meter EMF exposure	14 common new symptoms (both severe and moderate) among those exposed and symptomatic, 13 apparent neuropsychiatric: Insomnia, tinnitus, pressure in the head, concentration difficulty, headaches, memory problems, agitation, dizziness, fatigue, skin tingling/burning, involuntary muscle contractions, eye/vision problems, numbness; These ranged in prevalence from 63% to 19% of those experiencing symptoms, such that most symptomatic people experienced multiple symptoms.
Dasdag et al. (1992)	People working in MW broadcasting or at a television transmitter station	These groups suffered from headache, fatigue, irritability, stress, sleepiness, loss of appetite, loss of hearing.
Dwyer and Leeper (1978)	People working in radiofrequency EMFs	Headache, eyestrain, dizziness, disturbed sleep, daytime sleepiness, moodiness, mental depression, memory impairment, muscle and/or cardiac pain, breathing difficulties, increased perspiration, difficulty with sex life.
Eger and Jahn (2010)	Living near mobile phone base station	Neuropsychiatric symptoms, with most showing dose–response relationships: depression; headache; cerebral symptoms; dizziness; disorders of optical and acoustic sensory systems; sleep disturbance; skin changes; with the exception of dizziness, all of these had $p < 0.001$.
Johnson Liakouris (1998)	Study of personnel in U.S. embassy in Moscow exposed to microwave EMFs	Statistically significant increases in neurological (peripheral nerves and ganglia), dermographism (skin responses), irritability, depression, loss of appetite, concentration difficulties, peripheral ganglia and nerve dysfunction.
Khan (2008)	Excessive mobile phone use	Complaints of headache, fatigue, impaired concentration, memory disturbance, sleeplessness, hearing problems.
Kolodynskii and Kolodinska (1996)	Children living near a Radio Location Station, Latvia	Memory dysfunction, attention dysfunction, lowered motor function, slowed reaction time, lowered neuromuscular endurance.
Lamech (2014)	Exposure to wireless smart meter radiation in Victoria, Australia	The most frequent symptoms to develop after smart meter radiation exposure were insomnia, headache, tinnitus, fatigue, cognitive disturbances, dysesthesias (abnormal sensation), dizziness.
Navarro et al. (2003)	Living near cell phone base station	Statistically significant dose response relationships for fatigue, irritability, headache, nausea, loss of appetite, sleep disorder, depressive tendency, feeling of discomfort, difficulty of concentration, loss of memory, visual disorder & dizziness.
Oberfeld et al. (2004)	Living near cell phone base station	Statistically significant dose–response relationships for headache, fatigue, irritability, loss of appetite, visual disorder, nausea, sleeping disorders, dizziness, poor concentration, memory loss.
Oto et al. (1994)	Occupational exposure of 25 workers to either UHF television broadcasting (10) or to 1062 kHz medium wave broadcasting (15)	10 neuropsychiatric changes were assessed, all showing statistically significant changes compared with controls: Somatization*, obsessive compulsivity*, interpersonal sensitivity, depression, anxiety*, hostility*, phobic anxiety*, paranoid ideation, psychoticism*, sleeping disturbance. *$p < 0.001$.
Sadcikova (1974)	Occupational exposure to microwave radiation, including at <.07 mW/cm^2	Heaviness in head*, fatigue*, irritability*, sleepiness, memory loss*, cardiac pain*, dermographism (skin sensitivity)*, hyperhidrosis* * significant increase with time of exposure.
Salama and Abou El Naga (2004)	High cell (mobile) phone use	Most common effects were headache, ear ache, sense of fatigue, sleep disturbance, concentration difficulty, face burning sensation. The first three of these had very high statistical significance for correlation with extent of cell phone use.
Santini et al. (2003)	Living near cell phone base stations	Each of the following neuropsychiatric symptoms showed statistical significant dose–response relationships: nausea, loss of appetite, visual disturbance, irritability, depressive tendencies, lowered libido, headache, sleep disturbance, feeling of discomfort, fatigue.
Schüz et al. (2009)	Mobile phone use	Found a small, statistically significant increase in migraine and vertigo. Also found an apparent lowered occurrence of Alzheimer's, other dementia, Parkinson's and epilepsy – these latter were interpreted as being due to perhaps early symptoms of the developing diseases lowering probability of acquiring a mobile phone.
Söderqvist et al. (2008)	Use of mobile phone among adolescents	Increased mobile phone use was associated with increases in tiredness, stress, headache, anxiety, concentration difficulties and sleep disturbances.
Thomée et al. (2011)	High mobile phone use	High mobile phone use was associated with statistically significant rises in stress and sleep disturbance, with somewhat weaker association with depression.
Waldmann-Selsam et al. (2009)	Digital TV signaling	Constant headaches, pressure in head, drowsiness, sleep problems, tightness in chest, shortness of breadth, depressive mood, total apathy, loss of empathy, burning skin, inner burning, leg weakness, pain in limbs, stabbing pain in various organs, weight increase.

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stations, listed in Table 3 and also with the two studies of people who become exposed to radiation from smart meters. The studies listed in Table 3 under Chu et al. (2011) (see also Chia et al., 2000; Oftedal et al., 2000) are of a special type. Here people making very long (over 1 h) cell/mobile phone calls develop headaches an hour or more following the initiation of the long call. So these occur within a specific time range following initiation of these long calls, such that headache would only occur very infrequently in that time frame by chance. So here again, there is a strong association. While there is no question that many of these studies show high strength of association, it is also clear that it is becoming progressively more difficult to do these studies. As exposures become almost universal *in countries around the world, it is getting difficult if not* impossible to find good negative controls. There may be a similar problem in doing animal studies, such that it may be necessary to raise animals in Faraday cages in order to avoid exposures that would otherwise occur as a consequence of our near ubiquitous EMFs.

Biological credibility is extremely strong here, with three aspects of the biology predicting that these low intensity fields cause widespread neuropsychiatric effects. This was discussed above and is reconsidered in the following section.

Consistency within the different epidemiological studies and with other types of studies. The epidemiological studies listed in Table 3 and also those showing neuropsychiatric effects that were cited in Raines (1981) have been performed in many different countries with different cultures. They have been performed in multiple countries in Western Europe, Eastern Europe, the Middle East and in East Asia, as well as in the U.S. and Australia. They are, therefore, not limited to one or two cultural contexts. This is deemed, therefore, an important indicator of causality. We also *have a surprising consistency of apparent neuropsychiatric effects* of different fields, including various occupational exposures and exposures to cell/mobile phone base stations, exposure to the phones themselves, exposure to smart meter pulses, and other EMFs (see Table 3). Pulsation patterns, frequencies and exact intensities may produce various biological responses (Pall, 2015; Pangopoulos et al., 2013; Belyaev, 2015) so it is a bit surprising that we have as much consistency as we do have across different types of exposures. We also have consistency with the biology discussed in the previous section. Because elevated VGCC activity produced by genetic polymorphism (Table 1) produces diverse neuropsychiatric effects, it is not surprising that elevation of VGCC activity produced by microwave EMF exposure apparently also produces diverse neuropsychiatric effects. Similarly because non-thermal EMF exposures produce widespread changes in brain structure and function in animals (Tolgskaya and Gordon, 1973), it is not surprising that the neuropsychiatric symptoms, which are produced as a consequence of brain dysfunction are produced by such EMFs.

Time sequence: It is clear that the all of these effects follow exposure in the various studies that have been published. In some studies, it is also clear that longer occupational exposure times produce increased symptom prevalence. These include Dwyer and Leeper (1978) and Baranski and Edelwejn (1975). These observa*tions all support a causal relationship between exposure to EMF* and the development of neuropsychiatric symptoms.

Dose–response relationship: It is assumed, here, that biological effects have a positive correlation with the intensity of the apparent causal stressor. This is not necessarily true of EMF effects, because it has been shown that there are "window effects" where specific intensities have larger biological effects, than *do either lower or higher intensities* (Pall, 2015; Pangopoulos et al., 2013; Belyaev, 2015). Nevertheless, where different intensities were studied in these epidemiological studies, they do show the dose–response relationship assumed here including Altpeter et al. (2000), Dwyer and Leeper (1978), Eger and Jahn (2010), Lerner (1980), Navarro et al. (2003), Oberfeld et al. (2004), Salama and Abou El Naga (2004), Santini et al. (2003) and Thomée et al. (2011). Thus these data do fit well to the assumed dose–response relationship, found in most causal roles. The Altpeter et al. (2000) study showed a special type of evidence for causality: during a 3-day period when the broadcasting tower was turned off, the melatonin levels recovered to near-normal levels. The studies of headache occurrence on prolonged cell/mobile phone calls (typically well over one hour) listed under Chu et al. (2011) in Table 3 also suggest the assumed dose–response relationship (see also Chia et al., 2000; Oftedal et al., 2000 and earlier citations listed *in Frey, 1998). Because such headaches only occur with prolonged* cell/mobile phone calls, these studies also provide evidence for a dose–response relationship because low doses are ineffective. Furthermore these same studies provide evidence for such a dose–response relationship from another type of observation. Because the headaches occur predominantly on the ipsilateral side of the head which receives much higher EMF exposure intensity, rather than on the contralateral side of the head, which receives much lower intensities, this provides an additional type of evidence for the predicted dose–response relationship.

While the evidence is convincing that the various neuropsychiatric apparent consequences of microwave EMF exposure are in fact caused by such exposures, there may be somewhat more controversy about another EMF-neuropsychiatric linkage. Havas et al. (2010) have reported a similar list of neuropsychiatric symptoms in electromagnetic hypersensitivity (EHS) patients. They found that each of the following symptoms were common in EHS: poor short term memory; difficulty of concentration; eye problems; sleep disorder; feeling unwell; headache; dizziness; tinnitus; *chronic fatigue; tremors; body pain; difficulty speaking; tingling* sensation in feet or hands; difficulty writing; difficulty walking; migraine. The similarity of these symptoms to the most commonly found symptoms following non-thermal microwave EMF exposures (Table 3), suggests that EHS is a genuine sensitivity to EMFs. In the bottom row in Table 2, sensitivities were found in rodent studies following non-thermal exposure that suggest a possible animal model for the study of EHS. Each of these EHS-related issues needs to be followed up experimentally.

8. Discussion and conclusions

In the previous section, each of the five criteria for assessing whether an epidemiological association is causal, were considered. Those five are (Hennekens and Buring, 1989): (1) strength of association; (2) biological credibility; (3) consistency; (4) time sequence; (5) dose–response relationship. Each of these five provide strong support for causality such that the combination of all five provides compelling evidence for causality. Low-intensity microwave frequency EMFs do cause diverse neuropsychiatric symptoms. While each of these five is important here, the one that is most important is the criterion of biological credibility.

Three related sets of biological observations each predict that low-intensity microwave EMFs produce widespread neuropsychi*atric effects:*

1. Such EMFs act via activation of VGCCs, acting through the VGCC voltage sensor which is predicted to be exquisitely sensitive to these EMFs (Pall, 2015). VGCCs occur in high densities throughout the nervous system and have essential roles throughout the nervous system in releasing neurotransmitters and neuroendocrine hormones. These properties predict, therefore, that these low intensity non-thermal microwave EMFs cause widespread changes in the nervous system, causing, in turn, diverse neuropsychiatric effects.

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2. Elevated VGCC activity, produced by an allele of the CACNA1C gene which encodes the channel of the main L-type VGCC in the brain, produces various neuropsychiatric effects (Table 1). This predicts, that low intensity non-thermal microwave frequency EMFs which also produce elevated L-type and other VGCC activity, therefore produce widespread neuropsychiatric effects.
3. Studies reviewed in the Tolgskaya and Gordon, 1973 publication (Table 2) have shown that the cells of the mammalian nervous system show high sensitivity to various non-thermal microwave and lower frequency EMFs, being apparently more sensitive than any other organ in the body of rodents. These studies predict that the human nervous system is likely to be similarly sensitive to these EMFs, predicting, therefore, widespread neuropsychiatric effects in humans.

We not only have biological credibility but also more importantly, each of these distinct but interrelated biological considerations predicts that low-intensity, non-thermal microwave EMFs produce widespread neuropsychiatric effects. That common prediction is verified by extensive data summarized in citations provided by the Naval Medical Research Institute Research Report (June 1971), data provided by The Raines (1981) NASA report, and by 26 epidemiological studies summarized in Table 3.

The most commonly reported neuropsychiatric symptoms from these studies are summarized in Table 4.

A total of 22 different studies described in Table 3 were used for data for this table, but not 4 others that only assessed a single neuropsychiatric end point. The Altpeter study which only assessed sleep disturbance/melatonin depletion and the three studies listed under Chu et al. which only assessed headache occurrence following long cell phone calls, listed in Table 3 were not included. Because many of the studies only assessed from 3 to 7 specific symptoms, it is not surprising that the numbers of studies reporting a specific symptom fall far below 22. Where several symptom descriptions were included under one heading, such as dysesthesia, if a study had more than one of these symptom descriptions, it was only counted once.

All the symptoms listed in Table 4 should be considered established parts of microwave syndrome (Hocking, 2001; Johnson Liakouris, 1998). Even if the statistical significance in each study was of the lowest statistical significance ($p < .05$) one would expect only 1 positive study to occur at random out of the 22 studies included here. Because many individual symptoms were not surveyed in many individual studies, the expectation is substantially lower than that. Each of these, having shown positive results in 5 or more studies are highly unlikely, therefore, to have occurred by chance. Stong statistical significance is also seen for individual neuropsychiatric effects reported to have $p < 0.001$ in the Eger and Jahn (2010) and Oto et al. (1994) studies (see Table 3).

Table 4
Commonly reported neuropsychiatric symptoms following microwave EMF exposure.

Symptom(s)	Numbers of studies reporting
Sleep disturbance/insomnia	17
Headache	14
Fatigue/tiredness	11
Depression/depressive symptoms	10
Dysesthesia (vision/hearing/olfactory dysfunction)	10
Concentration/attention/cognitive dysfunction	10
Dizziness/vertigo	9
Memory changes	8
Restlessness/tension/anxiety/stress/agitation/feeling of discomfort	8
Irritability	7
Loss of appetite/body weight	6
Skin tingling/burning/inflammation/dermographism	6
Nausea	5

EEG changes may well be part of microwave syndrome, as well. While none of the studies described in Table 3 measured EEGs, six studies of human occupational exposure cited in the Raines (1981) showed EEG changes (Baranski and Edelwejn, 1975; Bise, 1978; Dumanskij and Shandala, 1974; Lerner, 1980; Sheppard and Eisenbud, 1977). Murbach et al. (2014) cited 10 human studies in support of their statement that "the most consistently reported effects (of mobile phone use) in various studies conducted by different laboratories are changes in the electroencephalogram (EEG) power spectrum." Three recent studies (Lustenberger et al., 2013; Schmid et al., 2012a,b) and several earlier studies cited in Wagner et al. (1998) have each shown EEG changes in sleeping humans exposed to non-thermal pulsed microwave fields. Two recent studies showed EEG changes in persons exposed to Wi-Fi fields (Maganioti et al., 2010; Papageorgiou et al., 2011). Lai (1997) described 8 animal studies showing changes in EEG patterns in animals exposed to non-thermal EMFs and three additional animal studies were described in Tolgskaya and Gordon (1973). With the exception of the 6 studies cited in the second sentence in this paragraph, all of these are direct experimental studies which are not, therefore, susceptible to the questions of causality that can be raised about epidemiological studies. It is the author's view that future studies should consider studying EEG changes as an objectively measurable assessment of brain physiology and that before and after increased exposure studies should be considered when a new EMF source is to be introduced into human populations. While such studies must be done carefully, given the complexity of EEGs, even very small numbers of individuals may produce highly statistically significant results in well designed studies analyzed with paired *t*-tests.

One of the citations from the previous paragraph, Bise (1978) reviewed earlier studies of low level microwave frequency exposures in humans and concluded that such EMFs produced the following neuropsychiatric effects: headache, fatigue, irritability, dizziness, loss of appetite, sleepiness, sweating, difficulty of concentration, memory loss, depression, emotional instability, dermographism, tremor, hallucinations and insomnia. The strong similarity of this list from 37 years ago and the list in Table 4 should be noted. The Bise (1978) list is based on occupational exposure studies whereas the current list in Table 4 is based primarily on EMF exposures from cell/mobile phone base stations, from heavy cell phone usage and from smart meters, *three types of exposures that did not exist in 1978*. The strong similarity between the Bise (1978) list and the current one 37 years later alone produces a *compelling argument that the 11 neuropsychiatric effects found on* both lists are caused by exposure to multiple types of low-intensity microwave EMFs.

The pattern of evidence is compelling in support of the earlier statement of Levitt and Lai (2010) that "the primary questions now involve specific exposure parameters, not the reality of complaints or attempts to attribute such complaints to psychosomatic causes, malingering or beliefs in paranormal phenomena."

*We can barely imagine how the combinations of neuropsychi*atric effects, including those in Table 4, will influence human behavior and social interactions, now that the majority of the human populations on earth are exposed to ever increasing intensities and diversity of microwave frequency EMFs. You may recall that three of the occupational exposure studies cited in (Raines, 1981 showed increasing prevalence of neuropsychiatric symptoms with years of exposure to consistent patterns of EMF exposure intensities (Dwyer and Leeper, 1978; Sadcikova, 1974;

Baranski and Edelwejn, 1975). With ever increasing exposures in human populations, we have no idea what the consequences of these ever increasing exposures will be.

Conflict of interest

The author declares no conflict of interest.

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APPENDIX J

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

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ABSTRACT

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

Keywords

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

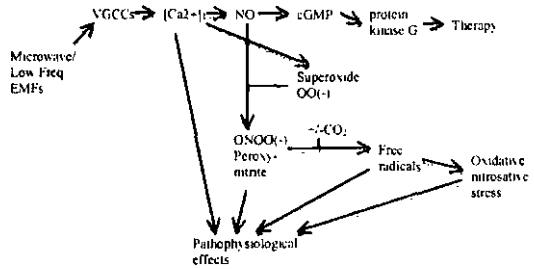

Figure 1. EMFs Act via Downstream Effects of VGCC Activation to Produce Pathophysiological and Therapeutic Effects. Taken from Ref. [24] with permission.

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

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

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

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

Taken from ref [24] with permission.

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

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

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

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

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

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

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

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

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

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

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

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

6. Conclusions

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

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APPENDIX K

Electromagnetic Hypersensitivity (EHS)

I have discussed elsewhere how microwave/lower frequency EMFs act via VGCC activation to produce excessive intracellular calcium [Ca2+]i and various additional consequent effects in the cells or our bodies. My goal in the part that follows, is to discuss how these same mechanisms can help us understand the *probable mechanisms of electromagnetic hypersensitivity* (AKA electrohypersensitivity) often abbreviated EHS. I have not published on EHS, although I have seven papers published on the similar sensitivity condition, multiple chemical sensitivity (MCS) (the key paper is a 50 page paper: General and Applied Toxicology, 3rd Edition, John Wiley & Sons, pp. 2303-2352). This is a key paper, in part, because this was the only time when MCS was recognized by distinguished professional toxicologists as a disease of toxic exposure).

Now in MCS, the 7 classes of chemicals that produce sensitivity each act to produce excessive activity of the NMDA receptors. The activated NMDA receptors produce excessive calcium in the cell and they produce biological effects largely through increases in intracellular calcium [Ca2+]i. There is also a classic sensitizing chemical toluene diisocyanate (TDI) which also produces increases in [Ca2+]i by activating two other receptors (TRPV1/TRPA1). You have already seen that EMFs act via VGCC activation and increased [Ca2+]i . It is my opinion, that this central role of excessive [Ca2+]i in each of these hypersensitivity responses, is not coincidental and that to a reasonable degree of scientific confidence, sensitivity responses in the body can be produced by excessive [Ca2+]i.

There are several other things that one needs to know in order to understand how excessive VGCC activity and [Ca2+]i can produce sensitivity in the brain. Firstly, it is important to note that the release of every neurotransmitter in the brain is controlled by VGCCs acting through [Ca2+]i and the neurons throughout the nervous system have very high densities of VGCCs, VGCCs of multiple types. Secondly in the Tolgskaya and Gordon review (#2 in our review list) it was found that in animal studies of exposures to low-intensity microwave frequency EMFs, the organ most affected by these low-intensity EMFs was the nervous system (including the brain) followed by the heart and the testis – three organs that each have very high densities of VGCCs. Many other organs were also affected, but these showed the top three changes. It is my opinion that to a high level of scientific certainty and confidence, there is an important correlation between VGCC densities and the impacts of low-intensity EMFs that is due to the causal role of the VGCCs in producing biological effects following EMF exposures.

Now, let's get back to sensitization by EMFs. What is called long-term potentiation (LTP), an important process that increases sensitivity of the synapses in the brain is thought to have a key role here. LTP is known to be stimulated by both elevated VGCC activity and elevated NMDA activity with both

acting in part by raising [Ca2+]i. LTP activity is known to have an important role in learning and memory. It is my opinion, therefore, that to a reasonable degree of scientific confidence that VGCC stimulation by EMFs, act in the brain to stimulate LTP such that the brain has "learned" in effect to become sensitive to EMFs and that this is part of the EHS mechanism. A similar mechanism with chemicals acting via NMDA receptor elevation may produce chemical sensitization in the brain in MCS. Each of the following consequences of VGCC activation have well documented roles in producing LTP, roles that are discussed in three of my MCS papers: [Ca2+]i, nitric oxide, superoxide, and peroxynitrite.

Elevated [Ca2+]i, nitric oxide, superoxide, peroxynitrite and oxidative stress are all produced following VGCC activation (see Fig. 1) and each of these are also thought to be important parts of what is called the NO/ONOO(-) cycle, a primarily local biochemical vicious cycle thought to have central causal roles in many different chronic inflammatory diseases, depending on where it is localized in the body. Among the cycle elements reported to be elevated in the absence of apparent EMF exposure in EHS patients are oxidative stress, peroxynitrite and the inflammatory cytokines. It is my opinion, therefore that it is more likely than not that the NO/ONOO(-) cycle has a role in EHS, explaining, in part, the chronic nature of EHS.

It is also my opinion, that it is more likely than not that the local nature of the NO/ONOO(-) cycle and the local nature of LTP (some synapses may be sensitized but not others) explains why different EHS patients differ from one another in the symptoms that they express on exposure.

There are three other probable aspects of EHS, in my judgment:

1. The VGCCs and also the voltage-gated sodium channels are each activated by two protein kinases, protein kinase A and protein kinase C each of which may contribute to the sensitivity responses in EHS. There are two enzymes that produce cAMP, the activator of protein kinase A, enzymes whose activities are greatly increased elevated [Ca2+]i. Those two enzymes have been studied in great detail by Dr. Daniel Storm and his colleagues at the University of Washington for their important roles in the brain. It is my opinion, that it is more likely than not that this mechanism increasing protein kinase A and VGCC sensitivity, is more likely than not to contribute to such VGCC sensitivity in EHS in both the brain and in peripheral tissues.
2. Histamine, which is released by activated mast cells in both the brain and peripheral tissues probably has a role in EHS. Histamine levels have been shown to be elevated following low-intensity microwave frequency EMFs (see reviews 2,3 and 8, in Appendix D). Gangi S and Johansson O. at the prestigious Karolinska Institute in Sweden reported in a paper published in 2000, that when skin tissue of EHS patients became flushed following EMF exposure (and all EHS patients do not show this), a skin

biopsy showed that mast cells were activated in those tissues (unlike normal tissues) such that they are much more active in releasing histamine. It has been shown that activated VGCCs can activate mast cells to release histamine (see Suzuki et al Mol Immunol. 2010 Jan;47(4):640-8). I am also aware of anecdotal reports from EHS patients that they find that certain antihistamine drugs are helpful to them in lowering sensitivity responses, providing weak confirmation for a histamine role. Histamine can act, through its receptors, to raise both protein kinase A and protein kinase C activity, which can act, in turn as discussed above, to produce increased sensitivity of the VGCCs. It is my opinion, therefore that to a reasonable degree of scientific confidence, that elevated histamine has an important role in causing EHS, acting through each of the mechanisms discussed in this paragraph.

3. Dr. Cornelia Waldmann-Selsam in Germany has contacted me about a specific EHS patient she has (designated S) and she has given me permission to talk about her patient. Her patient S is a woman who shows an extraordinary level of sensitivity described as a woman with EHS. S has lost her parathyroid function due to an accident – she is therefore greatly impaired ability to regulate blood calcium levels. When S is exposed to extremely low levels of EMF exposure – such as from out in the forest where she lives – hikers walk somewhere not too far away from S's house – use cell phone – she reacts to it. Her blood levels of calcium drop dramatically to well below normal. Interpretation: Her VGCCs are highly sensitive to EMFs, such that very low intensity EMFs lead to vast calcium influx into cells, thus greatly lowering blood calcium. This argues that her VGCCs are extremely sensitive to EMFs. Now one must always be skeptical about observations about single individuals. However there is a long history in medicine of single individuals, because of their individual special properties, leading to insights on much more generally applicable mechanisms. It is my opinion, that given the information provided in 1-3, that EHS is characterized by hypersensitivity of the VGCCs to very low intensity EMFs which lead, in turn massive influx of calcium ions into cells, thus producing in the case of S, a drastic lowering of blood calcium levels.
4. The increased sensitivity of the VGCCs and also the voltage-gated sodium channels, as mentioned above, and the possible massive influx of calcium and sodium ions into the cytoplasm, may lead to massive pumping of both sodium and calcium ions out through the plasma membrane of the cell in order to attempt to restore normal ion balances. It is not unusual for normal cells to use 20 to 25% of the energy in the cell in the form of ATP to run the plasma membrane sodium/potassium ATPase and calcium ATPase that are involved in such pumping. If one has massive influxes into the cell of calcium and sodium, then it is quite possible that massive ATP utilization may ensue to attempt to restore a normal ion balance. Because this is expected based on well-established mechanisms, it is my opinion that it is more likely than not, that EHS people on reacting to EMF

exposure may suffer from massive depletion of ATP energy in the cells that are both impacted by EHS and exposed to such EMFs.

We have then the confluence of a series of individually well documented mechanisms which together provide a plausible physiological explanation to EHS. It is my opinion that to a reasonable degree of scientific confidence, we have a series of mechanisms leading to hypersensitivity of the VGCCs themselves and also hypersensitivity to their effects via excessive LTP and consequent synaptic sensitization and also initiation of what is called the NO/ONOO(-) cycle which makes it all chronic.

APPENDIX L

PECO Energy Company's Answers to Interrogatories and Requests for Documents of Complainant Maria Povacz, Set I

Povacz I-22: Has the Povacz Intended Smart Meter been tested and/or approved by the Federal Communications Commission ("FCC") or the Pennsylvania Public Utility Commission ("PUC")?

PECO Answer to Povacz I-22:

The communications' modules that PECO uses with the Landis+Gyr Focus AX-SDR meter have been approved by the Federal Communications Commission.

Responsible Witness: Glenn Pritchard

PECO Energy Company's Answers to
Interrogatories and Requests for Documents
of Complainant Maria Povacz, Set I

Povacz I-23: Before deciding to install AMI Smart Meters on, or inside, the homes, buildings, and businesses throughout your service area, did you produce an analysis to assure that the radiofrequency/microwave radiation from the AMI Smart Meter System would be safe for your customers, especially for your elderly, disabled, and sensitive customers?

a. If so, please provide a copy of any and all such analyses;
b. If not, how did PECO establish that the AMI Smart Meter System is safe for customers?

PECO Answer to Povacz I-23:

PECO relied upon the Federal Communications Commission requirement that Advanced Meter Infrastructure meters must comply with FCC limits for maximum permissible exposure to radio frequency fields.

Responsible Witness: Glenn Pritchard

PECO Energy Company's Answers to
Interrogatories and Requests for Documents
of Complainant Maria Povacz, Set I

Povacz I-24: Did your analysis consider the radiofrequency/microwave radiation from a single AMI Smart Meter or the radiation from all components of the AMI Smart Meter System, including

(a) all AMI Smart Meters in a community,
(b) all intermediate wireless relay devices in a community, such as all Wireless Collector Smart Meters,
(c) all Wireless Repeaters, all wireless transmitters/receivers required to communicate between the intermediate wireless relay devices and PECO or its agents?
(d) all future uses for which the Smart Grid has been proposed to be used.

PECO Answer to Povacz I-24:

See response to Interrogatory Povacz I-23. The FCC radiofrequency safety limits are available on the FCC website at www.FCC.gov.

Responsible Witness: Glenn Pritchard

PECO Energy Company's Answers to
Interrogatories and Requests for Documents
of Complainant Maria Povacz, Set I

Povacz I-26: How did your analysis, if any, regarding the safety of the PECO AMI Smart Meter deployment, address the radiofrequency/microwave radiation already present from other sources in each community in which you planned to install or did install your AMI Smart Meter System?

PECO Answer to Povacz I-26:

PECO relied on the Federal Communication Commission (FCC) requirement that smart meters must comply with its limits for maximum permissible exposure to radio frequency fields. Information on what the FCC considered can be found on the FCC website (FCC.gov).

Responsible Witness: Glenn Pritchard

PECO Energy Company's Answers to Interrogatories and Requests for Documents of Complainant Maria Povacz, Set I

Povacz Interrogatory I-30: Has PECO concluded that the radiation from its AMI Smart Meter System is safe for human beings? If so, what is the primary basis for such a conclusion?

PECO Answer to Povacz I-30:

Yes. The primary bases for this conclusion are: (1) compliance with FCC requirements; and (2) the expert evaluations of Mr. Pritchard, Dr. Davis and Dr. Israel.

Responsible Witness: Glenn Pritchard, Dr. Christopher Davis, Dr. Mark Israel

PECO Energy Company's Answers to
Interrogatories and Requests for Documents
of Complainant Maria Povacz, Set I

Povacz Interrogatory I-31: Did PECO rely on independently researched published biomedical research papers or reports to reach a conclusion regarding the safety of AMI Smart Meters used wirelessly for human beings? If so, please provide copies of any such papers or reports.

PECO Answer to Povacz I-31:

See PECO Answer to Povacz I-30.

Responsible Witness: Glenn Pritchard, Dr. Christopher Davis, Dr. Mark Israel

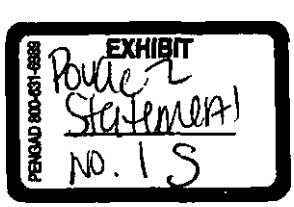
POVACZ STATEMENT NO. 1S

BEFORE THE
PENNSYLVANIA PUBLIC UTILITY COMMISSION

Maria Povacz	:	
	:	
v.	:	Docket No. C-2015-2475023
	:	
PECO Energy Company	:	

SURREBUTTAL TESTIMONY OF MARTIN L. PALL, Ph.D. ON BEHALF OF COMPLAINANT MARIA POVACZ

May 31, 2016



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SURREBUTTAL TESTIMONY
OF
MARTIN L. PALL, Ph.D.

A. INTRODUCTION AND PURPOSE OF TESTIMONY

1. Q. Please state your full name.

A. My name is Martin L. Pall.

2. Q. Did you submit testimony in this proceeding before?

A. Yes. I submitted Povacz Statement No. 1, my direct testimony, on April 18, 2016.

3. Q. What is the purpose of your surrebuttal testimony?

A. I am submitting surrebuttal testimony to respond to PECO Statements No. 3 and 4, the rebuttal testimony of Dr. Davis and Dr. Israel, respectively.

4. Q. How is your testimony organized?

A. This document is organized, first discussing issues raised in Dr. Davis' Rebuttal. This is followed by a second section discussing Dr. Israel's Rebuttal. My goal here is to discuss various issues raised by Dr. Davis and Dr. Israel in each of their Rebuttals.

B. RESPONSE TO DR. DAVIS

5. Q. Do you have any general comments about Dr. Davis's Rebuttal Testimony?

A. Yes, I do. Dr. Davis has many places in his rebuttal testimony where he makes unclear statements and many statements, including all of those which I consider to be controversial, which are completely undocumented – that is where he makes a statement but

provides no evidence whatsoever in his Rebuttal that tells us whether he is likely to be correct or not. When I was a graduate student at Caltech, then as now one of the top scientific institutions in the world, one of the first things I was taught is that science is always based on evidence – you always have to provide substantive evidence on any statement that you make. But Dr. Davis repeatedly gives us completely undocumented statements, so that we have to take his word for it (or not). That is not scientific.

6. Q. Do you have any comments about the first 10 pages of the Davis Rebuttal statement?

A. Most of this is fine. We do have some minor differences in terms of terminology, but those are minor issues and are not worth spending time on. The one statement that is problematic is fundamentally correct but has been commonly interpreted in ways that are incorrect. That is the sentence on p. 9 of the Davis Rebuttal stating that "The non-ionizing category of the electromagnetic spectrum consists of waves that do not have enough energy to break chemical bonds including chemical bonds in DNA." This is fundamentally correct and in fact, I started out my 2013 paper (Appendix G) which introduced the world to the EMF VGCC mechanism with: "The great puzzle, here, is that these EMFs are comprised of low-energy photons, those with insufficient energy to individually influence the chemistry of the cell, raising the question of how non-thermal effects of such EMFs can possibly occur." The answer to this question is that these EMFs as a whole, not the individual photons, activate voltage-gated calcium channels (VGCCs), with the excessive calcium levels in the cell producing various what are called "downstream effects" that can produce, in turn, the various health-related effects repeatedly reported to occur following non-thermal low intensity EMF exposures. The problem is that the statement that these photons cannot break chemical bonds in DNA, for example, has

been interpreted to mean that these low intensity EMFs cannot break such bonds through indirect effects. This interpretation is totally wrong. One other thing that is important here is that the indirect effects of VGCC activation have substantial similarities with effects of ionizing radiation exposure.

7. **Q. *So you think that indirect effects of VGCC activation produced by low-intensity EMFs may resemble effects of ionizing radiation?***

A. Yes I do. The way in which VGCC activation, for example, attacks DNA is through free radical breakdown products of peroxynitrite. Ionizing radiation also acts through free radicals, but in that case they are produced by a process known as Compton Scattering where the high energy photons knock electrons out of molecules, generating trails of free radicals (this was discovered by Arthur Compton who got the Nobel Prize in Physics in 1927 for this discovery). The important thing here is that both sets of free radicals, from ionizing radiation and from VGCC activation produced by microwave/lower frequency radiation can produce similar biological effects. So again, this destroys many arguments that have been made by industry supporters, including Dr. Davis, that microwave radiation cannot produce biological effects similar to those produced by ionizing radiation.

8. **Q. Dr. Davis on p. 12 of his rebuttal statement, states that "AMI meters do not generate electrical power; they measure the electrical power flowing into and being used in the house. They do not produce additional harmonics over and above the electrical power flowing into the meter" (emphasis added). Later he states referring to AMR/AMI meters that "Switching-mode power supplies generate radio frequency up to about 10MHz at low levels. Many modern**

electrical appliances use switching-mode power supplies." What was this in response to in your testimony and what is your response to this statement?

A. As best I can determine, this was in response to a statement in my testimony in the Murphy case, not in the Povacz case. The first and last sentences quoted above are not at issue – I agree with those. It's the italicized sentence that is most problematic. In order to see why this is problematic you have to look at the testimony I gave in the Murphy case. "Q. Laura Murphy has expressed several concerns about the AMR meter which PECO installed on her home. The switched mode power supply contained in the AMR meter has, by her account, affected the quality of the electricity which is circulating on the wiring in her home. She is especially sensitive to electric pulses and cannot tolerate fluorescent lights, LED lighting and any similarly pulsed electric apparatus due to her hypersensitivity to such influences, despite her desire to be conservative with electric consumption. Q. Can you give us some insights into the mechanics of the switched mode power supply? A. Yes. I have copied information from Wikipedia on these switched mode power supplies (Appendix M). You can see from the Appendix, that switch mode power supplies generate various high frequency transients (described in the document as harmonics). There is a small filter which is used to lower these which should lower, at least to some extent, biological effects. However, to determine how effective such filtering is, it is essential to do biological testing of the AMR meter. Because no such testing has been done, there are no scientifically valid assurances of safety for the AMR meter. Consequently, any assurances that PECO may give on this are not worth the paper they are written on. Compact fluorescent lights, conventional fluorescent lights with electronic ballasts, LED lights and most dimmer switches all produce high frequency transients similar to those produced by the switched mode power supplies. Consequently it should not be surprising that Laura Murphy reports being

sensitive to most of these. These are the type of observations that may suggest that Laura Murphy probably suffers from EHS." What Dr. Davis is doing here is taking a statement that has been shown to be false by previously documented testimony and repeating that falsehood. It can be argued, that Dr. Davis could, if he has some evidence to the contrary, disagree with the previous testimony and the previous documentation by clearly stating that disagreement and providing evidence supporting his position. However, that is not what Dr. Davis is doing here. I very much doubt that he has any such contrary evidence as it was very easy for me to find evidence for my position here – there is a large amount of such evidence available. So you can see here how important it is not to accept completely undocumented opinion – it is easy to slide over from that to falsehood.

9. Q. On p. 13 of his rebuttal, Dr. Davis states "by sending radio signals, it produces a radiofrequency field. The field is a natural result of sending radio signals" (emphasis added). Do you have any comments about this?

A. This is a bizarre statement about natural. There is nothing natural about these things. All of these are artificial and all artificial EMFs are polarized. A recent paper argues that polarized EMFs produce larger forces on charged groups (Panagopoulos DJ, Johansson O, Carlo GL. 2015 Polarization: A Key Difference between Man-made and Natural Electromagnetic Fields, in regard to Biological Activity. Sci Rep. 2015 Oct 12;5:14914. doi: 10.1038/srep14914). This argues that the impact of such artificial EMFs on the VGCC voltage sensor may be highly amplified.

10. Q. Dr. Davis claims that not exceeding the FCC guidelines is a "scientifically reliable" in guaranteeing safety (P.13, bottom of his rebuttal statement). He

then follows with a longer statement (p.14) claiming that these guidelines are experimentally based. Is this correct?

A. No, it is completely false, and Dr. Davis provides again not one iota of evidence for his claim. In appendix D of my Povacz and Murphy testimony, I listed 63 different reviews on low-intensity EMF effects, with most but not all of these peer-reviewed, each of which report one or more different non-thermal health-related impacts. So obviously these carry vastly more weight than do Dr. Davis' completely undocumented claims. Basically what Dr. Davis is telling you, is that he knows more about this than do the authors of these 63 different reviews, each of whom came to the diametrically opposite conclusion. Furthermore, there were 220 scientists, each of whom signed an appeal to the United Nations summarized as stating: International (including FCC) safety guidelines are inadequate because they do not take into consideration non-thermal effects. The 220 signers had collectively published over 2000 peer-reviewed studies on effects of low-intensity microwave frequency EMFs, a substantial fraction of the total literature in this area. There is a consensus among independent scientists on this. What Dr. Davis is telling you is that he, having no publication record whatsoever in this area, knows more about it than do the authors of over 2000 peer-reviewed publications. That is, of course, transparent nonsense. This is further documented by the EPA letter written by Norbert Harkin in Appendix B. This letter states that "The FCCs current guidelines, as well as those of the Institute of Electrical and Electronics Engineers (IEEE) and of ICNIRP, are thermally based. They are believed to protect against injury that may be caused by acute exposures and do not apply chronic non-thermal exposure situations. They are believed to protect against injury that may be caused by acute exposures that result in tissue heating or electric shock and burn. The hazard level (for frequencies generally at or greater than 3 MHz) is based on a specific absorption dose-

rate, SAR, associated with an effect that results from an increase in body temperature. The FCC's exposure guideline is considered protective of effects arising from thermal mechanisms but not from all possible mechanisms. Therefore, the generalization by many that the guidelines protect from human beings from harm by any or all mechanisms in not justified." You can see from this that Dr. Davis' claims here are completely fictional. I'd like to finish up this response with a quote which perhaps summarizes things well. This is a quote from Marko Markov (the editor of Electromagnetic Fields in Biology and Medicine, 2015 CRC publishers) who states on p. 18 the following: "I will use the word controversial once again. The hazard from high-frequency EMFs used in the 21st century communication is frequently represented as controversial, and it is absolutely incorrect. It is not a controversial issue; it is a conflict of interest of industry on the one side and of humans and the environment on the other."

11. Q. At the bottom of p. 15. Dr. Davis states the following: The FCC's reasons for its position are scientifically sound and also reflects the consensus of independent scientists who are expert in radio frequency bioelectromagnetics. Is this true?

A. It is absolutely stunning that Dr. Davis would generate this statement about independent scientists out of whole cloth, a statement which has no relationship whatsoever to the real science. So again, we have a completely undocumented statement where Dr. Davis is saying, in effect, that he knows much more than do the genuine independent scientists in this area and that he is going to pretend that none of their clearly expressed views on this subject exist. This statement has no place in science or in a document produced of an expert witness. So yet again, Dr. Davis gives us an example where failure to provide any documentation can easily slide over into outright falsehood.

12. Q. Dr. Davis has a series of statements on pp. 16-19 making a series of calculations that purportedly relate to relative effects of various EMF exposures. Are these biologically relevant?

A. No they are not. Firstly, Dr. Davis presents numbers in the PECO exhibits CD-1 through CD-7 but we have no evidence telling us where these numbers come from or whether they have any connection with reality. Dr. Davis has yet again provided no documentation whatsoever. Secondly, Dr. Davis' claims are based on a series of assumptions that are known to be false. They assume that one need only consider thermal effects whereas non-thermal effects are the predominant ones of concern. They falsely assume that there are no effects of pulsation patterns whereas it is known that, in most cases, pulsed EMFs are more biologically active than are continuous wave (non-pulsed) EMFs. They falsely assume that higher intensities always produce higher effects than lower intensities whereas it is known that in many cases, there are windows of exposure that produce maximum biological effects than either lower or higher exposures. In one study, it was found that an exposure window produced high effects and steady increases in exposure levels produced decreased biological effects even at intensities of 150 times that of the exposure window. So these effects can be massive. There are some adjustments for frequency in the FCC guidelines but because these are based solely on heating, it is unlikely that these have much biological relevance. When you put all of these together, you are playing games with these things such that these calculations are pretty close to meaningless. The only way to measure biological risk is to do biologically-relevant experiments. No such studies have been done by PECO or by anyone on the PECO meters. Consequently, we have no biologically relevant assurances of safety whatsoever.

13. Q. From the bottom of p. 19 though most of p. 20 of the Davis Povacz Rebuttal, he criticizes your VGCC mechanism. Can you take the first paragraph of that critique and comment on it?

A. Yes. Let's first say something about what a critique or other statement must be in order to be considered scientific. A scientific statement, of whatever sort, must be clear, including being clear in its implications, and must be supported by substantial evidence. That clarity and the evidence presented must provide to others with different views the information that they need to know in order to falsify the statement, if indeed it can be falsified. This whole structure is an important part of the process of science. Which is why statements that fail this structure are considered to be non-scientific. Now let's look at a couple of Davis' statements. He writes that "Dr. Pall's VGCC mechanism theory for how electromagnetic fields produce biological effects (and thus health effects) has not been generally accepted by experts in the field. I am familiar with mechanism theories like Dr. Pall's because I teach about them – and the lack of consistency and reproducible confirmation of any of them – in my Electromagnetics course." I'll deal with the "has not generally been accepted" issue later. What Dr. Davis argues is that he thinks that the VGCC mechanism is similar to other previous theories on possible low-intensity EMF effects; he also claims that the other theories lack consistent and reproducible confirmation (but he provides not one iota of evidence on this). But then, what does he conclude from that? Absolutely nothing. He seems to be arguing that because these other theories have failed, that this one will as well. That would be patent nonsense, but since he is unclear about this, I cannot accuse him of that. Let me just say that the other theories that I am familiar with, are all ad hoc theories that try to explain how low intensity EMF can produce biological effects. The VGCC theory is not ad hoc at all – rather it is data-driven. It is entirely based on diverse types of

empirical evidence that were discussed in great detail in my previous testimony, as well as in Appendixes F through J. This theory is very different from the others because of the extensive diverse types of empirical evidence. Consequently, suggesting as Dr. Davis does, that it is similar to the others while providing no criteria used for such "similarity," no evidence whatsoever for any such similarity is sheer nonsense. The other statement that Dr. Davis makes here is "(I should note that his VGCC theory reflects a fundamental lack of understanding of basic cell biophysics)." This statement is unclear – it does not state what this supposed fundamental lack of understanding is. It provides no evidence. It provides no logical framework. And most importantly, it provides no information that would allow it to be falsified. That may be Dr. Davis's strategy here but what it means is that this a completely unscientific statement that has no place in science and has no place in the testimony of an expert witness, in my opinion.

14. Q. Can you consider now the second such paragraph on p. 20?

A. Yes, of course. Dr. Davis states that "Since Dr. Pall published his VGCC mechanism in 2013, at least 6 expert science panels have conducted careful reviews of radiofrequency research." He then lists them ending with ICNIRP as follows: "The International Commission Non-Ionizing Radiation Protection (ICNIRP) says no on its web site. 'Acute and long-term effects of HF (high frequency including radio frequency) exposure below thermal threshold have been extensively studied without showing any conclusive evidence of adverse health effects.' None of those expert authorities accept Dr. Pall's VGCC mechanism theory; in sum it is not generally accepted by experts in the field." So let's look at this. If you look at the ICNIRP web site you will see that there are very few papers cited with the most recent of them dating from 2012 (see attachment). So they have never looked at the VGCC mechanism so they say nothing

about it. Consequently, it is meaningless to say that they don't recognize something that as far as we know they have never looked at. I have also looked at the 2015 Swedish Radiation Safety Authority Report that Dr. Davis mentions and they also have not looked at the VGCC mechanism. I read the report that was written for the Swedish Government by an International Series of Genuine Experts in 2014 and this was, in my opinion, much more scientifically based than was the Radiation Safety Report mentioned above. But this is what happens when lobbyists and bureaucrats get involved in these deliberations. When I visited Stockholm in March 2016, I gave an invited talk on the VGCC mechanism at the Swedish Parliament so it is clear that there is substantial interest at high levels in Sweden in the VGCC mechanism. It is very rare in science that a new concept is instantaneously endorsed by most scientists but, as I discussed in my testimony, the interest in this mechanism, the placement of my 2013 paper on the Global Medical Discovery web site as one of the top medical papers of 2013, the numbers of invited professional talks in different countries (with future ones going up to 31), numbers of citations of my 2013 paper (78), invitations to contribute papers on EMFs to special issues of journals. Each of these reflect a strong level of interest in this in the U.S. and Europe. What Dr. Davis is trying to do is to construct a 30 foot high wall and say that if I can't poll vault over that wall, I should not be admitted into the discussion – I suppose he sees this as his role as an expert witness.

15. Q. Do you have anything else to say about the ICNIRP quote from p. 20 ?

A. Yes. The ICNIRP quote says 'Acute and long-term effects of HF (high frequency including radio frequency) exposure below thermal threshold have been extensively studied without showing any conclusive evidence of adverse health effects.' You will note that the term conclusive evidence is not defined here. Industry lobbyists have demanded that this term include consistent effects in different cell types, consistently higher effects with increased exposure

intensities and that studies using similar SARs values produce similar responses. Each of these demands have often been accepted. Each of these demands are based on assumptions about the science that have been shown to be false. We know that different cell types respond differently, we know that effects are influenced by pulsation patterns (this and other types of evidence clearly show that SARs values are irrelevant). Window effects where certain windows of exposure produce maximum biological effects such that higher intensities produce much lower biological effects. It follows from this that if these criteria continue to be used, before any group of studies are considered conclusive, we will be here from now until doomsday and there will still be no biologically based safety standards. We even see industry-funded studies where the authors claim that they see no effects because of the failure to meet one of these criteria, even though most of the evidence clearly show effects. Let me give you another example of how this plays out in practice. When I critiqued the 2014 Canadian Report in my 2015 Reviews on Environmental Health paper (Appendix F), there was only one area where the report cited multiple studies and where they also came to the conclusion that there were what they called "inconsistencies in the literature," such that they threw them all out. So there are 22 such studies all in the area of cellular DNA damage (genotoxicity) and of those 14 came to the conclusion that there was cellular DNA damage produced by low-intensity non-thermal EMF exposures. The principles of science say that even one of these studies that apparently falsify the theory that only heating effects can occur (from EMF exposures) should lead us to throw out the theory – here we have 14 and those same principles argue powerfully that the theory that there are only heating effects should be thrown out. The authors of the Canadian Report (the Committee of Experts) threw all 22 studies instead, claiming there were "inconsistencies in the literature." I looked at each of these 22 studies carefully and found two very important things. Firstly there

were a number of studies where specific research groups using specific methodologies looked at cellular DNA damage in different cell types and found that some cell types produced such damage reproducibly but other cell types did not produce obvious damage. That is a terribly important observation because it tells you that the type of cell being studied is critical in determining the response to non-thermal EMF exposures. The Canadian Report and these other organizations (including ICNIRP and the FCC) each consider these inconsistencies, therefore blocking establishment of conclusive evidence of effects. When I examined all 22 different studies in the Canadian Report, there were no inconsistencies whatsoever, rather simply different cell types, different EMF and/or different biological end point being studied. The simple scientific principle that when you do different experiments you can get different results appears to be anathema to these "committees of experts" and also, as best I can determine, to Dr. Davis and Dr. Israel as well.

16. Q. Dr. Davis questions the effectiveness of therapy via low-intensity pulsed EMFs including for stimulation of bone growth, the most extensively studied example of such therapy. What do you think of his criticisms?

A. I think they are nonsense. There is a literature on using EMFs therapeutically to stimulate bone growth going back to 1974, with over 1400 papers on this, the majority of which are found in the PubMed database. This literature started using pulsed EMFs as the standard approach in the mid-1970s because such pulsed EMFs were shown to be more active therapeutically. In the more recent literature, the studies are focused so much on pulsed EMF therapeutic effect that they abbreviate these as PEMFs. About 20 years ago, the FDA started approving various devices producing such pulsed EMFs in order to stimulate bone growth in human patients and since that time many thousands have been so treated. Dr. Davis claims that

there are design flaws in these devices and also claims lack of replication of these studies but provides not a single example of either. Again we have claims from Dr. Davis but absolutely no documentation whatsoever on them. In effect, he is saying he has more expertise in this area than the dozens of published scientists and dozens more of published physicians who are genuine experts in this area, not to mention the FDA but then fails, yet again, to provide even a smidgen of evidence supporting his vaunted self view. Why then does Dr. Davis take this frankly ridiculous position? It is probably because he has staked out an equally ridiculous position that low intensity EMFs cannot have effects on the human body and he will stick with this position regardless of the vast amount of evidence of widely different types that shows the position to be completely without scientific merit.

17. **Q. On the top of p. 22 of his rebuttal statement, Dr. Davis claims that "The only wireless communications devices that use pulses to convey information are laser communication devices." Is this correct?**

A. No and this is an example of a major falsehood! If you go into the PubMed database and search under pulsed electromagnetic fields and (cell phone or mobile phone) you will find 55 hits – and if you look at these individually, you will rapidly find many studies that show that cell phones communicate via pulsations. If you look up the Panagopoulos, D. J., Johansson, O., Carlo, G. L. 2015. Real versus simulated mobile phone exposures in experimental studies. BioMed. Res. Int. 2015, article ID 607053, 8 pages paper, you will find a paper that clearly shows that cell phones communicate via pulsations. It also shows that whereas the vast majority of studies showed that genuine cell phones caused various biological effects, most of the studies on simulated cell phone radiation, that is devices producing the same wavelength as cell phones at the same intensity but with either no or much lower numbers of pulsations produced no

statistically significant effect. What real scientists will conclude from these studies is that cell phones produce various biological effects. What real scientists will also conclude is that the pulsations of EMFs have major roles in determining biological effects. What those following the industry line will say is that these are inconsistent results and therefore preclude us from concluding anything. Many other studies on pulsations produced by various devices could also have been found in the two other citations that I cited on this issue in my testimony. There are many other wireless communications devices that communicate via pulsations. I have included three sets of slides from Dr. Karl Maret that show that cell phones, cordless phones, smart meters and Wi-Fi each communicate via pulsations (https://vimeo.com/132039697) and Appendix T and U. Here is another example where the completely undocumented Rebuttal testimony of Dr. Davis has led not just to a falsehood, but a falsehood of Olympic proportions and one where the facts of the situation here could easily have been determined from the material provided in my testimony. The claim that only laser devices can communicate via pulsations is transparently ridiculous. If Dr. Davis can get away with this, then in my opinion, any expert witness can get away with anything.

18. Q. Dr. Davis states that there is a consensus among "expert panels" that only non-thermal effects are established pp. 23-24. Do you agree with this?

A. Before getting into this, the question that leads into Dr. Davis's statement has a falsehood in it that I want to correct. What I said was that there is a consensus among independent scientists that low level microwave frequency EMFs produce various non-thermal effects. I did not say that this consensus includes all scientists. Having corrected that, with the exception of the last sentence in Dr. Davis' statement here, I agree with most of it although I do think that he overstates the case. There are many statements in these "expert" reports that

express concern about specific types of non-thermal effects but where they still say it is inconclusive. So it is the case that we have a whole bunch of "expert" non-peer-reviewed statements that conflict wildly with the consensus among mostly peer-reviewed studies published by independent scientists (see appendix D in my direct testimony).

19. Q. What comments do you have on Dr. Davis' overall conclusions?

A. Such statements are, of course always self-serving, so we should not be surprised that Dr. Davis' conclusions are here as well. So what are the overall flaws that I see in the Davis Rebuttal? I think they are many and they are fundamental:

1. Dr. Davis strongly defends the basic theory also defended by industry that only thermal effects can occur. However there are thousands of individual studies that have falsified this theory, many cited in the 63 reviews provided in appendix D of my testimony and there are also in many other primary literature citations, each finding that there are non-thermal effects produced by various types of microwave frequency EMFs. It is the responsibility of ethical scientists given that massive flux of falsifying studies to either throw out the theory or, at minimum, to go through each of the individual studies that apparently falsify and show that each and every one of them are deeply flawed. However neither industry supporters nor Dr. Davis has done either. They are, therefore, on a quicksand of a theory of their own making.

2. Much of Davis claims are contradicted by both the non-viability of his theory also by: The finding that pulsed EMFs are in most cases more biologically active than non-pulsed EMFs; that there are often exposure windows that provide maximum biological effects but both lower and higher exposures produce much lower effects.; different cell types respond

differently. The criteria for "consistency" that have been used by various authorities have blocked the ability to conclude that non-thermal effects have occurred because the only way to conclude this is if each of these well-established findings do NOT occur. Their criteria, in practice, prevent any real science being produced by these "expert panels".

3. Davis has over and over again makes statements that are completely undocumented, leaving the reader with no way of knowing whether his statements are correct or not. In four cases, those unsupported statements were demonstrable falsehoods. These each raise questions about whether he has any genuine expertise in this area. Both his claim that only lasers can communicate via pulsations and his apparent ignorance about switching-mode power supplies, despite having been given extensive information on both of these in my testimony, raise serious questions whether he has any expertise whatsoever in these areas – he is certainly willing to make inexcusable falsehoods about each of these.

4. What Dr. Davis has attempted to do is to produce a narrative that argues that there wireless communications devices do not produce pulsations (no documentation and absolutely false based on a wide literature), that the PECO meters cannot produce dirty electricity (harmonics in the power lines): false, based on the known properties of switched-mode power supplies. He also argues therapeutic effects of pulsed EMFs including stimulation of bone growth do not exist (completely undocumented, ludicrous). Dr. Davis gives us a whole series of claims about the extremely low intensities for the PECO meters, claims that are (as is everything else in the Davis Rebuttal) completely undocumented and may, for all we know, have come out of Alice in Wonderland. In the past few days, there has been a powerful additional blow to the Davis narrative. The U. S. National Toxicology Program (NTP), last Thursday, May 26, 2016, announced that cell

phone radiation does cause cancer in rats – causing gliomas and schwannomas (See Appendix W). The NTP tested the hypothesis that cell phone radiation could not cause health effects and that hypothesis has now been disproved. Dr. Davis' narrative has been shown to be false, as demonstrated above, thousands of times. But if you need a smoking gun type evidence, the NTP study provides exactly that.

5. Dr. Davis has put many statements into his rebuttal that are clearly unscientific via standard criteria: They are unclear, they are undocumented and they often fail to make clear predictions that can be used to falsify them.

6. When you put all of these together, there is not much left, other than flaws.

C. RESPONSE TO DR. ISRAEL

20. Q. Dr. Israel states on p. 8 that "I usually do not rely on papers that are not subject to peer review." Is this correct?

A. No it is not. Dr. Israel relies heavily on statements published by public health organizations, none of which are peer-reviewed. And such public health documents often diverge strongly from the advice of people who were chosen to advise the health authorities. For example, when the 2014 Canadian Report came out, Dr. Martin Blank, a professor at Columbia University who had been advising them was so shocked by the Report that he spearheaded a petition signed by 53 prominent scientists, objecting to the overall tenor the Canadian Report. Furthermore. Dr. Anthony Miller, a cancer epidemiologist at the University of Toronto who had been advising them on cancer was so shocked by the final cancer statement that he prepared a series of PowerPoint slides (Appendix V) that were placed on the internet that set the record straight on cancer and EMFs. Dr. Israel throughout much of this document relies on many such

non-peer-reviewed documents, over and over again. The 2014 Canadian Report was also shown to be deeply flawed in my own 2015 Reviews on Environmental Medicine paper which critiqued. There is no reason to assume that these other similar documents are any more reliable than the deeply flawed 2014 Canadian Report so the strong reliance that both Dr. Israel and Dr. Davis placed on them for their rebuttal statements means that both of their documents are, in my judgment, deeply flawed. What should be clear is that neither Dr. Israel nor Dr. Davis has provided any evidence that these other reports are any more reliable than was the 2014 Canadian Report.

21. Q. Is Dr. Israel (on p. 8) correct about the Conrad study being non-peer-reviewed?

A. Yes he is. The Conrad study was not peer-reviewed but the Lamech study was peer-reviewed. These differ from each other in other ways which I will discuss further below.

22. Q. Dr. Israel (on p. 8) states that "The Lamech paper is based on claims made about adverse health symptoms from smart meters that were submitted to an unnamed public web site by 91 unidentified people in the state of Victoria, Australia." Is this a correct statement?

A. Part of it is not correct. There were 92 people in the study each of whom was identified. Their identification was not given in the paper, preserving their anonymity. This is very commonly done to prevent people's identities from being made public. This Dr. Israel error here is an important one to correct because the actual way the study was done means that it was impossible for unidentified people from contributing false information and thus corrupting the data in the study. These 92 people were from a larger group of 142 fully identifiable cases with each of the 92 either giving consent to having her/his data used or (in one case) where someone

had publicly self-identified and therefore such consent was not needed. What is strange about Dr. Israel's statement here is that he says nothing more about the 12 page peer-reviewed Lamech paper. I am providing a copy of the Lamech paper to the PUC as Appendix X because of its great importance. I'll have much more to say about Lamech later.

23. Q. Dr. Israel (p. 9) states that "These two papers only provide data on people's claimed symptoms and their personal belief that they were caused by exposure to smart meters. In addition, the data were not collected by a random sample of people exposed and not exposed to smart meters, but instead were collected from individuals who already identified their symptoms as having been caused by smart meters.." Are these statements correct?

A. There are both correct and incorrect parts to these two sentences. The Conrad study provides very substantial evidence that there was a major increase in apparent EHS following smart meter installation. Among what are viewed as classic EHS symptoms are lowered ability to use without symptoms or to tolerate use of cell phones, computers and Wi-Fi and Conrad, which was the larger of the two studies, documents very substantial lowering in ability to use without symptoms or to tolerate using each of these three EMF-emitting devices. Conrad also documents that all 49 individuals who reported being EHS before smart meter installation also reported that their EHS symptoms became "much worse" following smart meter installation. Conrad found that 2/3rds of the EHS individuals had substantial improvements in the EHS symptoms when they moved away from the smart meters. In contrast with the Conrad study, which asked many specific questions about symptoms, the Lamech study avoided asking any specific questions in order to avoid suggesting to any of the participants in their study any specific symptoms. What is striking and in my judgment is particularly important is that the

symptoms found by both Lamech and by Conrad are strikingly similar despite Lamech making major efforts to avoid suggesting any such symptoms. These included increases in EHS, increases in cardiac effects, including heart palpitations and arrhythmias and included many neurological/neuropsychiatric effects. The Lamech neurological/neuropsychiatric symptoms included: Insomnia, headache, tinnitus, lethargy, cognitive disturbance, dysesthesias (sensory changes), dizziness/loss of balance, nausea, pain (other than headache), anxiety/agitation/irritability/restlessness. The Conrad neurological/neuropsychiatric symptoms included: Fatigue, insomnia, concentration/attention difficulty, headache, agitation, dizziness, ear ringing/tinnitus, head pressure, dysesthesia (eye/vision, numbness), skin tingling,/burning. Given the care that Lamech made to avoid suggesting any symptoms, the similarities between the Lamech and Conrad symptoms are very striking. Given the finding that each of these many symptoms (including the cardiac and EHS effects) substantially increased following smart meter exposure and substantially decreased when moving away from smart meter exposures and the similarities of symptoms in the previous sentence in these two studies, it is difficult to avoid the inference that smart meter exposures are causing each of these symptoms. Nevertheless that is exactly what Dr. Israel has done. He states that "It is my medical opinion that the Lamech and Conrad papers do not provide scientifically reliable or useful data upon which to make a determination of causation of any symptom or condition identified in them." Dr. Israel fails to consider any of the important symptoms or other observations discussed above nor does he provide any other explanation for them that might provide another plausible way of explaining how they can all occur via some other mechanism other than smart meter causation.

24. Q. Dr. Israel states (rebuttal p. 9) that he also considered other papers that might contribute to various symptoms and health impacts. What do you think of his choices of papers here?

A. He does not give us any papers, so we have no idea what he looked at or whether he looked at anything. What is tragic here is that I provided Dr. Israel and others involved in this case with a detailed review of the literature on causation of various neurological/neuropsychiatric effects caused by low-intensity microwave frequency EMF exposures (Appendix I of my testimony). Despite (or perhaps because) there is so much relevant material in Appendix I, he completely ignores it.

25. Q. What are the relevant materials in Appendix I?

A. This was my paper on causation of widespread neurological/neuropsychiatric effects by low-intensity, non-thermal exposures to microwave frequency EMFs. It has several important parts to the paper: 1. It shows that the neurons of the nervous system including the brain have very high densities of VGCCs, because of the essential role of the VGCCs in the release of every neurotransmitter in the nervous system. This predicts that the nervous system including the brain should be highly sensitive to such EMFs, given that EMFs act via VGCC activation. 2. Extensive animal (mostly rodent) studies show that low intensity EMFs have massive effects on the nervous system including the brain; in general changes in cellular structures of tissues show that the three most sensitive tissues in the bodies of rodents to such non-thermal EMFs are the nervous system, including the brain, the heart and the testis. Other organs are also sensitive, but less so. Many of these studies were from old Soviet studies but there are also many studies from various Western countries and other countries as well,

confirming the sensitivity of the brain to such EMFs. When you get such massive effects of low-intensity EMFs on the structure of the brain, it is almost inevitable that widespread neurological/neuropsychiatric effects will also occur on exposure. 3. Genetic polymorphism studies of the main L-type VGCC in the brain show that elevated VGCC activity causes increased susceptibility to various neuropsychiatric diseases. 4. Epidemiological studies of exposure to various types of EMFs produce widespread neurological/neuropsychiatric effects. The most often types of effects found in 22 studies of various EMFs are: Sleep disturbance/insomnia; Headache; Fatigue/tiredness; Depression/depressive symptoms; Dysesthesia (vision/hearing/olfactory dysfunction); Concentration/attention/cognitive dysfunction; Dizziness/vertigo; Memory changes; Restlessness/tension/anxiety/stress/ agitation/feeling of discomfort; Irritability; Loss of appetite/body weight; Skin tingling/burning/inflammation/ dermographism; Nausea. The similarity of this list to the neurological/neuropsychiatric symptom list from the lists from the Lamech and Conrad studies are stunning and cannot be denied.

26. Q. Do you then conclude that the non-thermal EMF exposures cause these various neurological/neuropsychiatric effects?

A. Yes. But this conclusion is not just based on the epidemiological studies alone. The concentration of VGCCs in the brain, the massive effects of these EMFs on brain structure and function and the genetic polymorphism studies all have important roles in demonstrating causality. The case is extremely strong even if you eliminate these for consideration but becomes definitive when including them. The epidemiological studies were shown to provide strong evidence for causation using the Bradford Hill criteria:

1. Strength (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

2. Consistency (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.

3 Specificity: Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.

4. Temporality: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).

5. Biological gradient: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.

6. Plausibility: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).

7. Coherence: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".

8. Experiment: "Occasionally it is possible to appeal to experimental evidence".

9. Analogy: The effect of similar factors may be considered.

There are strong arguments for fulfillment of Hill criteria 1 through 7, providing a strong argument from epidemiology alone for causation.

27. Q. What does Dr. Israel conclude?

A. That there is no connection with smart meters (rebuttal p. 10). I guess if you ignore enough clearly relevant data, and you are Dr. Israel, you can conclude anything you want.

28. Q. Dr. Israel discussed (rebuttal p. 10) the differences between biological effects and health effects. What is that about?

A. As best I can determine, Dr. Israel (and Dr. Davis raised a similar issue) seem to be suggesting that some of the biological effects that I showed in my testimony that had been repeatedly reported to occur following low-intensity EMF exposures may not produce health effects. Let me say to both of them that those biological effects are as follows:

1) Widespread different neuropsychiatric effects, including changes in brain structure and function, changes in various types of psychological responses and changes in behavior.

2) At least 8 different endocrine (hormonal) effects.

3) Cardiac effects influencing the electrical control of the heart, including changes in electrocardiograms (ECGs) producing arrhythmias, changes that can be life threatening.

4) Chromosome breaks and other changes in chromosome structure.

5) Histological changes in the testes.

6) Cell death (what is now called apoptosis, a process important in neurodegenerative diseases).

7) Lowered male fertility including lowered sperm quality and function and also lowered female fertility (less studied). There are also reports of high levels of spontaneous abortion.

8) Oxidative stress.

9) Changes in calcium fluxes and calcium signaling.

10) Cellular DNA damage including single strand breaks and double strand breaks in cellular DNA and also 8-OHdG in cellular DNA.

11) Cancer which is likely to involve these DNA changes but also increased rates of tumor promotion-like events.

12) Therapeutic effects including stimulation of bone growth.

13) Cataract formation (previously thought to be thermal, now known not to be).

14) Breakdown of the blood-brain barrier.

15) Melatonin depletion and sleep disruption.

I suggest to Dr. Israel that if he wants to argue that some of these biological effects do not have health effects, he should make whatever specific argument on that that he wishes. I think the health effects of all 15 should be obvious, but perhaps he may wish to disagree. Barring that, he should not be wasting the PUC's time on this.

29. Q. Do you agree with Dr. Israel (rebuttal p. 11) that EHS should be referred to as idiopathic environmental intolerance (IEI)?

A. No, I don't. The two conditions that some argue should be lumped together under IEI are multiple chemical sensitivity (MCS) and EHS. While these are similar to each other and have substantial co-morbidity, they are not the same. I am attaching a 50 page review (Appendix Y) that I was chosen to write from amongst all scientists in the world, that when it was published establishes for the first time that MCS is a disease of toxic exposure - such that it is caused by chemical exposures is not, therefore, idiopathic. Although there is less evidence on EHS, there is no reason to think that it is idiopathic either.

30. Q. Dr. Israel states (p.12) that symptoms of EHS is not caused by EMF exposures. Do you agree with him?

A. No I don't and let me tell you exactly why. EHS individuals are heterogeneous - they don't all behave the same way. They differ both in overall sensitivity and in the specific regions of the body which have become hypersensitive. Nevertheless, it is possible to do studies that demonstrate that at least in a substantial fraction of EHS individuals, one can do double blinded provocation studies and get consistent responses with those individuals. For example, 25 years ago, Dr. William Rea and his colleagues showed that one can identify about ¼ of self-identified EHS individuals and successfully do double blinded, placebo controlled trials where specific individuals react specifically and with very high consistency to exposure to low intensity EMFs but not to sham exposures - all when done in double blinded fashion. I am attaching a copy of Dr. Rea's paper on this (Appendix Z). Dr. Magda Havas showed that she could do similar experiments to those published earlier by Rea and colleagues (Electromagn Biol Med.

2008;27(2):135-46. doi: 10.1080/15368370802072075. Dirty electricity elevates blood sugar among electrically sensitive diabetics and may explain brittle diabetes; Dirty Electricity Elevates Blood Sugar Among Electrically Sensitive Diabetics and May Explain Brittle Diabetes Electromagnetic Biology and Medicine Volume 27, Issue 2, 2008; Microwave radiation from 2.4 GHz cordless phone affects autonomic nervous system, Eur J Clin Oncol 2007;5:273-300). In the third citation immediately above Havas et al showed that certain EHS individuals developed instantaneous tachycardia (rapid heartbeat) when a cordless phone was turned on in double blinded fashion, but heart beat returned (again instantaneously) to normal when the cordless phone was turned off in double blinded fashion. It was possible to go back and forth repeatedly and again get instantaneous changes in heartbeat. It is my belief that it will be possible to develop assays for EHS that will work for larger groups of EHS individuals but it may never be possible to develop a single test that works for all of them.

What are the crucial issues with respect to doing these studies properly such that objectively measurable sensitivity can be demonstrated in EHS? According to Dr. Rea's and Dr. Havas' studies, the following are crucial: it is important to identify EHS patients that show consistent sensitivity responses and then use these for repeated double blinded studies. It is also important to use the proper measure for sensitivity for specific types of patients. Finally, as has been known for MCS for many years, it is important to put the individuals in a low chemical/EMF environment for several hours so that they are not already approaching maximum response levels before the exposure studies begin. If you don't do all of these things, you will not see any effect and you will falsely assume that no reliable provocation studies can be done with EHS as Rubin and others have assumed.

31. Q. Dr. Israel claims (rebuttal p. 15) that it is generally accepted that exposure to radio frequency fields do not cause, contribute to, or exacerbate idiopathic environmental intolerance. Do you agree?

A. Of course not. First of all, IEI has never been properly defined - there is no accepted case definition for IEI. It is, therefore, a phantom that there is no point in talking about. Now, Dr. Israel has proposed a theory and like all theories it is important to test the theory to see if it holds up on testing. Each of the four papers that I cited in the previous section have tested Dr. Israel's theory. Each of them has shown that some EHS patients respond reproducibly in blinded fashion to low intensity microwave frequency EMFs. It follows that each of these four studies have falsified Dr. Israel's theory. Now in science, when a theory has been falsified, the theory is thrown out. So the theory is gone based on these four studies and basic principles of science. That should be more than sufficient to take care of this issue.

32. Q. Are you aware of studies that contradict Dr. Israel's position on EHS?

A. Yes. It is important to add, that there are many contrary opinions to the views that Dr. Israel advocates:

Belyaev I, Dean A, Eger H, Hubmann G, Jandrisovits R, Johansson O, Kern M, Kundi M, Lercher P, Mosgöller W, Moshammer H, Müller K, Oberfeld G, Ohnsorge P, Pelzmann P, Scheingraber C, Thill R. 2015 EUROPAEM EMF Guideline 2015 for the prevention, diagnosis and treatment of EMF-related health problems and illnesses. Rev Environ Health. 2015;30(4):337-71. doi: 10.1515/reveh-2015-0033.

Carpenter DO. 2015 The microwave syndrome or electro-hypersensitivity: historical background. Rev Environ Health. 30:217-222.

McCarty DE, et al. 2011 Electromagnetic hypersensitivity: evidence for a novel neuological syndrome. *Int J Neurosci 121:670-676.*

Hagstrom M, J Auranen, R Ekman. 2013 Electromagnetic hypersensitive Finns: Symptoms, perceived sources and treatment, a questionnaire study. Pathophysiology 20:117-122.

Genuis SJ, Lipp CT. 2012 Electromagnetic hypersensitivity: fact or fiction. Sci Total Environ 414:103-112.

De Luca C, et al. 2014 Metabolic and genetic screening of electromagnetic hypersensitive subjects as a feasible tool for diagnostics and intervention. Mediators Inflamm 2014, Article ID 924184.

The first of these is a detailed 17 author paper on EHS from the EUROPAEM, the European Environmental Medicine Organization, with authors coming from 8 different countries. This is, to my knowledge, the highest medical organization anywhere in the world to take a clear position on EHS and it differs widely from the claims of Dr. Israel.

33. Q. Are there other factors at play?

A. Yes. There is one other point I would like to make with regard to Dr. Israel's position on EHS. EHS is one of a series of related medical conditions that are much more common in women than in men. Each of these medical conditions are largely neglected by modern medicine. It is my opinion that the position that Dr. Israel has taken that is apparently supported by these various "expert bodies" would not be tolerated if EHS had predominantly male victims. I think this is simple example of sex discrimination.

34. Q. Dr. Davis and Dr. Israel seem to be unaware of any recognition of EHS by the U.S. government. Does the U.S. Government Recognize EHS as a Sensitivity to EMFs?

A. Yes the National Institute of Building Sciences (NIBS), part of the U.S. government, *does recognize EHS as such a true sensitivity to EMFs on their web site:*

http://web.archive.org/web/20060714175343/ieq.nibs.org/ieq_project.pdf

The NIBS, is authorized by Congress as an authoritative source in service of the public's interest, and with funding from The Architectural and Transportation Barriers Compliance Board (Access Board), 2005; this includes the guidelines arm of the ADA (Americans with Disabilities Act).

P. 1, First Line with Logo:

"IEQ Indoor Environmental Quality: A project of the National Institute of Building Sciences (NIBS) with funding support from The Architectural and Transportation Barriers Compliance Board (Access Board)"

Excerpt: (Pg. 4, Introduction)

"As stated in the Background for its Final Rule Americans with Disabilities Act (ADA) Accessibility Guidelines for Buildings and Facilities; Recreation Facilities: http://www.access-board.gov/recreation/final.htm

"The Board recognizes that multiple chemical sensitivities and electromagnetic sensitivities may be considered disabilities under the ADA if they so severely impair the neurological,

respiratory or other functions of an individual that it substantially limits one or more of the [page break, NIBS IEQ Final Report 7/14/05 to page 5] individual's major life activities. The Board plans to closely examine the needs of this population, and undertake activities that address accessibility issues for these individuals."

Excerpt: (Pg. 87)

"Overview – Design

The Products & Materials Committee believes that particular attention is critical during building design to assure that the needs of chemically and electromagnetically sensitive people are accommodated to the greatest extent possible. In general, this means selection of construction materials that are low-emitting or non-emitting and selection of finishes that do not absorb or react with chemicals emitted by other materials or products in the building. To begin to address some of the concerns of electromagnetically sensitive persons, areas of the building can be designed to have reduced electromagnetic fields. By making indoor environments that are safer for the most vulnerable among us, we can create indoor environments that are healthier for everyone, especially children...".

Excerpt: (Pg.88)

"...In addition, during building design particular attention must be paid to choice of electrical appliances, equipment and products that may produce higher than necessary electromagnetic fields. The NIBS-IEQ Materials Committee recognizes that there are selections that can be made during building design and construction that can provide a more healthful environment for persons with electromagnetic sensitivities. A few of these considerations are:

Incorporation of a foil vapor barrier or other metal shielding feature into the walls around electric equipment can reduce certain electromagnetic fields.

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Wireless ("bluetooth" type) connections should be avoided, or areas of their use should be "contained" by using foil-backed drywall or other incorporation of a foil or metal barrier. New construction should use twisted metal clad wiring and/or twisted wire placed in metal conduit.

Fiber optic connectivity is preferred for computer networks communication because these data lines may be run without concern for stray emissions..."

Excerpt: (Pg. 88)

"Overview - Building Operations and Maintenance Building managers must also pay close attention to materials brought into the building environment by tenants or others to assure that these materials are consistent with provision of an accessible, healthy building for persons with multiple chemical sensitivities, electromagnetic sensitivities, and/or other health disorders. ..."

It can be seen from the above, that the U.S. government does recognize EHS as a true sensitivity to EMFs such that people who suffer from EHS should be accommodated for their disability under the ADA. This document specifically recommends that specific steps be taken to lower exposure of EHS people to low-intensity EMFs of various sorts including wireless communications and dirty electricity. It follows from this that the U.S. government position is diametrically opposed to Dr. Israel's position, as well.

35. Q. Dr. Israel states that "I considered the sequence and timing of the events but unfortunately it was no help in determining the cause of Ms. Povacz's symptoms. When one event occurs shortly after another, that does not prove that the first event cause the second event." Is this accurate?

A. The second part of it is accurate, but the first in inaccurate. It is correct to say that the timing does not prove that the second event is caused by the first event. But to say that the timing is of no help in determining causation is simply wrong. Timing (what is often called temporality) is often viewed as the most important of the Hill criteria. What is obviously true is that if the changes occurred before the smart meters went in, that would tell us the smart meters could not be the cause. When the timing goes the other way it does argue for causation, although that alone is insufficient to draw a conclusion. What one needs to do then is to look at other available evidence. I am shocked here by Dr. Israel's failure to look for other evidence and I am also shocked by his apparent gross ignorance of the Hill criteria. What he does is another rush to judgment where he states (P. 17, lines 16-18) that "I do not know what caused Ms. Povacz symptoms. But based on the medical and scientific studies and my education, training and experience, I confident (sic) they were not caused by radio frequency fields from the AMI meters.

36. Q. What other evidence is relevant to Ms. Povacz's symptoms?

A. So the symptoms here are listed on p. 15 are "disrupted sleep pattern, frequent headaches and constant buzzing." What do we know about those symptoms? The buzzing sounds like a tinnitus-like condition. If you look at the Lamech study, she finds that insomnia is the most common symptom associated with smart meters, headache is the second most common

symptom and tinnitus is the third most common symptom. And, let me remind you again, that Lamech took great care not to suggest any symptoms in her study. In the Conrad study these are all common symptoms but less common than in Lamech. In the Conrad study, insomnia was the second most common symptom, headache was the fourth most common symptom and tinnitus was the sixth most common symptom. Among the symptoms caused by various low-intensity EMFs (see Appendix I), sleep disturbance/insomnia were the most common symptom, followed by headache as second most common. Tinnitus was found but was far down the list. The conclusion is obvious: It is highly probable that Maria Povacz's disrupted sleep pattern, frequent headaches and tinnitus were all caused by PECO's smart meters.

37. **Q. What is your opinion about causation of Ms. Povacz's symptoms (pp17-18) or widespread pain/body aches, buzzing in the ears, eye floaters, lack of concentration and memory loss?**

A. I can't say anything about eye floaters. All these other symptoms are commonly associated with smart meters (Lamech, Conrad). With the exception of buzzing in the ears/tinnitus, which is less common, they are also commonly caused by low-intensity microwave frequency EMF exposures of various sorts (Appendix I). It is highly probable based on these studies and the occurrence of these symptoms following PECO smart meter installation, that with the possible exception of floaters in the eye, the other symptoms were caused by PECO smart meter installation.

38. Q. Dr. Israel discussed (pp.19-20) three papers that are favorite papers of his that were published in this area. Can you discuss the Ziemann et al (2009) paper?

A. Yes, I'd be happy to discuss this paper. Dr. Israel also spoke of this as this as a strong favorite of his in his testimony in the Krieder case. Let's discuss several aspects of this paper. 1. On p. 456 of Ziemann et al, the authors make clear that they are studying the effects of simulated cell phone radiation, not actual cell phone radiation (I am attaching a copy of the Ziemann et al paper as Appendix AA). In the Panagopoulos study (Panagopoulos, D. J., Johansson, O., Carlo, G. L. 2015. Real versus simulated mobile phone exposures in experimental studies. BioMed. Res. Int. 2015, article ID 607053, 8 pages), it was shown that, almost all studies of true cell phone radiation produced biological effects, whereas the majority of simulated cell phone studies found no biological effects. This raises an important question about why Ziemann et al opted to study simulated cell phone radiation. Panagopoulos et al interpreted their study as being due to the much greater pulsations produced by genuine cell phones as compared with simulated cell phone radiation, with the pulsations known to have roles in producing much greater biological effects. 2. Because much of the funding of the Ziemann et al paper (see pp.462-463) came from industry sources, this raises the issue of whether industry has a vested interest in covering up the actions of genuine cell phone radiation. 3. The study is described as being a two years study of radiation effects. However the cells examined for micronuclei (their marker for genotoxicity or cellular DNA damage), in mouse erythrocytes, and such erythrocytes have a lifespan of only about 30 days; because of the inherent instability of micronuclei in replicating cells, such micronuclei in erythrocytes may possibly be generated over at most a 30 day period. It is highly misleading to describe this as a two year study when only the last 30 days are relevant to generating the marker being studied. 4. In rats and humans, erythrocytes containing micronuclei

are selectively removed from circulation very quickly (see p. 459 of Ziemann et al). While Ziemann et al claim that mice do not have a similar mechanism for selective removal, the only citation that they provide was of a study published by Chaubey et al (1993) showing that this was apparently true with Swiss mice; Ziemann et al chose to use B6C3F1/CrlBR mice, a different inbred mouse strain which may well therefore behave quite differently from Swiss mice. It follows from this that we have no idea whether the strain studied is similar to Swiss mice with regard to selective removal of erythrocytes containing micronuclei. 5. Ziemann et al show that male and female mice behave quite differently with regard to levels of micronuclei (Tables I and III); however in their experimental study (Figure 2), males and females were combined in doing the statistics. What that inevitably does is to produce greater variations in micronuclei levels within different animal groups, making it substantially more difficult to detect any statistical significance among different animal groups in the study. 6. In section A of Figure 2, there were only 8 animals in each group studied. In secton B of Figure 2, there are only 5 to 9 animals in each animal group studied. These tiny numbers mean that there is only extremely low statistical power to detect any effects of EMF exposure and therefore these tiny studies make it almost impossible to say anything at all about the results whatsoever. 7. The Ziemann et al study provide none of their raw data; consequently we are in a situation where have no way of judging whether their statistical analysis was done properly. We also have no way to use any such data as part of a meta-analysis of multiple studies, which may have much more power than do any single study (particularly such a tiny one). Consequently, the lack of statistical significance they report, cannot be properly assessed by the reader. 8. When one does a study looking at the possible effects of some variables, in this case a couple of simulated cell phone radiation studies, the most you can say about an apparent negative result is that "we did not see any statistically

significant effects." When you have tiny studies such a described under 7 above, then the lack of statistical significance tells you almost nothing. But even with a very large study such as with thousands of mice including many hundreds in each experimental group, all you can say is that "we did not see any statistically significant effects." 9. What do Ziemann et al conclude? They state in their title (and elsewhere) that there is an "Absence of genotoxic potential of 902 MHz (GSM) and 1747 (DCS) wireless communication signals." Did they study these EMFs in all organisms and all cell types? No, of course not. Did they study all possible pulsation patterns of these two frequency EMFs? No, of course not. Did they study all types of genotoxicity found following low-intensity EMF exposures? No, of course not. So this title alone should tell any competent scientist that the paper is deeply flawed, completely apart from the preceding 8 flaws, with each of the 8 adding substantially to the flaws in this paper.

39. Q. So why, in your opinion, did Dr. Israel choose this deeply flawed paper as his number one favorite paper?

A. Either he is incompetent or he has extraordinary bias. Neither one of these should be acceptable in an expert witness, in my judgment.

I have had no time to similarly examine the other two papers that are among Dr. Israel's favorites. Both were published in the journal "Radiation Research" which according to Microwave News (Vol. XXVI, No. 4; July 2006, pp.1-4, has had a predilection for publishing negative results on EMFs, paid for by industry, even those that run counter to previous studies where independent scientists found positive results - that is biological effects of low-intensity EMFs. Microwave News states that "Wireless companies like Motorola have fostered the spurious view that negative studies cancel out positive ones. Their strategy is this: First seed the

journals with no-effect papers that run counter to previously published work which does show biological changes. They argue: 'If we couldn't replicate the effect, it cannot be real.' The assumption here is that industry science is superior to everyone else's.'"

It can be seen from this is that it is not difficult to cherry pick a few carefully chosen, deeply flawed papers from the industry-supported literature to tell a story that supports the industry point of view. Such cherry picking is, of course, scientifically meaningless.

40. Q. Ms. Povacz raised a question regarding her hypothyroidism and its possible causation by the PECO smart meter (p.21). She raised this question of the Esmekaya et al (2010) paper in the International Journal of Radiation Biology where pulsed 900 MHz EMFs caused multiple changes to the cellular structure of the thyroid, inducing apoptosis. Dr. Israel stated that there were no data comparing the thyroids of the EMF-exposed animals with non-exposed controls. He also stated that no thyroid hormone levels were measured, arguing that there should have been such measurements. What is your opinion of this paper and the information provided by Dr. Israel?

A. I think that this is an interesting paper, involving stimulation of apoptosis by low-intensity 900 MHz pulsed EMFs. I would note that on p.1114 of the paper, the authors state that no apoptosis was observed when a continuous wave 900MHz EMF was used in place of the pulsed EMFs. They also observed, also on p. 1114 that the apoptotic response (or lack of same) was cell-type specific, again emphasizing the fact that many responses to low intensity EMFs depend on the type of cell being studied. Dr. Israel's claim that they did not compare irradiated animals with non- irradiated animals is sheer nonsense. Such comparisons were made

throughout p.1110 including Fig. 2 and in the text in terms of various structural changes. They compared in each case controls with sham irradiated and RF-exposed thyroid tissues. They show large changes in follicular area and in colloid area through such comparisons (p. 1131). They also do histochemical comparisons including caspase-9 levels (characteristic of apoptotic-like changes). There are further such comparisons in Fig. 4, Table 1 and in the text on p.1112 and on Fig. 5 of p. 1113. The claim that Dr. Israel makes that there were no comparisons with non-exposed controls is completely false and it is difficult to see how even a very superficial reading of this paper could have lead to that inference being drawn. With regard to Dr. Israel's claim that thyroid hormone levels should have been measured, that is a difficult argument for him to make. Given the known correlation of the changes seen on RF-exposure with much lowered function including follicular and colloid changes with lowered thyroid function, such measurements may be superfluous. In addition raising caspase-3 and caspase-9 leading to apoptosis will certainly not do anything to raise thyroid function, quite the contrary.

41. Q. Dr. Israel also states that the deSeze 1998 study of anterior pituitary function provides, as he states "very strong evidence that exposure to radiofrequency fields does not cause hypothyroidism in humans." What is your opinion?

A. My opinion is that this is more nonsense. All of the evidence in the Esmekaya paper is that EMF effects are direct ones on the thyroid gland tissues, so the anterior pituitary has nothing to with it. It is certainly false to state, as Dr. Israel does, that the deSeze study provides "very strong evidence that exposure to radiofrequency fields does not cause hypothyroidism in humans." My opinion is that Dr. Israel is playing very nasty games with Ms. Povacz.

42. Q. *So what is your opinion on Ms. Povacz's thyroid dysfunction?*

A. The release of thyroid and many other hormones are controlled by the VGCCs, as I discussed in my direct testimony. Consequently, VGCC activation by the low-intensity EMF exposure can lead initially to increased hormone release, but over the longer term it can lead to hormone exhaustion. I don't know enough about autoimmunity to know in what ways this might lead to autoimmune problems in the thyroid. But it is my opinion that Ms. Povacz's initial thyroid exhaustion were produced by the EMFs produced from the PECO meter.

43. Q. Do you have a similar opinion about her adrenal exhaustion?

A. Yes, indeed. I have a very similar opinion about PECO meter radiation leading to adrenal exhaustion.

44. Q. Dr. Israel claims (p.24) that there is no known mechanism by which radio frequency EMFs can cause chest pains, rapid heartbeats, arrhythmias and palpitations. What is your opinion?

A. My opinion is that Dr. Israel does not know the literature in this area. As was noted here previously, both the Lamech and the Conrad studies showed that smart meter exposures were associated with both arrhythmias and with heart palpitations. There is a much larger literature on microwave frequency EMFs, some of which is summarized in the Table on p. 16 of my testimony. I have summarized this literature in a professional presentation that I made to the cardiac center in Marseille Hospital, Marseille, France in March 2015. I am attaching an English copy of my slides for the Marseille talk that were translated into French for the actual talk (Appendix AB). What you will note is that there are many studies on this topic and that the

VGCC mechanism provides a mechanism by which EMFs can produce each of these diverse effects. The mechanism of action is that the EMFs are acting on the VGCCs within the pacemaker cells of the sinoatrial node of the heart, cells that have very high densities of VGCCs. My opinion is that given the wide scientific information available on cardiac effects of low-intensity EMF exposure and that both smart meter studies showed associated cardiac effects, it is highly probable that Ms. Povacz's cardiac changes were caused by the PECO meter EMFs.

45. Q. What is your opinion on the cause of Ms. Povacz's sleep disturbance, fatigue and lethargy (p. 25)?

A. Firstly, let me state that Dr. Israel is wrong when he states that there are no studies on fatigue causation by low-intensity EMFs. There was a very interesting study in Germany (Altpeter, E., Battaglia, M., Bader, A., Pluger, D., Minder, C.E.. Abelin, T., 2000. Ten Years Experience with Epidemiological Research in the Vicinity of the Short- Wave Broadcasting Area Schwarzenburg: What does the Story Tell Us?, http://www.salzburg.gv.at/Proceedings_%2819%29_Altpeter.pdf.). In this study, a shortwave radio broadcasting antenna was reported to disrupt sleep in locals, with the sleep disruption being accompanied by and presumably caused by lowered melatonin levels. During a 3-day period, the broadcasting antenna was shut down. During that 3-day period, sleep returned to normal as did the melatonin levels. This strongly argues that the sleep deprivation and melatonin depletion were both caused by the shortwave radio broadcasting EMFs.

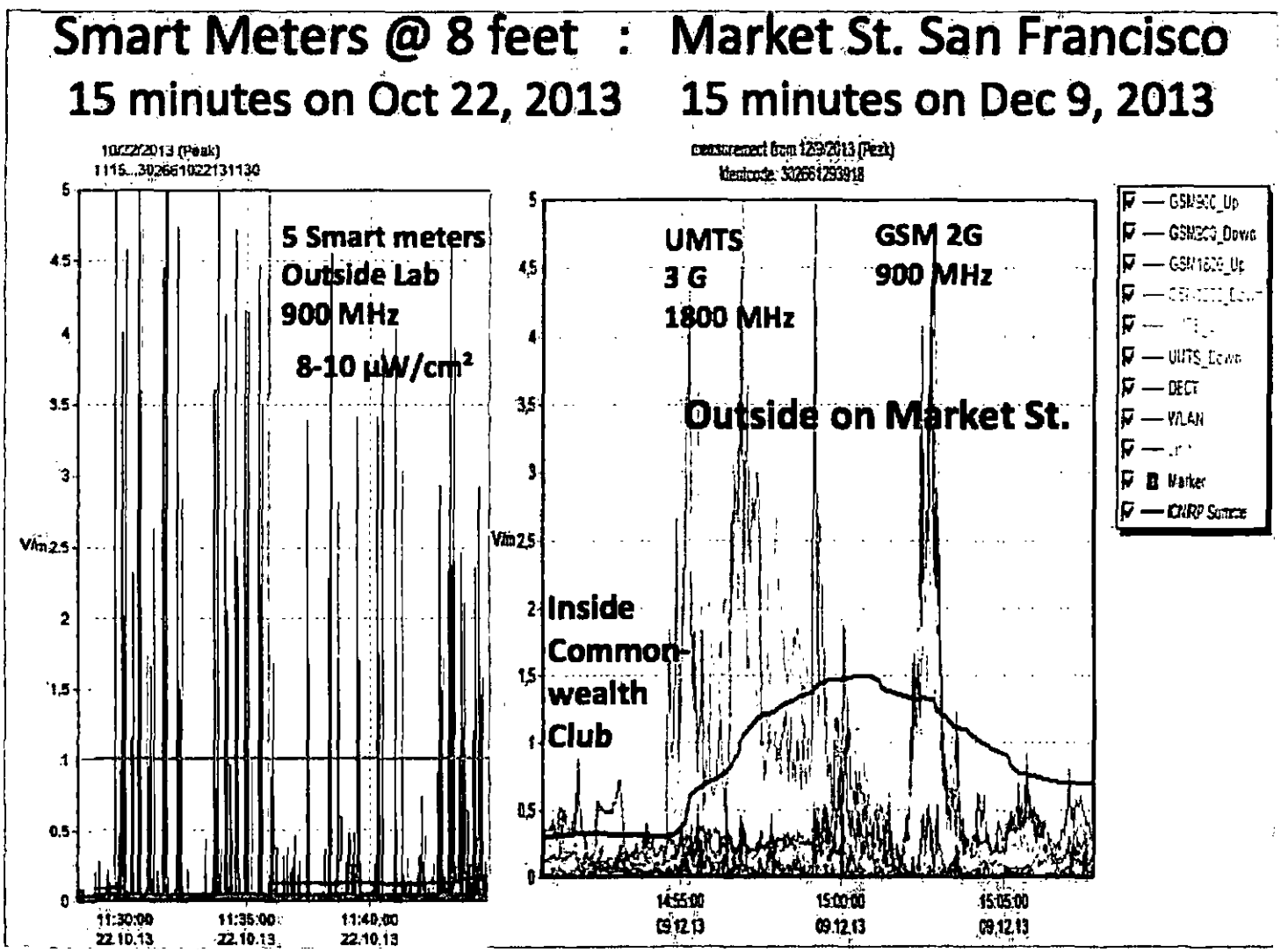
The Lamech study of smart meter radiation, found a linkage between smart meters and all three of these symptoms, sleep disturbance, fatigue and lethargy. The Conrad study looked at two of these, sleep disturbance and fatigue and found that these were each commonly

associated with smart meter exposure. In Appendix I, it was shown that various EMFs produce both sleep disturbance and fatigue. It is my professional opinion, from all of this information, that it is highly probable that PECO's smart meter radiation is the cause of Ms. Povacz's sleep disturbance, fatigue and lethargy.

46. Q. Does that conclude your surrebuttal testimony?

A. Yes.

APPENDIX T



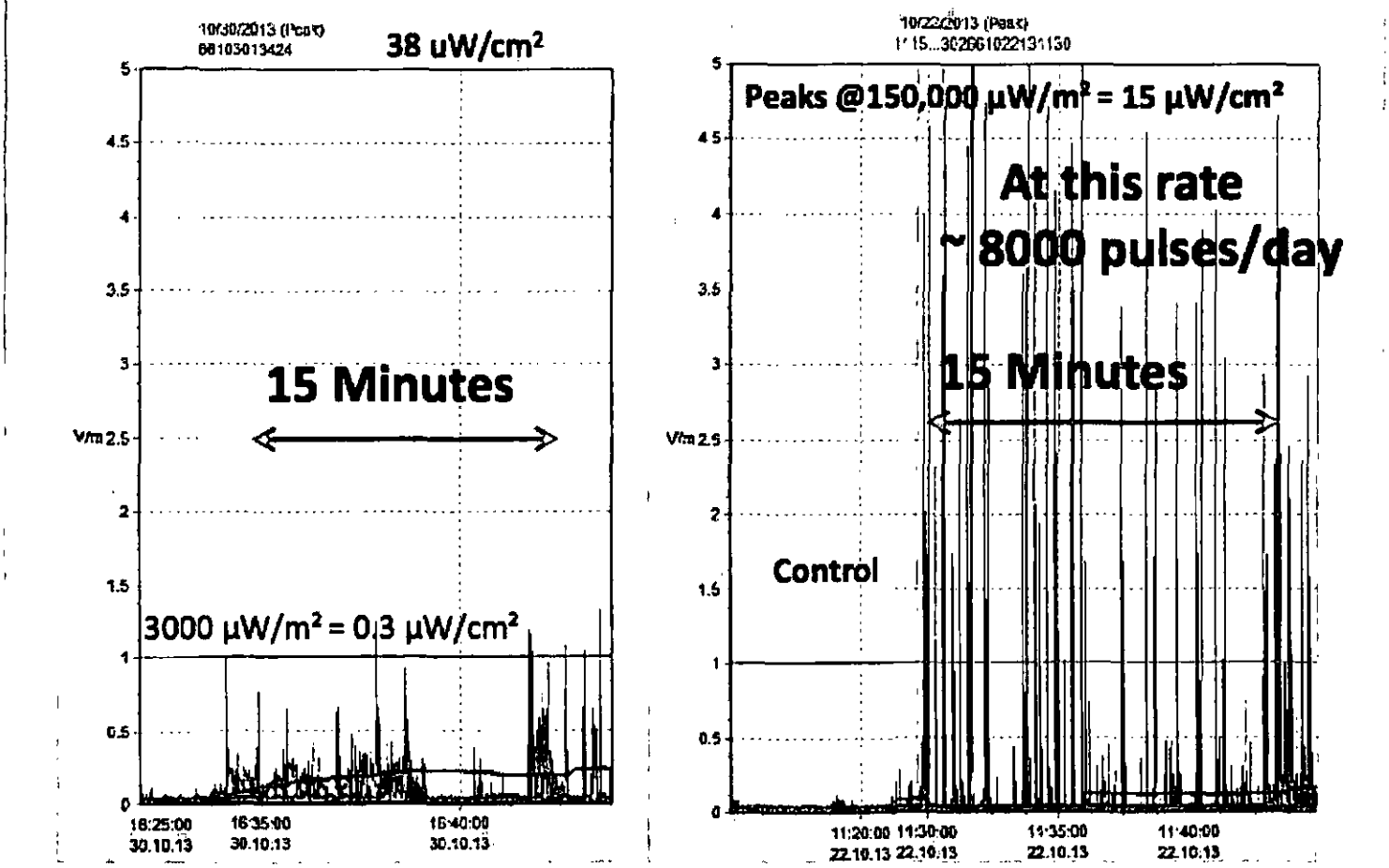
From Dr. Karl Maret: Presented at the Commonwealth Club, San Francisco, Jan 2014

Various Exposure Limits for 900 MHz

- 0.001 $\mu W/cm^2$ Salzburg, Austria Guidance for Safety and Sleep Disturbances (Schwarzenburg Study)
- 0.1 $\mu W/cm^2$ "Precautionary limit" Austria Bioinitiative Working Group (1000 $\mu W/m^2$)
- 4.5 $\mu W/cm^2$ ECOLOG-recommendation (Germany)
- 8.8 $\mu W/cm^2$ Tell Report on PG&E Smart Meter emission
- 10 $\mu W/cm^2$ Exposure limit in Russia, Poland, Hungary Switzerland, Luxemburg, Bulgaria
- 12 $\mu W/cm^2$ Measured Peaks from SM @ 4 feet
- 600 $\mu W/cm^2$ US Exposure limit by FCC (Heating effects)

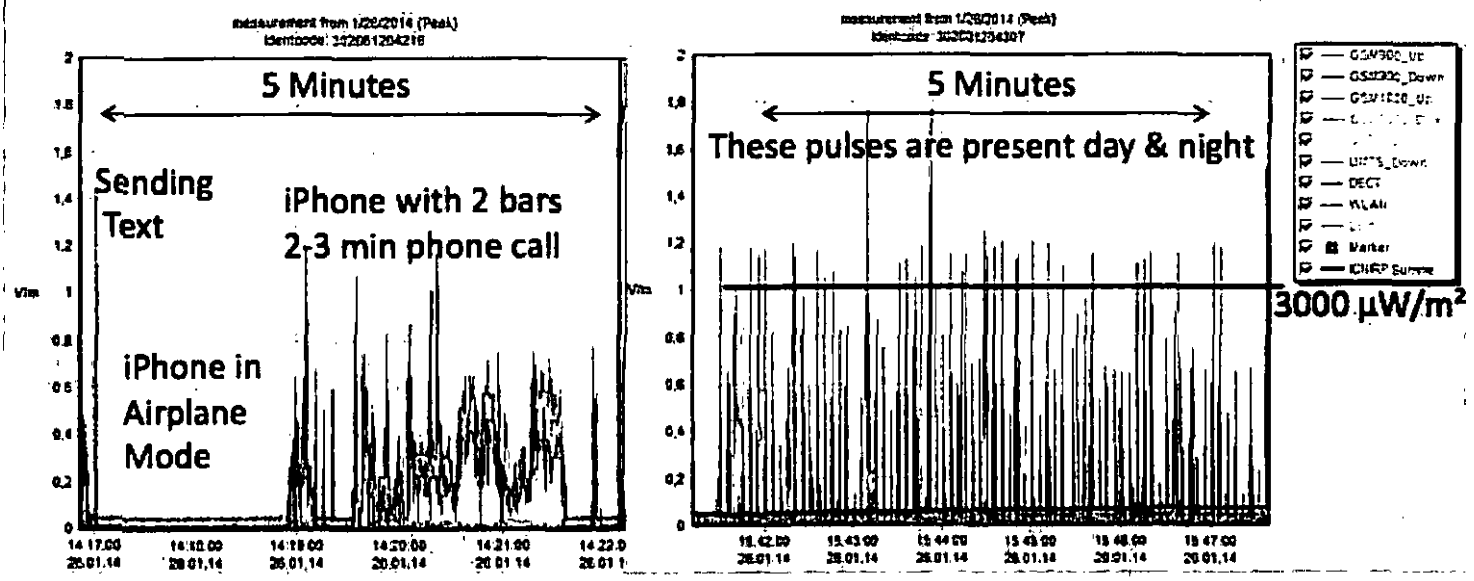
Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

iPhone during call vs. 8ft. from 5 Smart Meters



Dr. Karl Maret, Presented at the Commonwealth Club, San Francisco, Jan. 2014

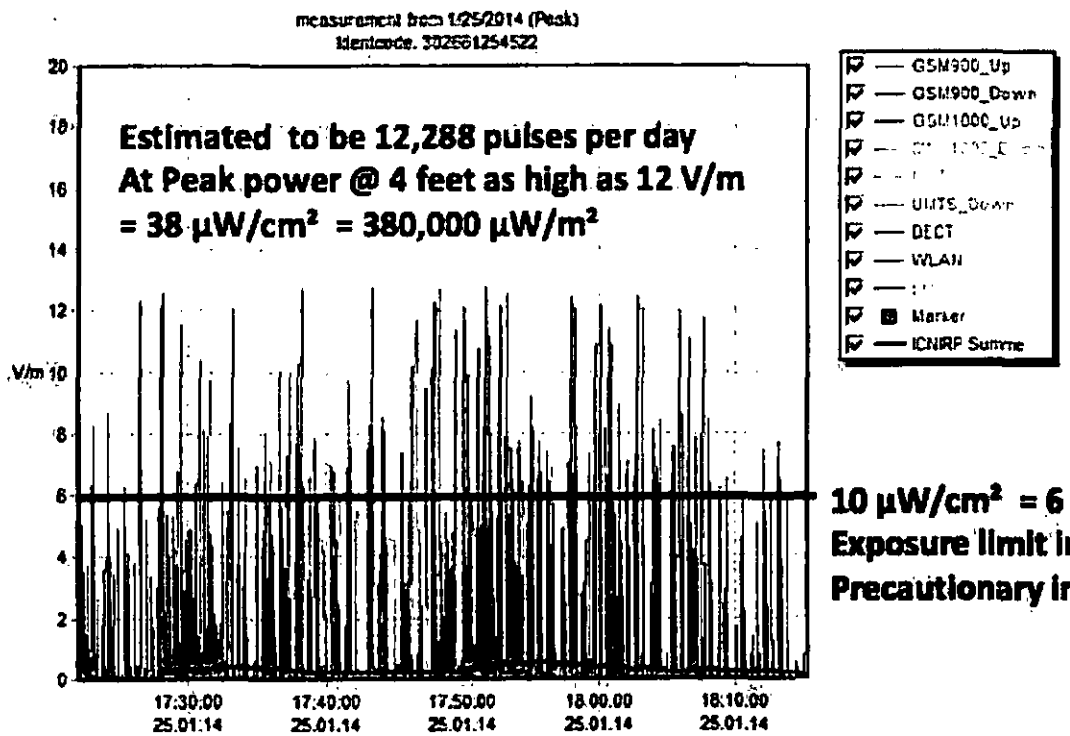
Personal Dosimeter Whole Body Comparison iPhone vs. 5 Smart Meters (inside building)



- Whole Body Exposure from both iPhone and inside building with 5 Smart Meters on outside wall show similar peak levels.
- This short burst pulsed EMFs from Smart Meters is new to living systems and should have been studied prior to deployment.

Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

Daily Pulses Generated by Smart Meter



- Depends on Duty Cycle and other meters in the Mesh network
- Data from 5 meters shows 340 pulses in 40 minutes =12,288/day
- Emissions are brief (5 msec), but fast pulses affect nervous system

Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

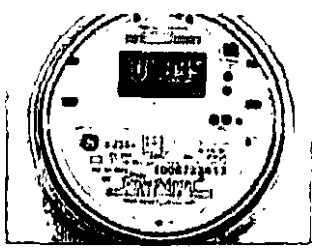
What some Customers have reported after Smart Meter Installations

- **Numerous Customers are reporting headaches, sleep problems, ringing in the ears, searing ear pain, nausea, dizziness, agitation and other symptoms since the Smart Meters were installed.**
- **These people may be suffering from *Electromagnetic Hypersensitivity Syndrome (EHS)***
- **EHS is estimated to affect 3 - 5% of the population or more**

Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

2011 Survey after Smart Meters Installation

- 443 respondents to a survey, 93% over 40 years of age
- 78% from California, 73% women, 49% reported EHS
- 76% had meters installed neighborhood > 6 months, 41% had meters installed in their homes

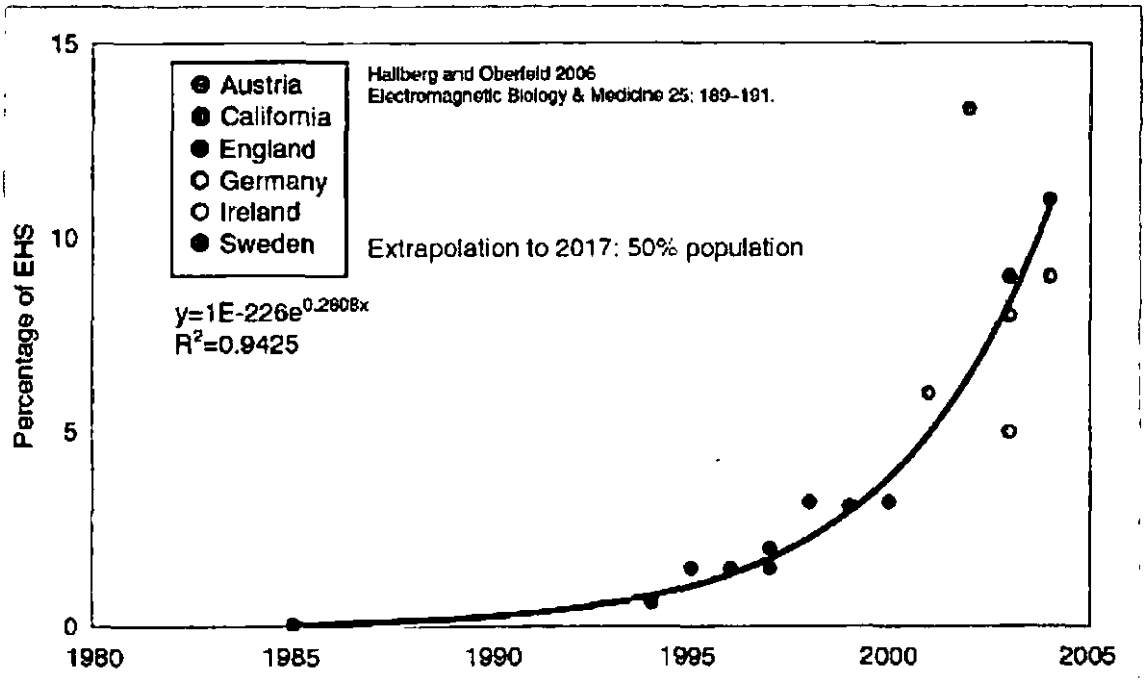


- Complaints:
  - Sleep Issues = 49%
  - Stress, anxiety, irritability = 43%
  - Headaches = 40%
  - Ringing in Ears = 38%
  - Heart Problems / palpitations = 26%

- Source: Halteman, Ed (2011) Wireless Utility Meter Safety Impacts Survey. Available at http://emfsafetynetwork.org/wp-content/uploads/2011/09/Wireless-Utility-Meter-Safety-Impacts-Survey-Results-Final.pdf

Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

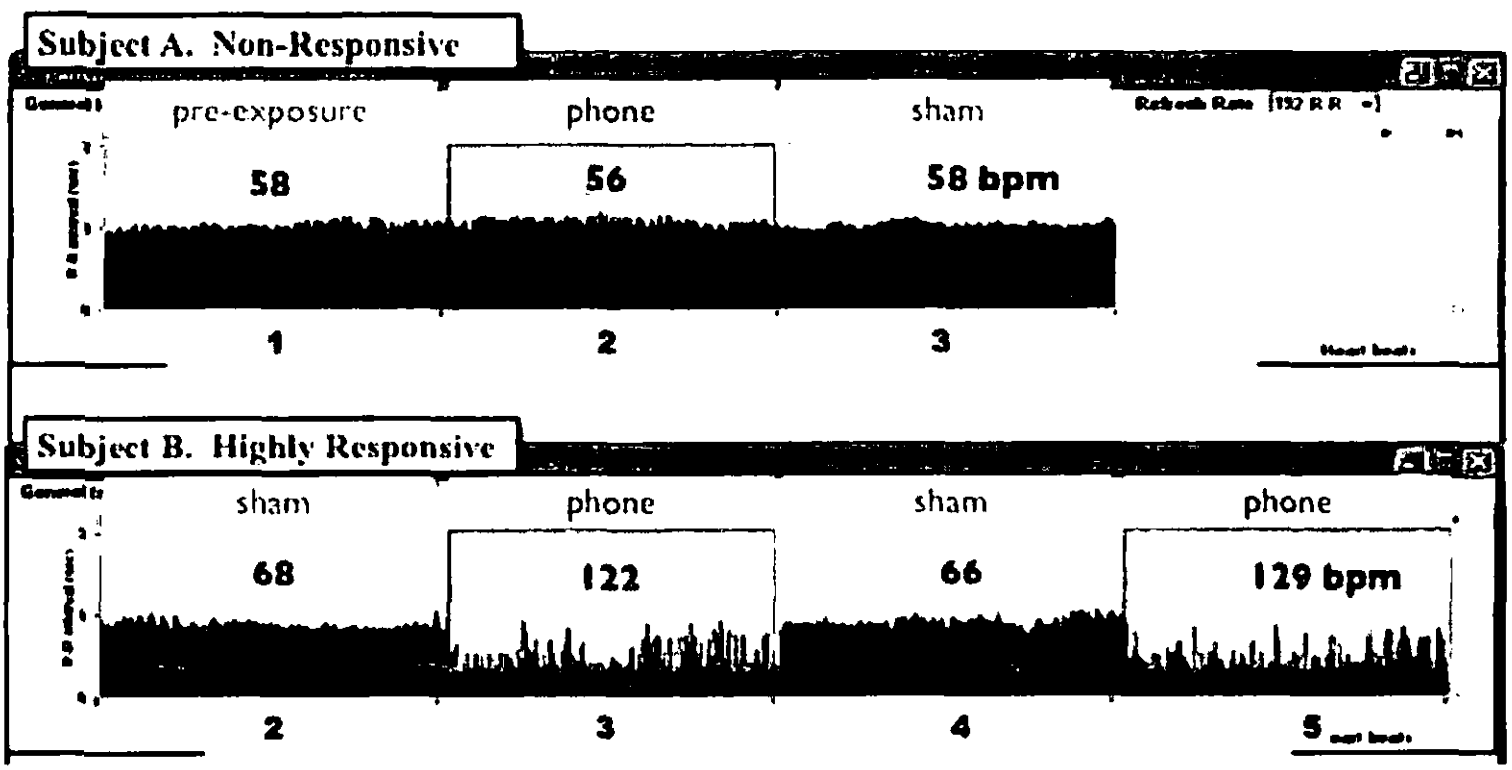
2006: Estimated EHS Population Growth



- **2013 California Population with EHS estimated at 3% would be 1,150,000 people. Most of these people would be unaware of their hypersensitivity.**

Dr. Karl Maret, presented at the Commonwealth Club, San Francisco, Jan. 2014

Objective Heart Rate Variability changes in EHS subject on Double Blinded Exposure to 2.4 GHz Cordless Phone



- Source: Magda Havas 2013

APPENDIX U

EMF Health Concerns associated with RF Metering in California's Smart Grid

Dr. Karl Maret

President, Dove Health Alliance

As part of Panel

"The High (?) Road to a True Smart Grid"

THE Commonwealth Club OF CALIFORNIA

Jan 28, 2014

WHO Health Definition

"State of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

- ***Electromagnetic Fields (EMFs)*** are now an emerging health hazard
- The current scientific debate is centered on whether long-term, low level (non-thermal) exposure can evoke biological responses and influence people's well-being.

2011: EMFs pose a Potential Health Hazard

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE N° 208 **31 May 2011**

IARC CLASSIFIES RADIOFREQUENCY ELECTROMAGNETIC FIELDS AS POSSIBLY CARCINOGENIC TO HUMANS

Lyon, France, May 31, 2011 -- The WHO/International Agency for Research on Cancer (IARC) has classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer[1], associated with wireless phone use.

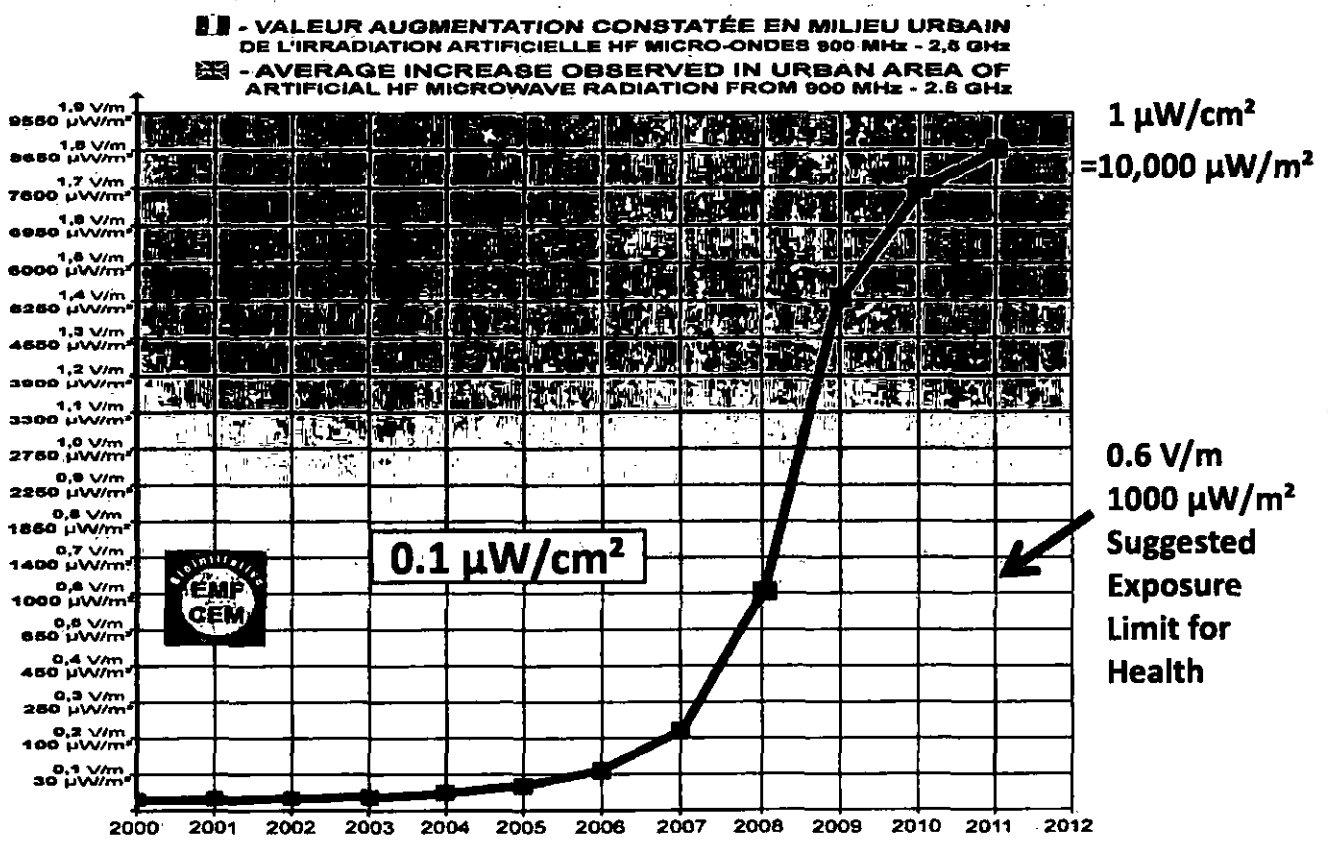
This classification applies to all RF-emitting devices, including WiFi.

- Robert A. Baan, PhD, IARC

This classification justifies the implementation of the Precautionary Principle.

- Dr. Darius Leszczynski, IARC

Exponential Rise in Microwave Radiation Levels



Courtesy: Next-Up Organization

Public Health (2008) 122, 113–124

ELSEVIER

PUBLIC HEALTH

JOURNAL OF THE ROYAL INSTITUTE OF PUBLIC HEALTH

www.elsevierhealth.com/journals/pubh

Review Article

Fielding a current idea: exploring the public health impact of electromagnetic radiation

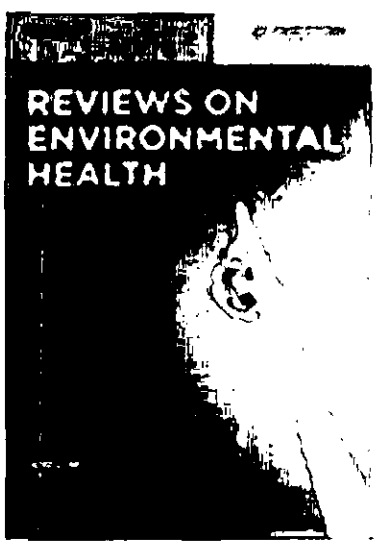
Stephen J. Genuis*

Faculty of Medicine, University of Alberta, 2935–66 Street, Edmonton, AB, Canada T6K 4C1

- 2008 review article surveying 112 peer reviewed studies
- Concludes that there is strong epidemiological evidence of considerable potential for injury and affliction as a result of non-ionizing radiation exposure from EMFs.
- Evidence for reproductive dysfunction, cancer and CNS dysfunction
- Describes industrial vested interests that biased scientific research, promote doubt and uncertainty to minimize potential harm of EMFs

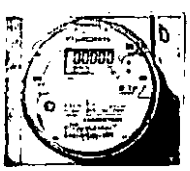
2013: Human disease resulting from exposure to electromagnetic fields

Volume 28, Issue 4 (Nov 2013)



- Good review of state of science and dangers of EMFs by David Carpenter MD published recently
- This review also summarizes that excessive exposure to Radio Frequency Radiation (RFR) increases risk of cancer, male infertility, and neurobehavioral abnormalities.

Sources of Radio Frequency Radiation

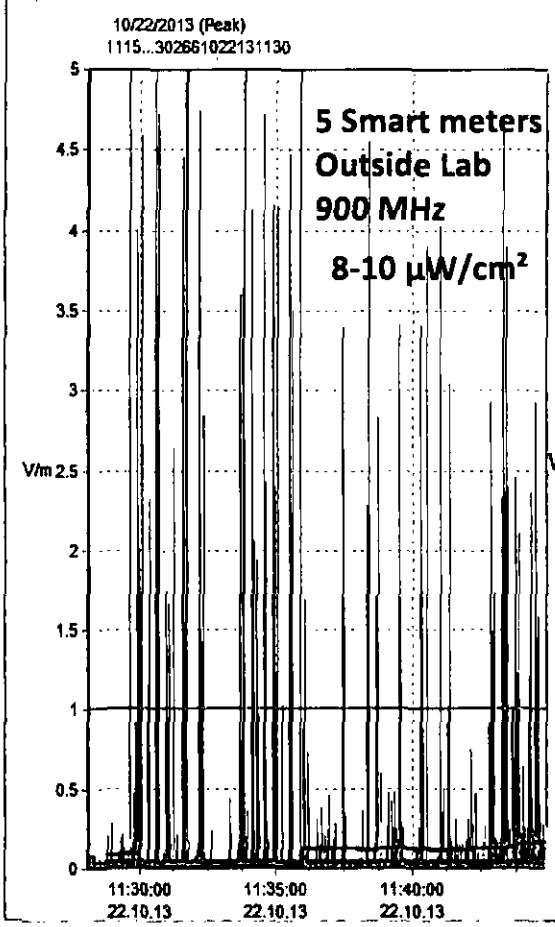
- Cell Phones 
- Cordless Telephones (especially DECT) 
- Smart Meters – Home Area Networks 
- Wi-Fi in Homes 
- High Power Radio & TV Towers 
- Satellites – Communication, GPS 

Scientific Studies on Health Effects of Smart Meter Emissions

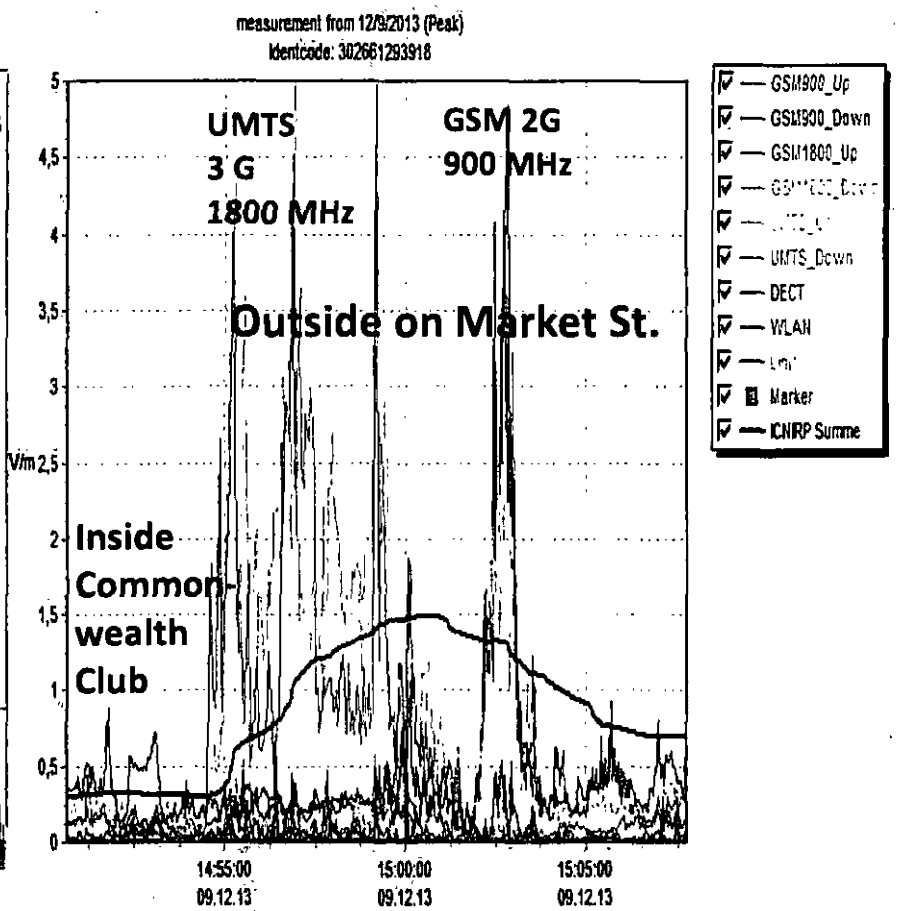
- None were carried out by the utility industry prior to deployment
- The industry's assertion that non-thermal microwave exposure is harmless is not substantiated by science
- Exposure guidelines are only for short-term exposure (30 min) not for long-term or cumulative exposure
- Smart Meters affect Whole Body with Non-thermal radio frequency radiation, similar to cell towers

Smart Meters @ 8 feet : Market St. San Francisco

15 minutes on Oct 22, 2013



15 minutes on Dec 9, 2013



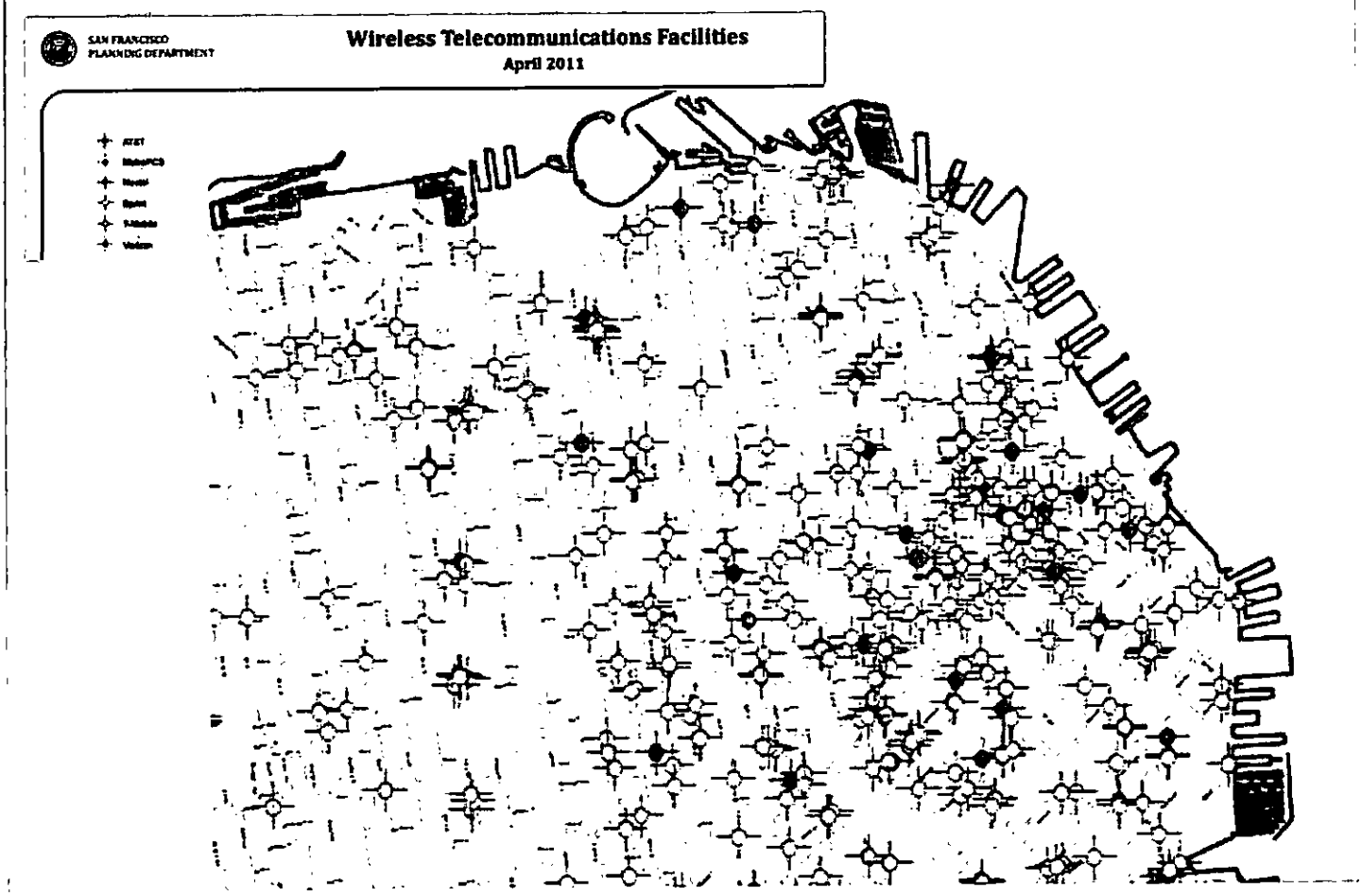
2010: Review of 10 Cell Tower studies

Epidemiological Evidence for a Health Risk from Mobile Phone Base Stations

VINI G. KHURANA, LENNART HARDELL, JORIS EVERAERT, ALICJA BORTKIEWICZ, MICHAEL CARLBERG, MIKKO AHONEN

- Int. J Occup. Envir Health, Vol 16(3):263-267, 2010
- Analysis of 4 studies were from Germany, and 1 each from Austria, Egypt, France, Israel, Poland, Spain
- 7 studies showed altered neurobehavioral effects near cell towers
- 3 studies showed increased cancer incidence Effects occurred < 500 meters from cell towers
- Authors recommended lower exposure guidelines

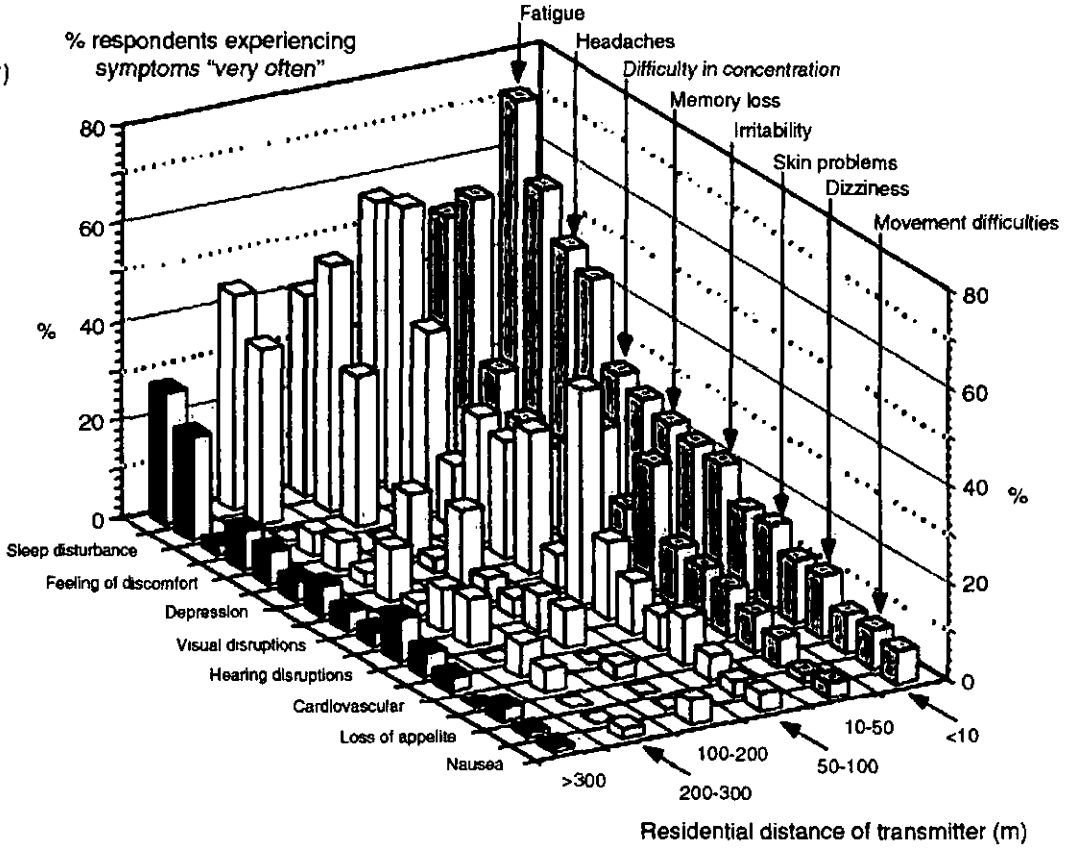
San Francisco Cell Towers Map (2011)



Neurobehavioral Symptoms near Cell Towers

Rapid aging syndrome (RAS)
Electro-Hyper-Sensitivity (EHS)

1. Fatigue
2. Sleep disturbance
3. Headaches
4. Feeling of discomfort
5. Difficulty concentrating
6. Depression
7. Memory loss
8. Visual disruptions
9. Irritability
10. Hearing disruptions
11. Skin problems
12. Cardiovascular
13. Dizziness
14. Loss of appetite
15. Movement difficulties
16. Nausea

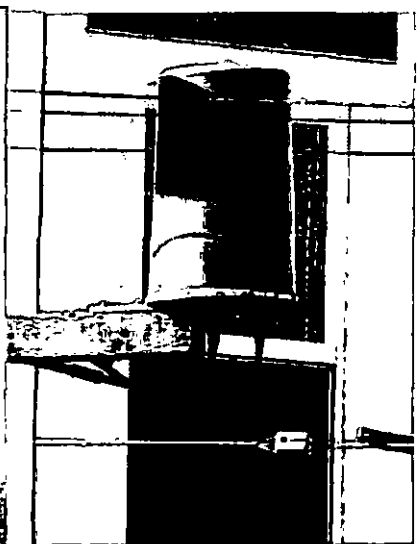


Work of Santini et al (France): Pathol Biol. 2002;50:S369–73.

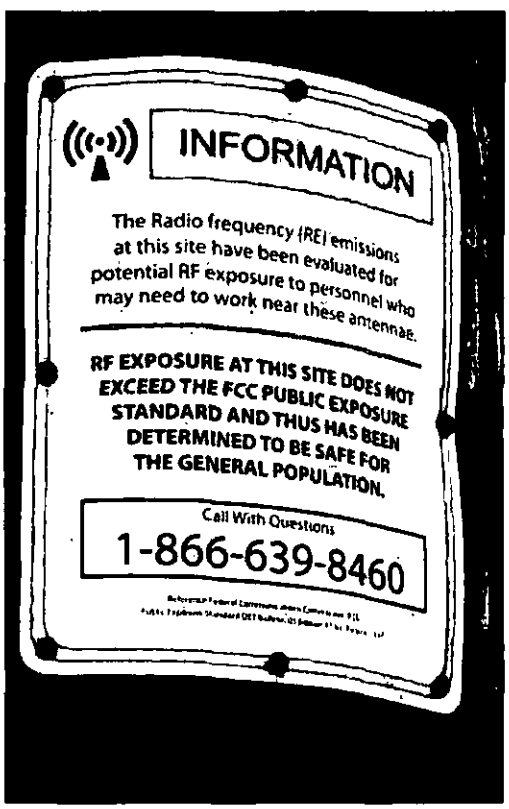
Cell Towers Adverse Health Effects

- Neurobehavioral Changes
- Increased Cancer Risk
- Hormonal Changes
- Conditions similar to Microwave Sickness already known about since the 1960's.

New Utility Pole Mini Cell Towers add EMFs



Antenna near
695 Central Ave.
San Francisco



- Safety of these Devices are based only on Thermal Exposure Criteria uses (Antennas from NextG Networks)

2013: International Concerns about Wi-Fi

Electromagnetic Biology and Medicine, June 2013; 32(2): 200–208

ISSN 1536-8378 print/ISSN 1536-8386 online
DOI: 10.3109/15368378.2013.776430

informa
healthcare

Wi-Fi technology – an uncontrolled global experiment on the health of mankind

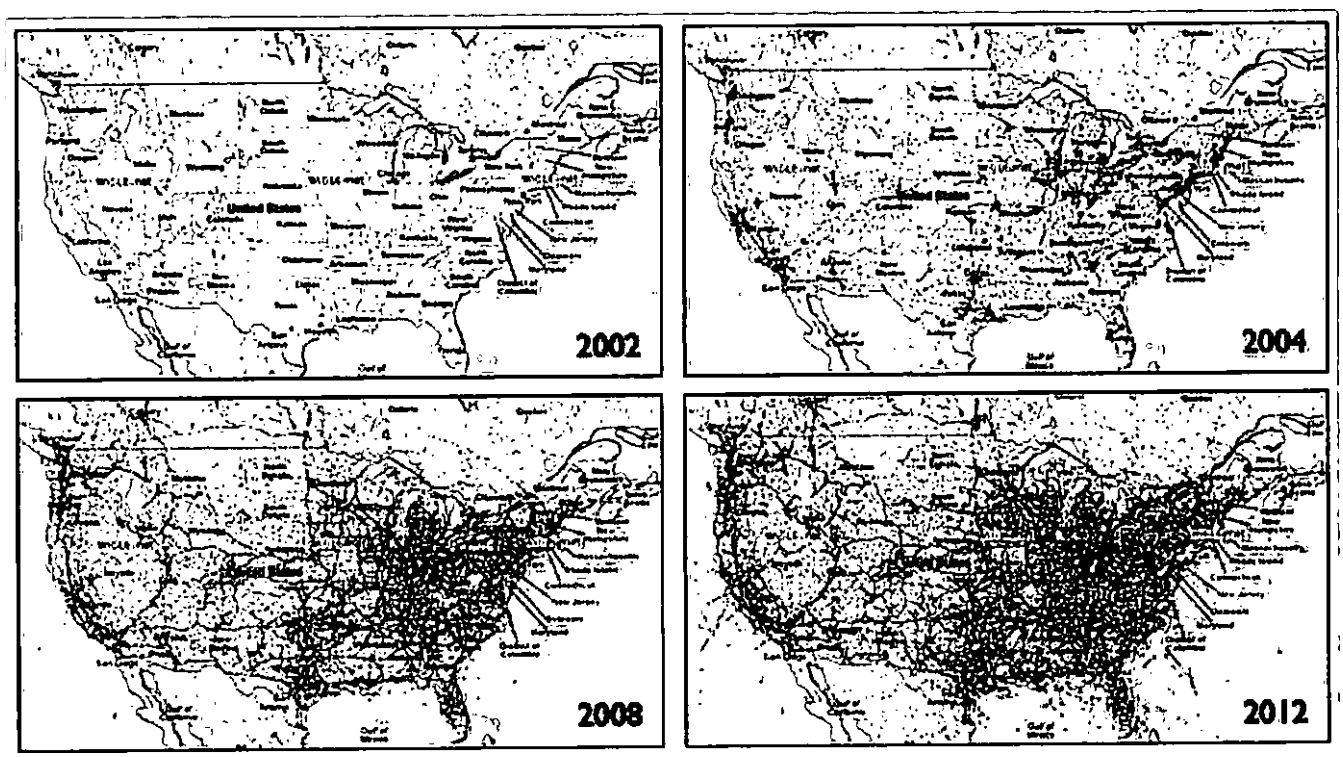
Marko Markov[1] & Yuri G. Grigoriev[2]

[1]Research International, Williamsville, NY, USA, and [2]Russian National Committee of Non-Ionizing Radiation Protection, Moscow, Russia

U.S. has done little research on Microwave Exposure since 1996 Telecommunications Act became law

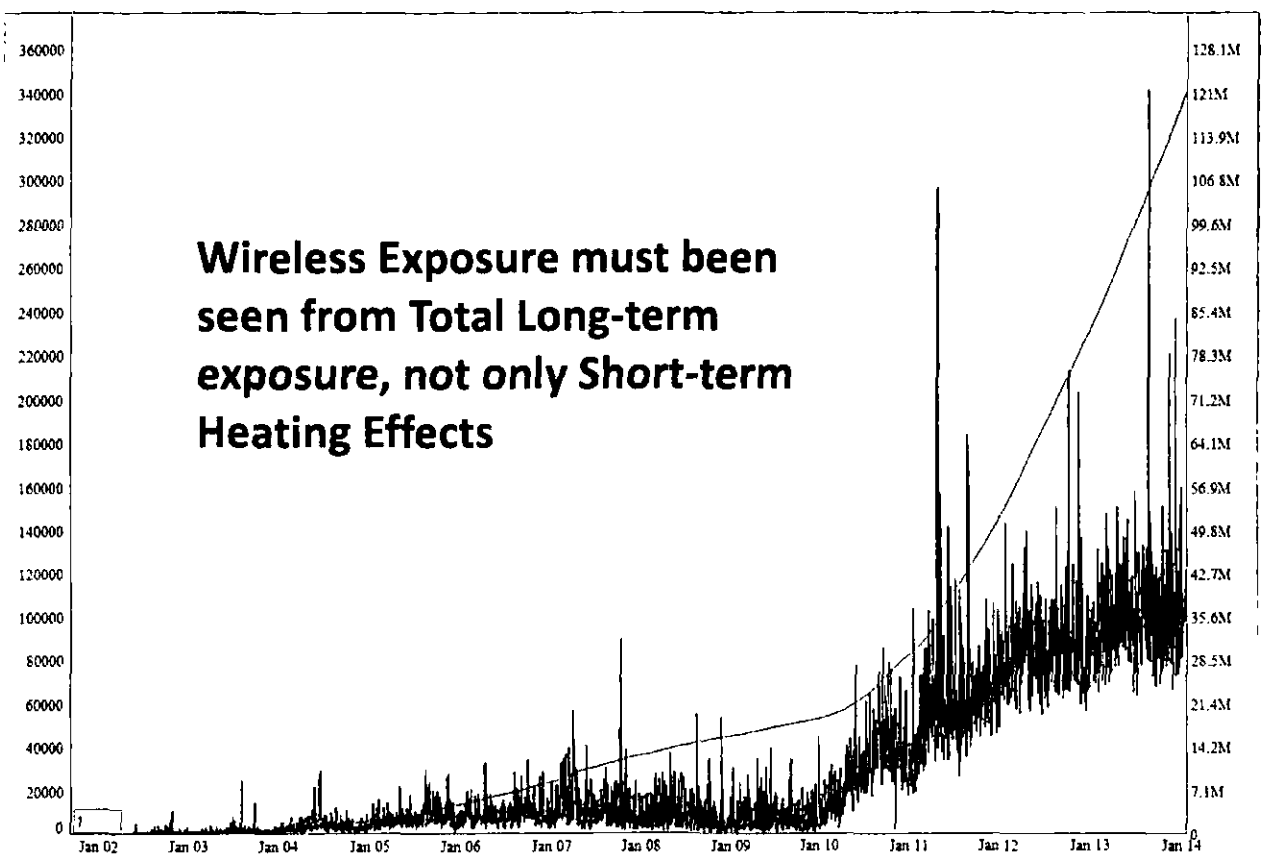
Russians have done extensive research on Microwave Impacts on Health and have lower exposure guidelines

Growth in WiFi Networks 2002 - 2012



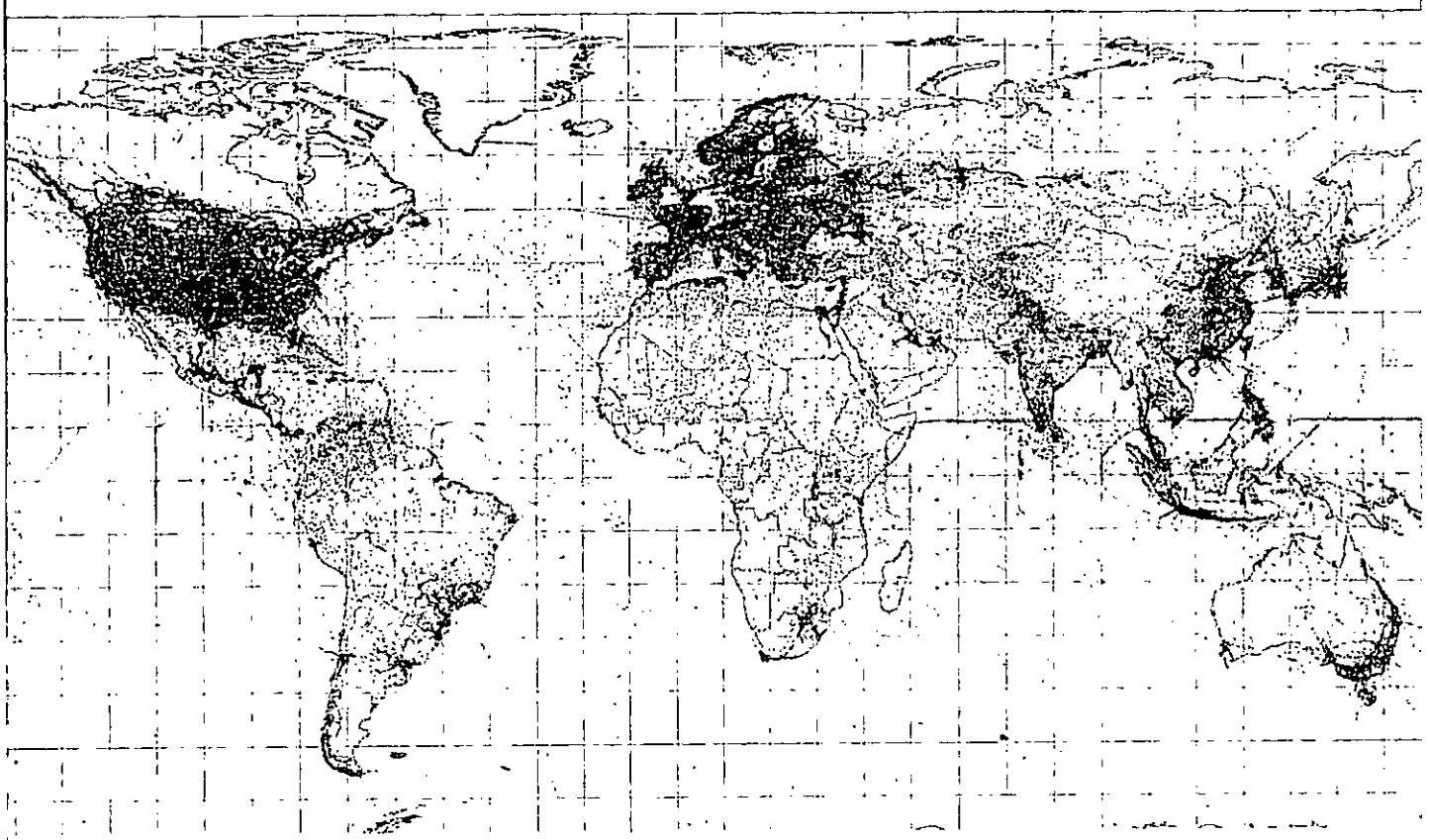
- Source: www.wigle.net

Growth in WiFi Networks 2002 - 2013



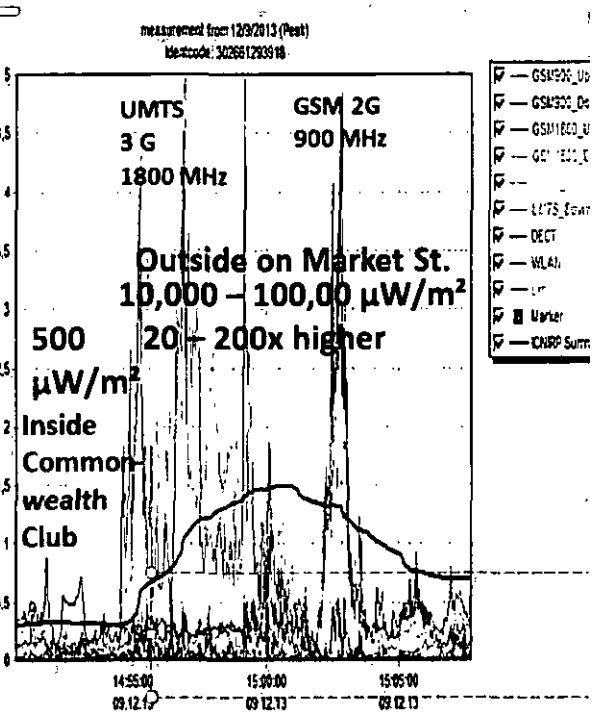
- Source: www.wigle.net WiFi in the World = 120 Million Networks

Wireless Map of World 2014



- Source: www.wigle.net

Wireless Map: San Francisco Center



EMF Measurements by Dr. Maret
Dec 9, 2013 3 pm Market St.

- Source: www.wigle.net

WiFi Reported Health Effects (2.45 GHz)

- Neurological: Headaches, dizziness, concentration difficulties, insomnia, fatigue, numbness/tingling
- Cardiac: Palpitations, arrhythmias
- Eyes: Pressure in eyes, poor vision
- Ears: Ringing in ears
- Other: Skin problems, digestive problems, impaired smell, light sensitivity
- Long-term Effects: Not fully studied since technology is new but increasingly widespread. WiFi is mostly always on and will add to total body burden over time.

- **Current Exposure Guidelines are for Short-term only**
- **Solution: Wired (Ethernet) system are faster and do not radiate**

Feb 2013: Harvard Pediatric Neurologist and Neuroimaging Specialist Dr. Martha R. Herbert advises against Wi-Fi Deployment in LA Schools

HARVARD MEDICAL SCHOOL

Martha R. Herbert, Ph.D., M.D.
Assistant Professor, Pediatric Neurology
Director, TRANSCEND Research Program
www.transcendresearch.org
transcend@partners.org

TRANSCEND

MASSACHUSETTS GENERAL HOSPITAL

Martinos Center for Biomedical Imaging
149 13th Street, Room 10.018
Boston, Massachusetts 02129
Phone: (617) 724-5920
Fax: (617) 812-6334
mherbert1@partners.org

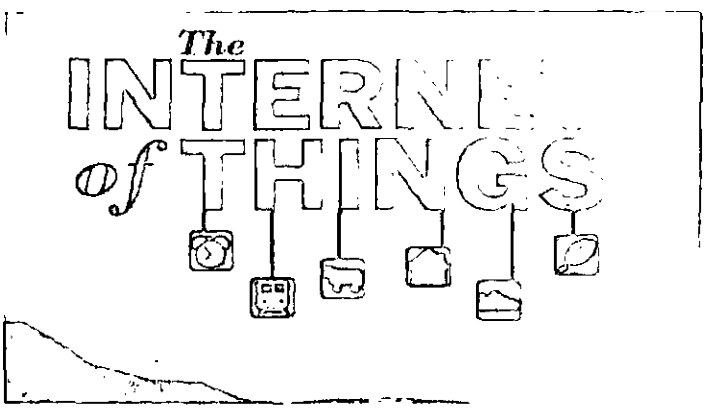
TO: *Los Angeles Unified School District*
FROM: Martha R Herbert, PhD, MD
RE: Wireless vs. Wired in Classrooms
DATE: February 8, 2013

LA Unified School District Wireless Initiative to place Wi-Fi in all schools

- Response by Harvard pediatric neurologist and neuroscientist Martha Herbert, PhD, MD

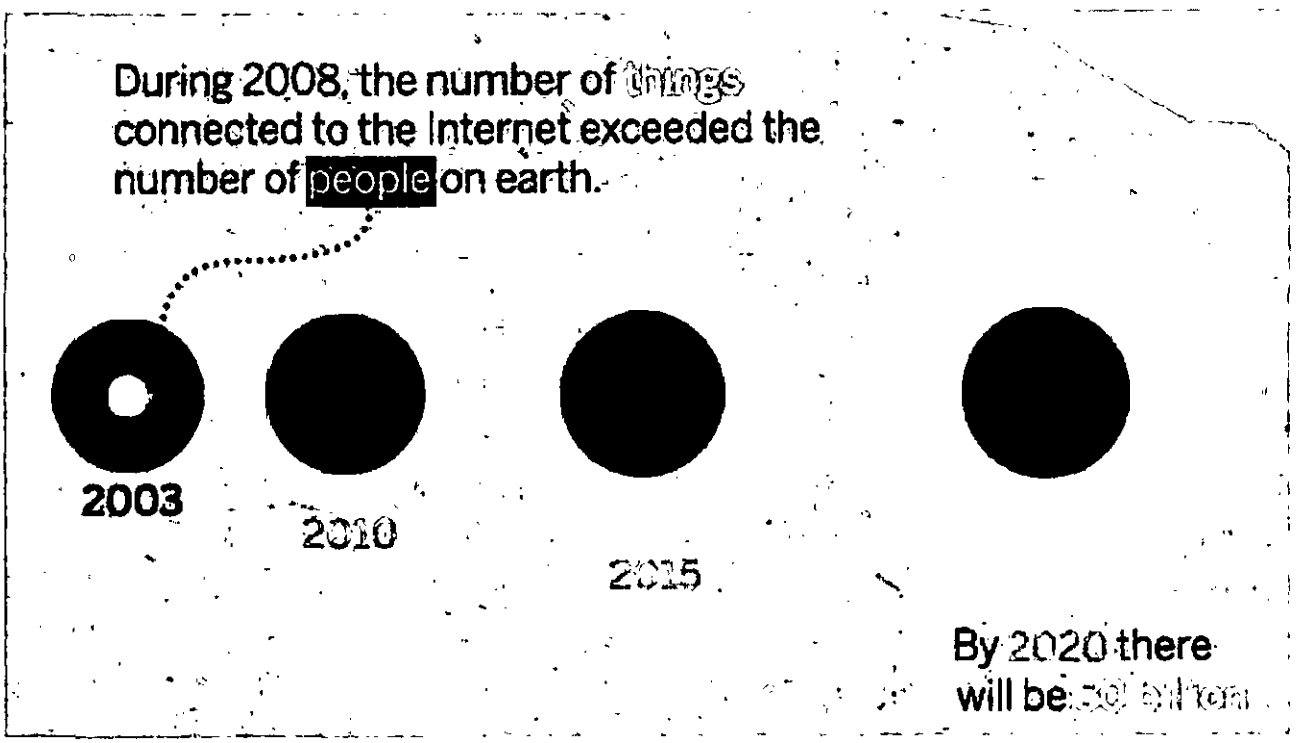
- "EMF/RFR from wifi and cell towers can exert a disorganizing effect on the ability to learn and remember, and can also be destabilizing to immune and metabolic function. This will make it harder for some children to learn, particularly those who are already having problems in the first place. "

Internet of Things (IoT)



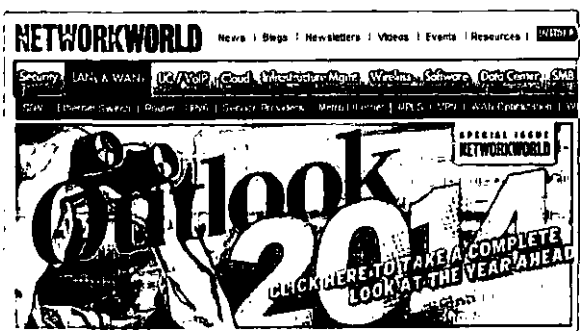
- Devices connecting to the internet/web via low power radios are now being developed for creating a wireless, internet connected life
- According to Gartner and ABI Research there will be between 26 - 30 billion devices on the Internet of Things by 2020
- Health concerns have not been considered in design.

The Internet of Things is Growing



- Potentially massive levels of EMF Exposure may result

IoT is Big Business: Smart Meters Industry as part of it



News
What to expect of Internet of Things in 2014

- Current IoT includes GPS, electronic toll devices, WiFi enabled plugs sockets and light switches, WiFi appliances, smart parking meters, among others
- Estimated Research firm IDC predicts shift will generate $9 Trillion by 2020; GE estimates $15T by 2020 which would equal the annual U.S. GDP.
- Health concerns and potential costs are not considered

How Much Microwave Radiation Today?

- 1980 Background Microwave was 0.001 $\mu W/cm^2$ (0.06 V/m)
- Now in cities can be around 3 $\mu W/cm^2$ (~3 V/m)
- Background RFR has increased more than 1000 – 3000 x !!
- MESH Networks from Smart Meters will add to this
- Microwaves effects often have slow onset; direct causality is hard to prove --> Typically > 10+ year latency for cancer

- PREVENTION is the Key >>Precautionary Principle (Europe)
- French Government is Currently Implementing this regarding EMF Exposure

2009: European Parliament advocates the Precautionary principle on EMFs

P6_TA(2009)0216

European Parliament

Health concerns associated with electromagnetic fields

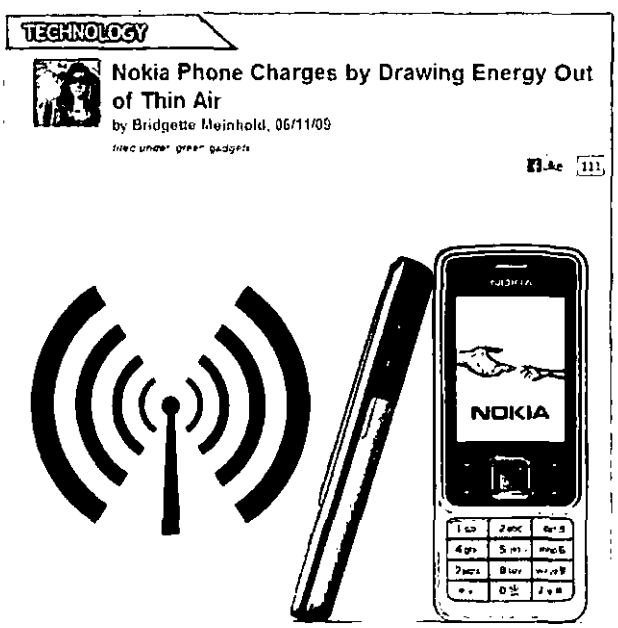
European Parliament resolution of 2 April 2009 on health concerns associated with electromagnetic fields (2008/2211(INI))

- Health Concerns from EMFs of concern in Europe
- Recognizes Electrohypersensitivity is a disability

27. Is greatly concerned about the fact that insurance companies are tending to exclude coverage for the risks associated with EMFs from the scope of liability insurance policies, the implication clearly being that European insurers are already enforcing their version of the precautionary principle;

28. Calls on Member States to follow the example of Sweden and to recognise persons that suffer from electrohypersensitivity as being disabled so as to grant them adequate protection as well as equal opportunities;

Increasing Levels of Background RF



- So far, their device can collect up to 5 milliwatts (mW) of power, and their short term goal is to collect 20 mW of power, which is just enough to keep the phone charged in standby mode.
- **HOW IS THIS LEVEL OF AMBIENT RF AFFECTING LIVING SYSTEMS ?**

http://inhabitat.com/nokia-phones-pull-energy-out-of-thin-air/

How did EMF Exposure Guidelines Originate?

In 1960's, most EMF researchers were only concerned with Tissue Heating Effects

Microwave Safety Standards – 1966

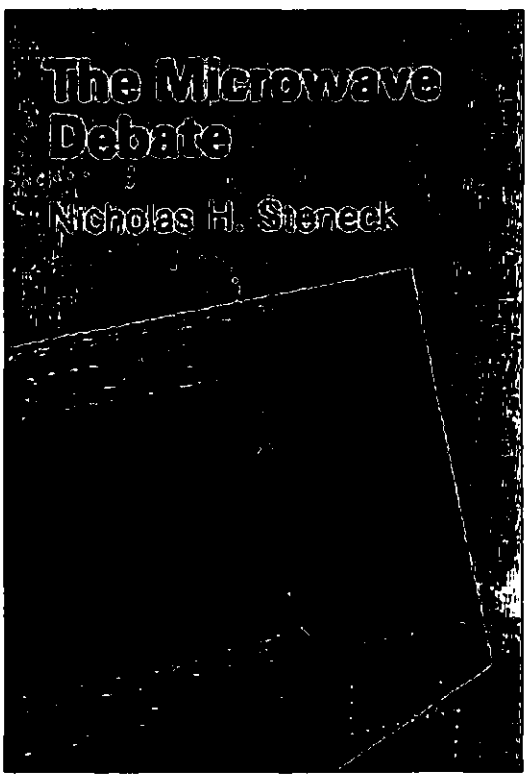
Based only on Thermal Considerations: (Hasn't changed yet)

- Parties that deliberated on ANSI Standard C95.1-1966
- This standard was developed by producers for industrial and military users, not by health experts for all citizens
- Wireless technologies were not widespread then

American Petroleum Institute
Armed Forces Institute of Pathology
General Dynamics
National Aeronautics and Space Administration
U.S. Department of the Air Force, Office of the Surgeon General
U.S. Department of the Air Force, Rome Air
U.S. Department of the Army, Electronics Command
U.S. Department of the Army, Environmental Hygiene Agency
U.S. Department of the Army, Materiel Command
U.S. Department of the Army, Office of the Surgeon General
U.S. Department of the Interior, Bureau of Mines
U.S. Department of the Navy, Bureau of Medicine and Surgery
U.S. Department of the Navy, Bureau of Naval Weapons
U.S. Department of the Navy, Bureau of Ships
U.S. Department of the Navy, Marine Corps
U.S. Department of the Treasury, Coast Guard
U.S. Public Health Service[41]

MIT Prof. Nicholas Steneck 1984

- Wrote how military and industry research had been the primary drivers of RF and microwave technology.
- "What community has the greatest interest in expanding the use of RF technology? The military and industry, whose values are most strongly represented in [safety exposure standard] C95.1-1982... At heart C95.1-1982 is a military industrial standard."

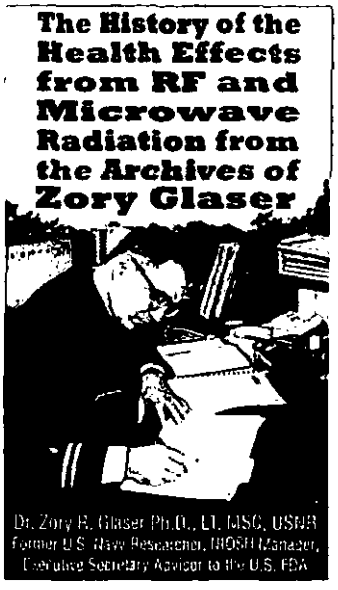


Military Studied Microwave Effects

- Extensive Studies done in 1970s

DEFENSE INTELLIGENCE AGENCY

BIOLOGICAL EFFECTS OF
ELECTROMAGNETIC RADIATION
(RADIOWAVES AND MICROWAVES)
EURASIAN COMMUNIST COUNTRIES (U)



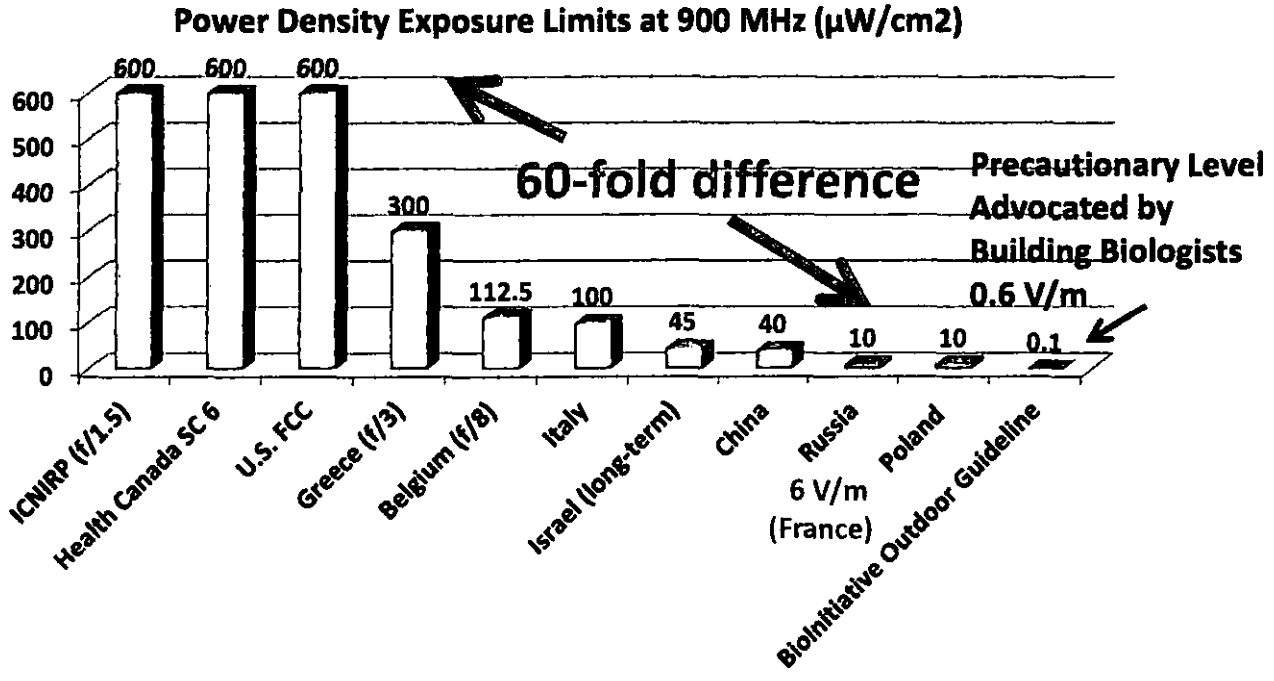
- 1976 DoD, Defense Intelligence Agency Report outlined Soviet research results

Soviet research has produced guidelines which were used to establish a value of 10 $\mu W/cm^2$ per working day as the maximum admissible value for microwave irradiation. Higher exposures, at values of 0.01 to 0.1 mW/cm^2, are permissible for up to two hours per day or 1 mW/cm^2 for 15 to 20 minutes per day. Protective glasses are required in the latter case.

- 10 $\mu W/cm^2$ recommended, current U.S. standards are 600 $\mu W/cm^2$; Smart Meters produce fields of 9^+ $\mu W/cm^2$

Many records available at: www.magdahavas.com

Power Density Exposure Limits at Smart Meter Frequencies can vary by Countries



- Bioinitiative guidance based on Non-thermal exposures to EMFs is considerably lower at 0.1 µW/cm^2

Bioinitiatives Report 2012

- 29 Authors: 9 MDs, 21 PhDs authored the report
- Experts from 10 countries: USA (10), Sweden (6), Austria (2), Canada (2), Greece (2), India (2), Italy (2), Denmark (1), Russia (1), Slovak Republic (1)
- Had over 2-1/2 Millions hits 30 days after it was released. Total report had 1480 pages
- Covers 24 sections including Fetal and neonatal Effects, Autism and ASD, Genotoxic and Metabolic Mechanisms of low intensity EMFs, Stress response, immune impacts, impacts on blood-brain barrier, need for application of precautionary approaches
- Calls for lower exposure guidelines, 1000 $\mu W/m^2$ (0.1 $\mu W/cm^2$)

Various Exposure Limits for 900 MHz

- 0.001 $\mu W/cm^2$ Salzburg, Austria Guidance for Safety and Sleep Disturbances (Schwarzenburg Study)
- 0.1 $\mu W/cm^2$ "Precautionary limit" Austria Bioinitiative Working Group (1000 $\mu W/m^2$)
- 4.5 $\mu W/cm^2$ ECOLOG-recommendation (Germany)
- 8.8 $\mu W/cm^2$ Tell Report on PG&E Smart Meter emission
- 10 $\mu W/cm^2$ Exposure limit in Russia, Poland, Hungary Switzerland, Luxemburg, Bulgaria
- 12 $\mu W/cm^2$ Measured Peaks from SM @ 4 feet
- 600 $\mu W/cm^2$ US Exposure limit by FCC (Heating effects)

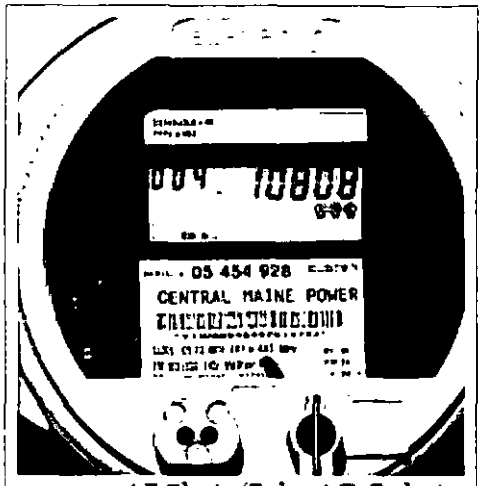
Maine Public Utilities Commission didn't address smart meter safety, court says

By DAVID SHARP,The Associated Press
Posted July 12, 2012, at 8:03 p.m.

PORTLAND, Maine — Maine's highest court ruled Thursday that state regulators failed to adequately address safety concerns about Central Maine Power's smart meters but the ruling had no immediate impact on more than 600,000 smart meters already installed in homes and businesses across the state.

The Supreme Judicial Court ordered the Maine Public Utilities Commission to reconsider a complaint that raised health concerns, and lead plaintiff, Ed Friedman of Bowdoinham, urged the panel to use the opportunity "to hold full evidentiary hearings on this and look at it under the bright lights."

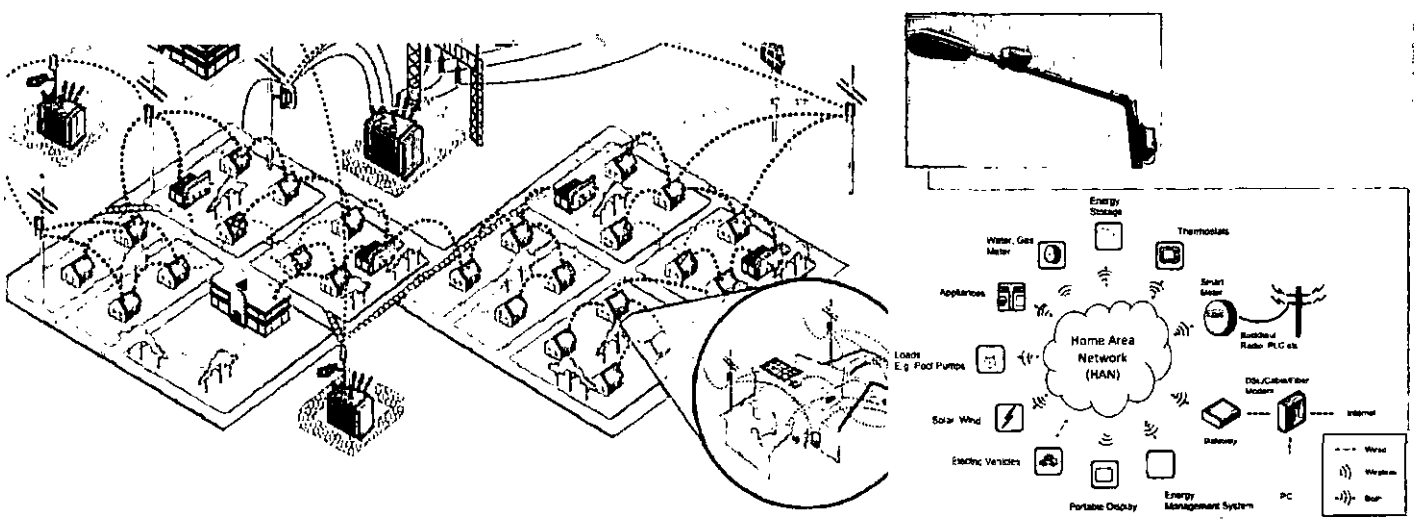
"We understand that the horse is out of the barn in terms of the meters being in, but they should've vetted these smart meters for safety before they were deployed instead of waiting until they're deployed to see that there's well-known biological effects," Friedman said.



AP Photo/Robert F. Bukaty

A new Central Maine Power smart meter displays electricity usage at a business in Freeport in fall 2010.

Mesh Networks & Home Area Network



- Smart meters (at 902-928 MHz) in Neighborhood are connected in a Mesh Network passing information back and forth to central collection points at higher placements.
- Home Area Network is to link appliances and devices wirelessly together (2.4 GHz Zigbee or similar WiFi) and is within the Smart Meter architecture. Appliance WiFi may not be disabled.

Living within the Wireless HAN (Home Area Network)

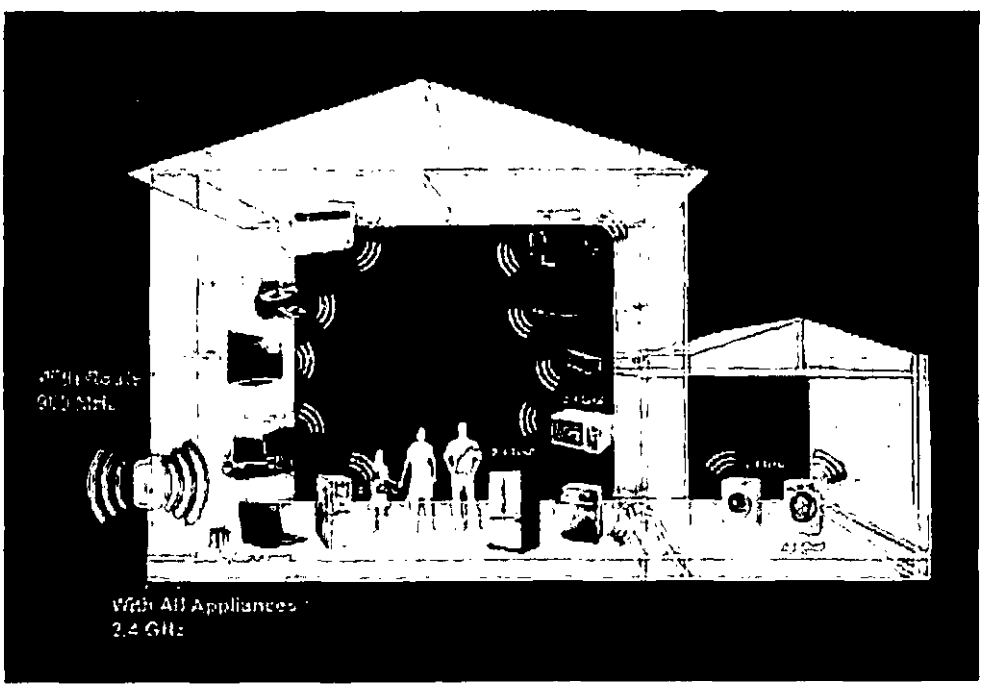


Image: Take Back your Power

- What are the Long-term Health Effects of his System?

Additional Issues in the Internet of Things

- International Data Corporation predicts that there will be more than 30 Billion wireless connected devices in the world by 2020.
- Between Dec 23, 2013 – Jan 6, 2014 home wireless devices, including at least one smart refrigerator, were hijacked in first proven cyber-attack originating from connected appliances

Source: http://www.cnn.com/2014/01/17/tech/gaming-gadgets/attack-appliances-fridge/index.html?hpt=hp_bn5

SOLUTIONS FOR STATE AND LOCAL GOVERNMENT
GOVERNMENT TECHNOLOGY

WIRELESS

Santa Clara, Calif., Combines Public Wi-Fi with Smart Metering

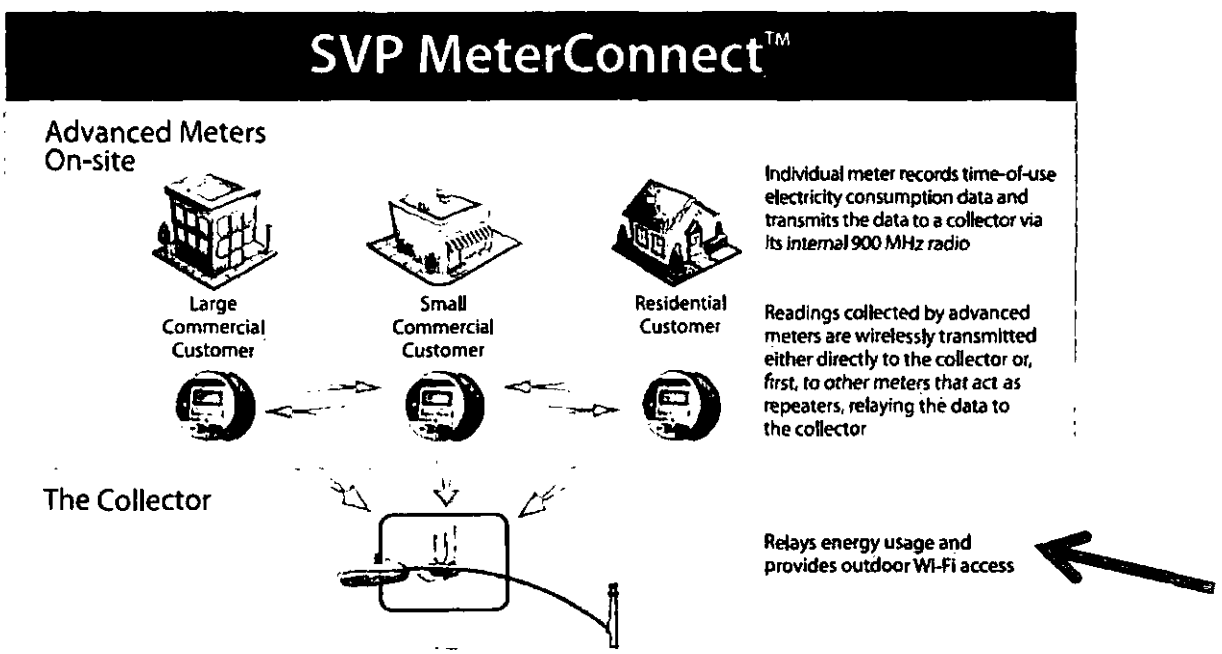
The new advanced smart metering program sends meter data across a secure Wi-Fi channel while also providing free Wi-Fi access to the public.

BY SARAH RICH / APRIL 16, 2013

- Smart Meters are being used in Santa Clara by municipal electric utility, Silicon Valley Power, as Public WiFi Transmitters
- Will increase Continuous 2.4 GHz Wireless Microwave Exposure
- Only 2 channels of 16-channel Wi-Fi network in use; expansion plans are already in the works.

www.govtech.com/wireless/Wi-Fi-Network-Transmits-Smart-Meter-Data-in-Santa-Clara-Calif-.html

Silicon Valley Power SM Public WiFi

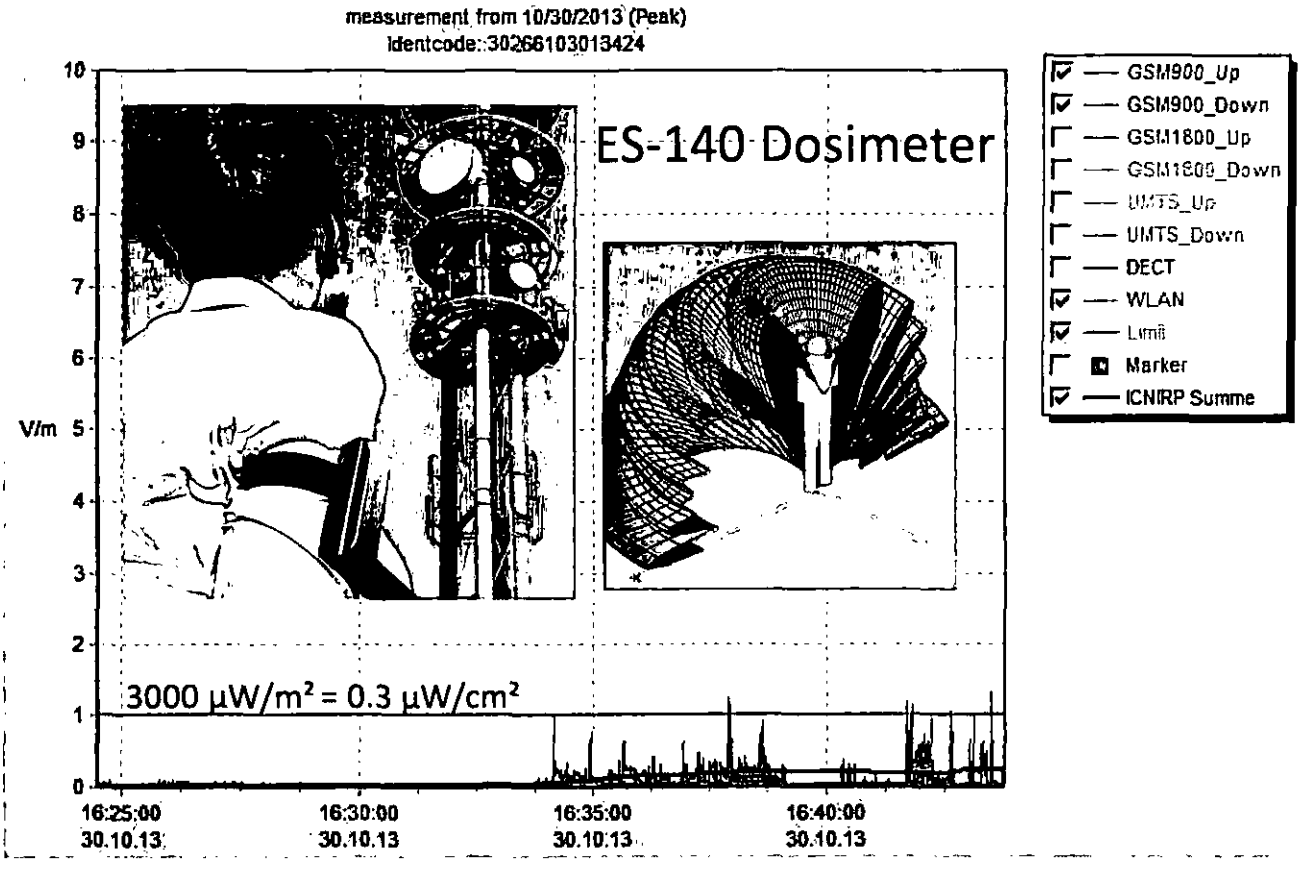


- According to company's website, SVP's Elster Smart Meters will emit 75% less EM radiation than PG&E's Smart Meters.
- Will transmit less frequently and at low power than PG&E

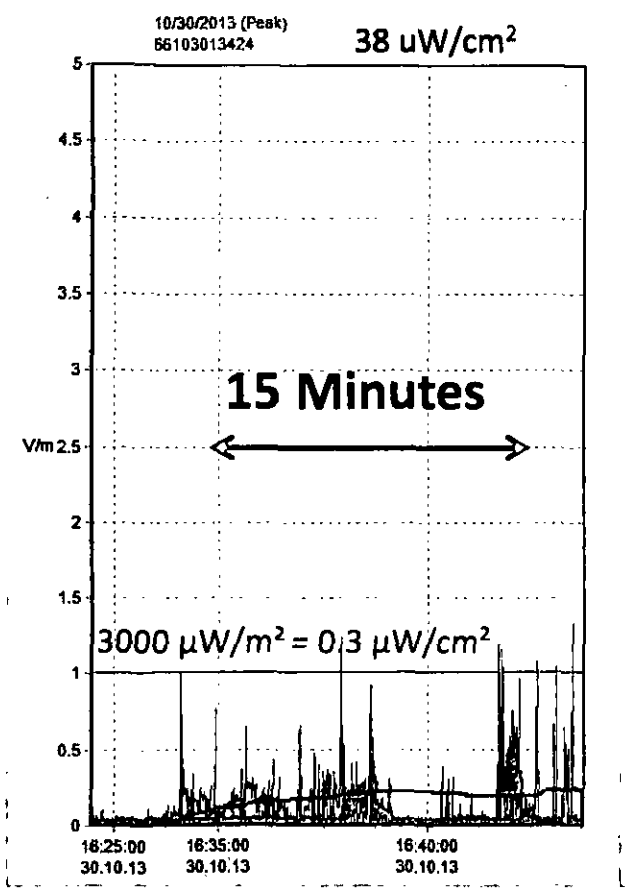
http://siliconvalleypower.com/index.aspx?page=1970

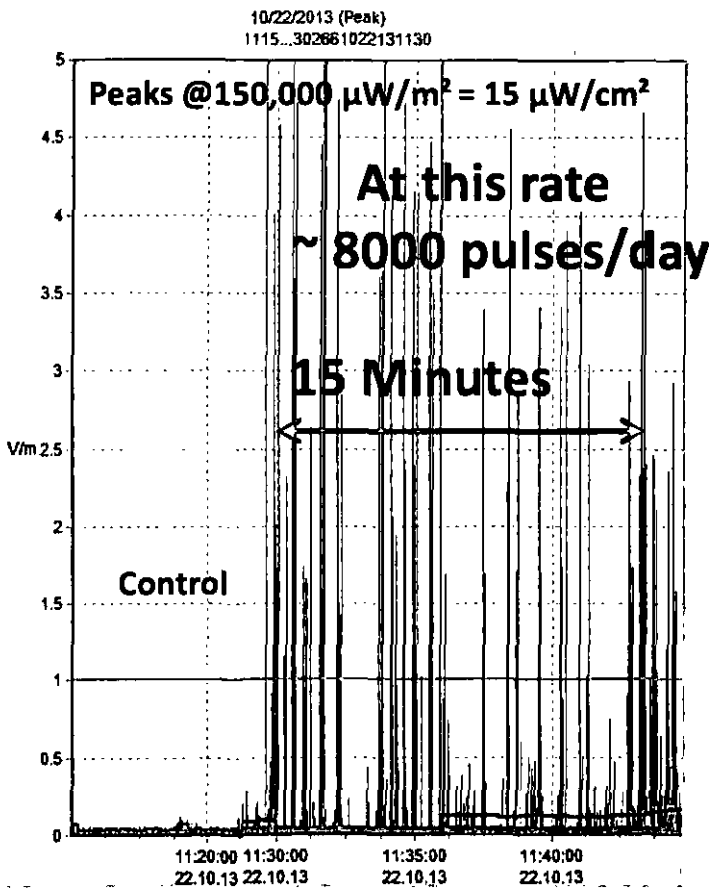
iPhone at 3 feet from Subject

Recorded Oct 30, 2013 for 15 minutes

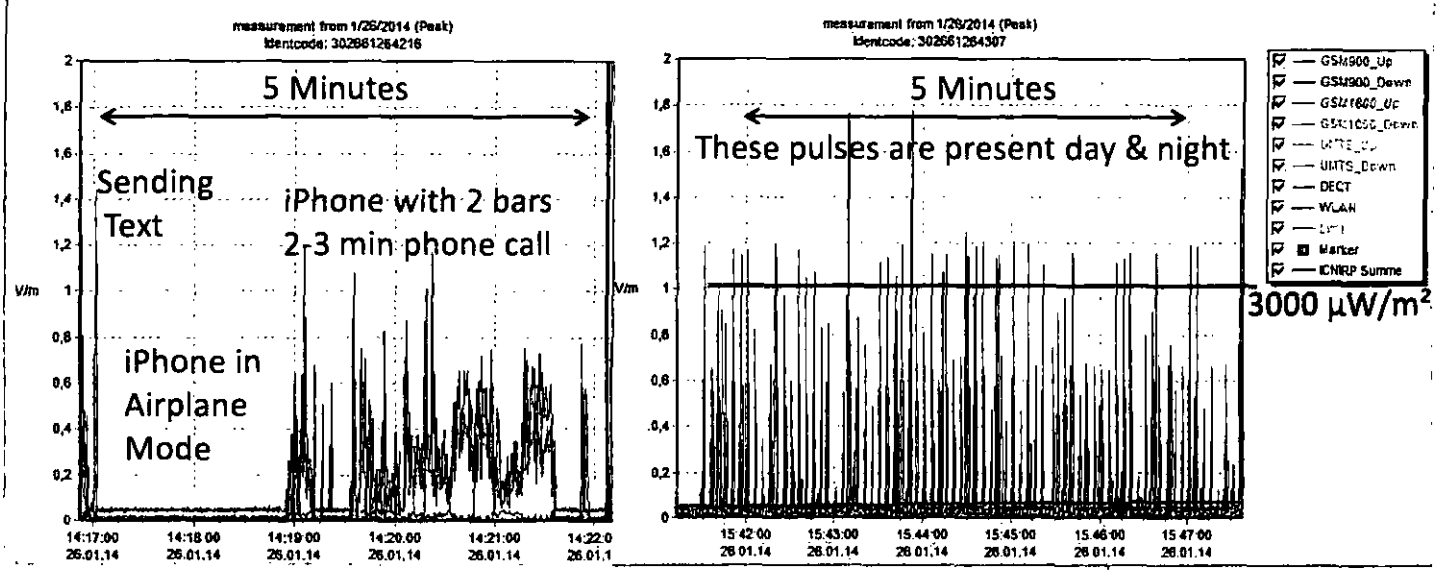


iPhone during call vs. 8ft. from 5 Smart Meters



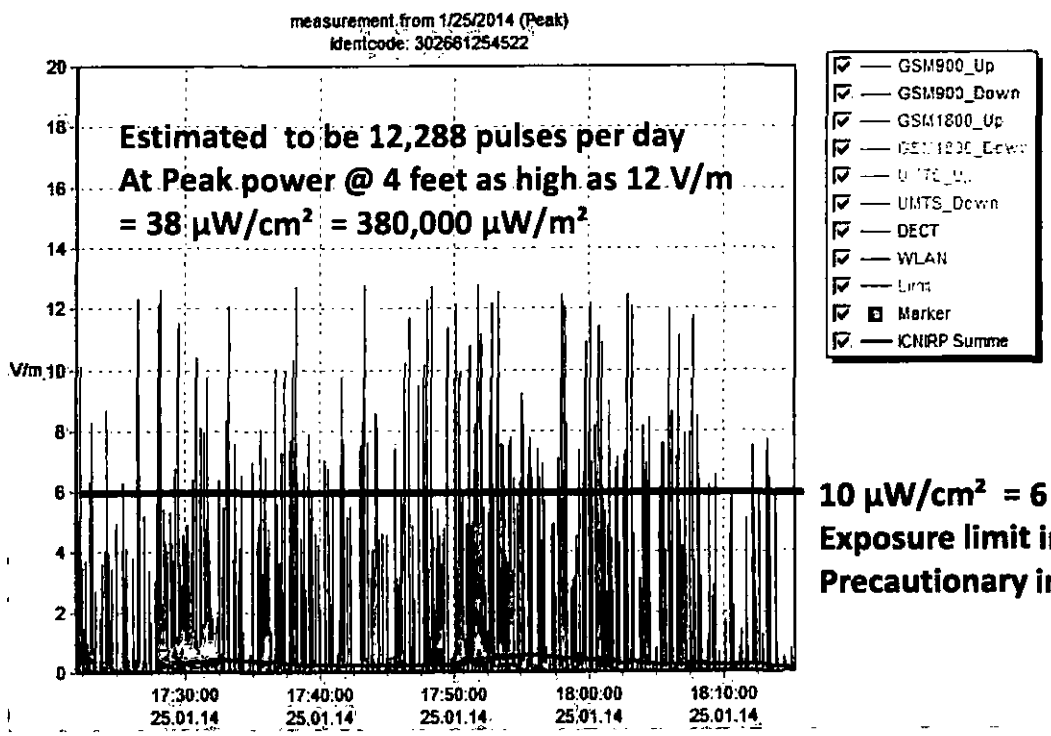


Personal Dosimeter Whole Body Comparison iPhone vs. 5 Smart Meters (inside building)



- Whole Body Exposure from both iPhone and inside building with 5 Smart Meters on outside wall show similar peak levels.
- This short burst pulsed EMFs from Smart Meters is new to living systems and should have been studied prior to deployment.

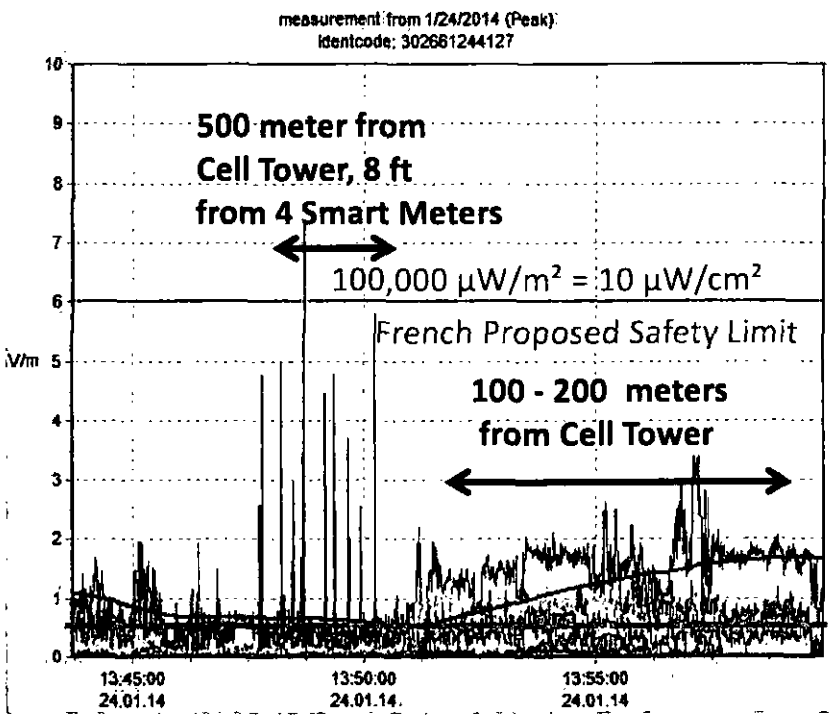
Daily Pulses Generated by Smart Meter

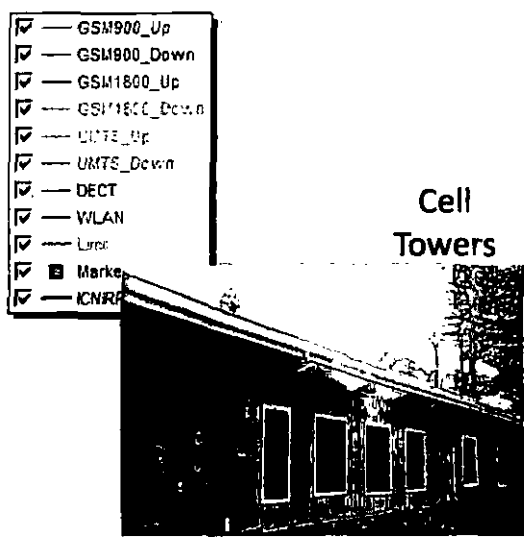


10 µW/cm² = 6 V/m
Exposure limit in Russia
Precautionary in France

- Depends on Duty Cycle and other meters in the Mesh network
- Data from 5 meters shows 340 pulses in 40 minutes =12,288/day
- Emissions are brief (5 msec), but fast pulses affect nervous system

Actual Smart Meter Peak Measurements near Cell Tower in Aptos

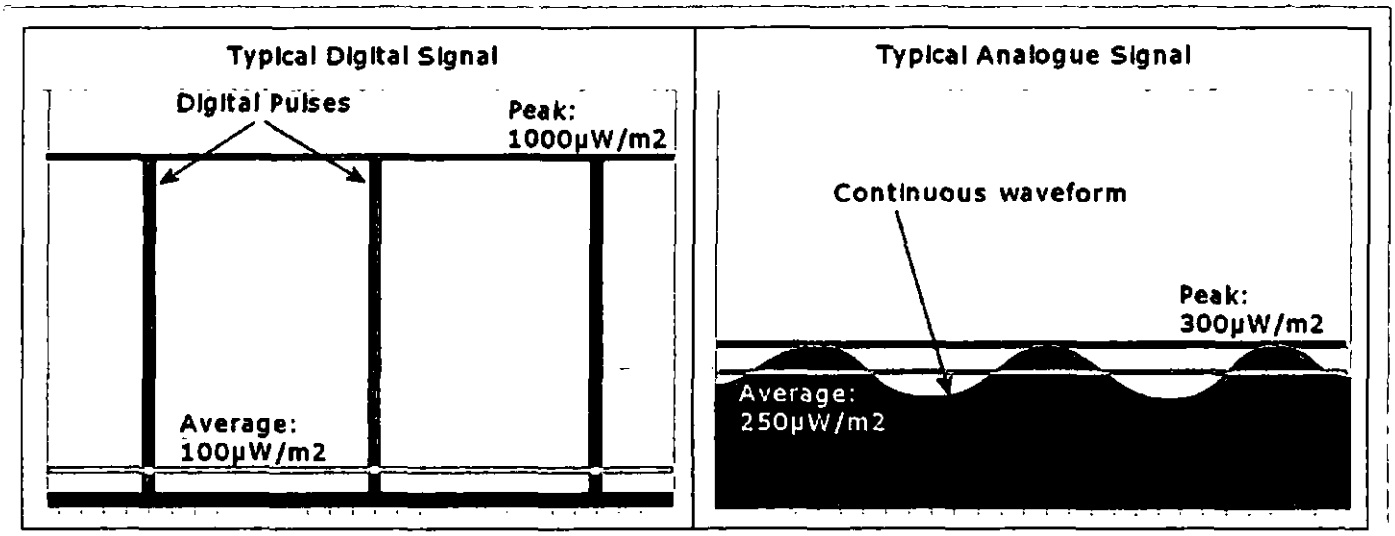




Precautionary Limit
0.6 V/m
0.1 µW/cm²

- Smart Meters measured at 2.5 meters (8 feet)

Peak Levels in Digital Signals are Higher



- Smart Meters send out high intensity short pulses
- Peak pulse intensities trigger biological systems more powerfully
- Average power levels underestimate the problem

Effect of Pulsed Microwaves

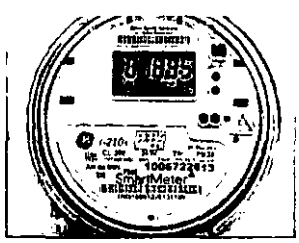
- Causes leakage in the protective Blood Brain Barrier
- Affect the Opiate-Dopamine Neurotransmitters
- Affect Sex Hormone levels
- Shown to Decrease Sperm Production in Men
- Shown to affect Heart Rate and Heart Rate Variability
- EEG changes – also in sleep, reduction of learning, memory problems
- Shown to lower Hormones : Melatonin – pineal gland hormone – affects sleep
- Pulsed EMFs were estimated to have 2-1/2 times more adverse effects than continuous microwave radiation

What some Customers have reported after Smart Meter Installations

- Numerous Customers are reporting headaches, sleep problems, ringing in the ears, searing ear pain, nausea, dizziness, agitation and other symptoms since the Smart Meters were installed.
- These people may be suffering from ***Electromagnetic Hypersensitivity Syndrome (EHS)***
- EHS is estimated to affect 3 - 5% of the population or more

2011 Survey after Smart Meters Installation

- 443 respondents to a survey, 93% over 40 years of age
- 78% from California, 73% women, 49% reported EHS
- 76% had meters installed neighborhood > 6 months, 41% had meters installed in their homes



- Complaints:
  - Sleep Issues = 49%
  - Stress, anxiety, irritability = 43%
  - Headaches = 40%
  - Ringing in Ears = 38%
  - Heart Problems / palpitations = 26%

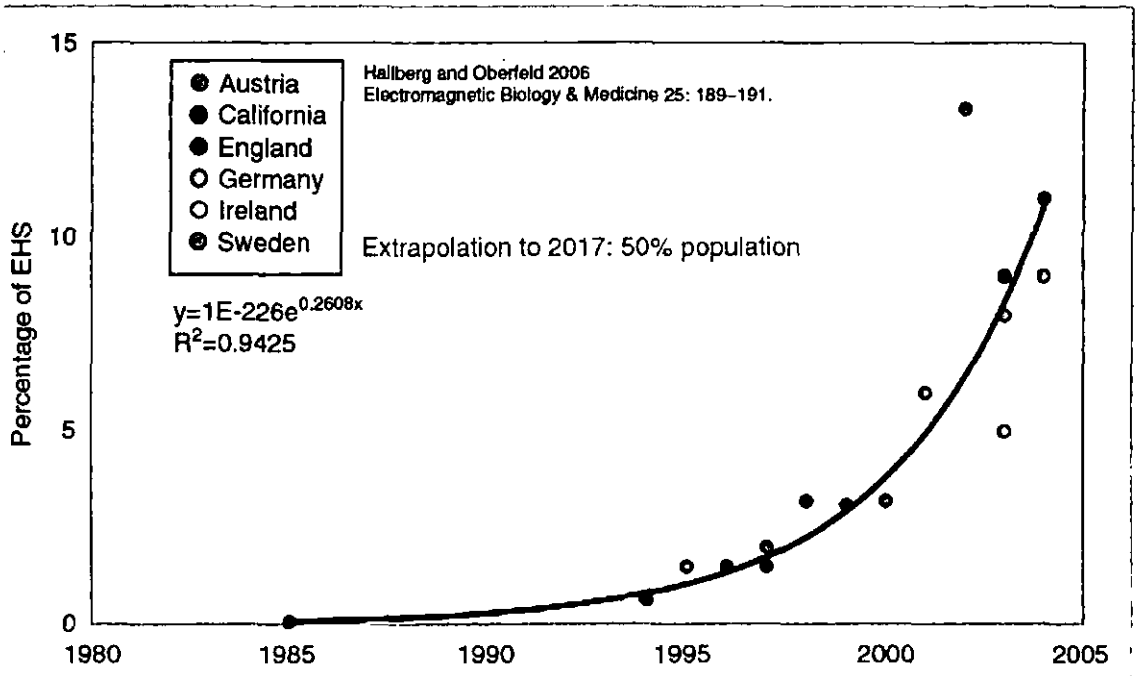
- Source: Halteman, Ed (2011) Wireless Utility Meter Safety Impacts Survey. Available at http://emfsafetynetwork.org/wp-content/uploads/2011/09/Wireless-Utility-Meter-Safety-Impacts-Survey-Results-Final.pdf

Who is Most at Risk?

- Children and Babies (Brains developing & Skull is Thinner allowing greater EMF penetration)
- Immune compromised Individuals
- Elderly and Infirm
- Electrically Hypersensitive People and often people with Multiple Chemical Sensitivities

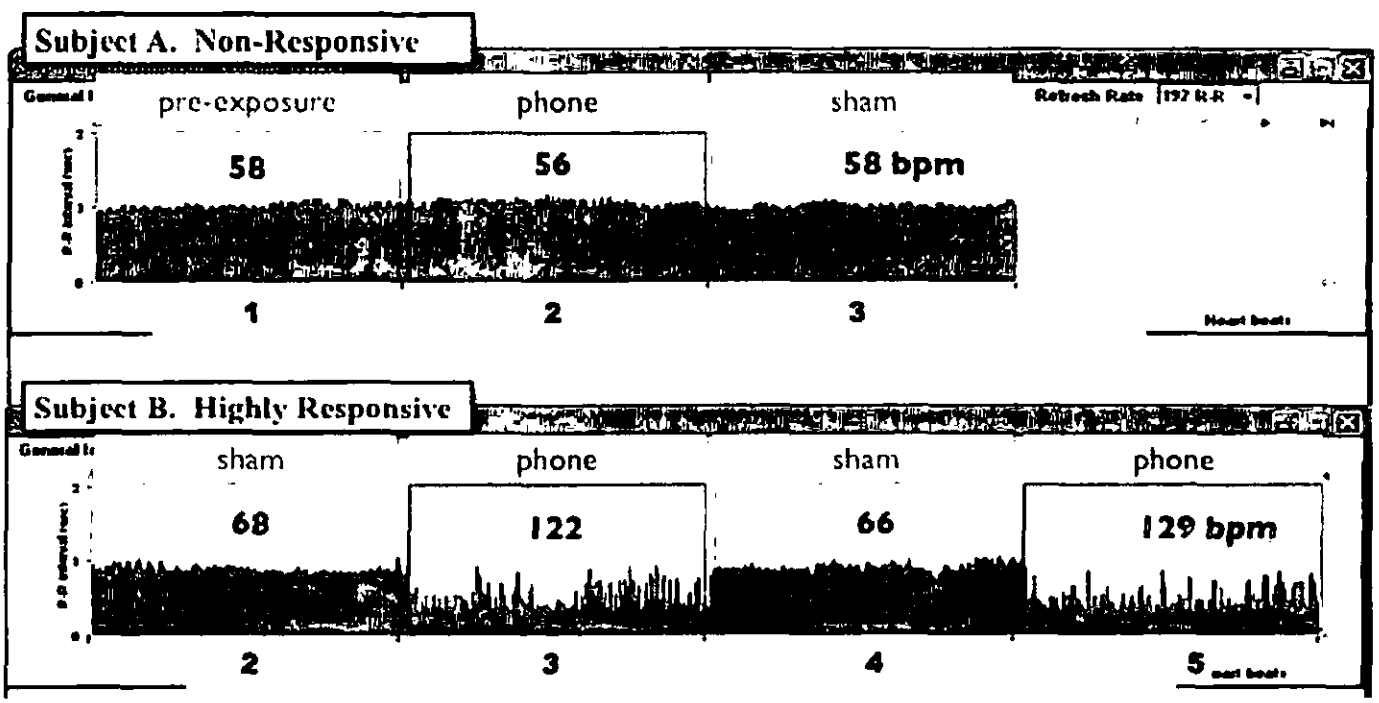
3 - 5% of general population in Europe are now Electrosensitive

2006: Estimated EHS Population Growth



- 2013 California Population with EHS estimated at 3% would be 1,150,000 people. Most of these people would be unaware of their hypersensitivity.

Objective Heart Rate Variability changes in EHS subject on Double Blinded Exposure to 2.4 GHz Cordless Phone



- Source: Magda Havas 2013

EHS: Somatic Response is not Conscious

Int J Neurosci. 2011 Jul 28. [Epub ahead of print]

ELECTROMAGNETIC HYPERSENSITIVITY: EVIDENCE FOR A NOVEL NEUROLOGICAL SYNDROME.

McCarty DE, Carrubba S, Chesson AL, Frilot C, Gonzalez-Toledo E, Marino AA.

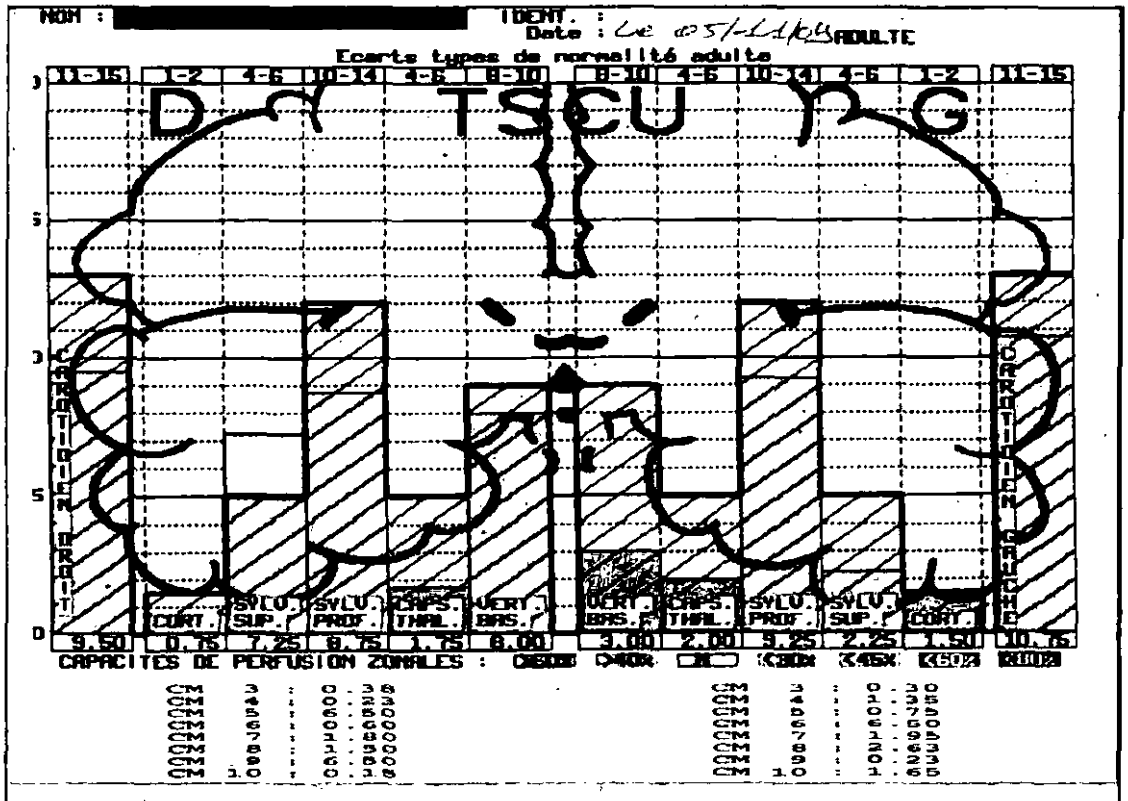
aDepartment of Neurology, LSU Health Sciences Center , Shreveport, LA , USA.

Abstract

ABSTRACT Objective: We sought direct evidence that acute exposure to environmental-strength electromagnetic fields could induce somatic reactions (EMF hypersensitivity). Methods: The subject, a female physician self-diagnosed with EMF hypersensitivity, was exposed to an average (over the head) 60-Hz electric field of 300 V/m (comparable to typical environmental-strength EMFs) during controlled provocation and behavioral studies. Results: In a double-blinded EMF provocation procedure specifically designed to minimize unintentional sensory cues, the subject developed temporal pain, headache, muscle-twitching, and skipped heartbeats within 100 s after initiation of EMF exposure ($P < 0.05$). The symptoms were caused primarily by field transitions (off-on, on-off) rather than the presence of the field, as assessed by comparing the frequency and severity of the effects of pulsed and continuous fields in relation to sham exposure. The subject had no conscious perception of the field as judged by her inability to report its presence more often than in the sham control. Discussion: The subject demonstrated statistically reliable somatic reactions in response to exposure to subliminal EMFs under conditions that reasonably excluded a causative role for psychological processes. Conclusion: EMF hypersensitivity can occur as a bona fide environmentally-inducible neurological syndrome.

PMID: 21793784 [PubMed - as supplied by publisher]

Effect of Electrosmog on Brain Perfusion

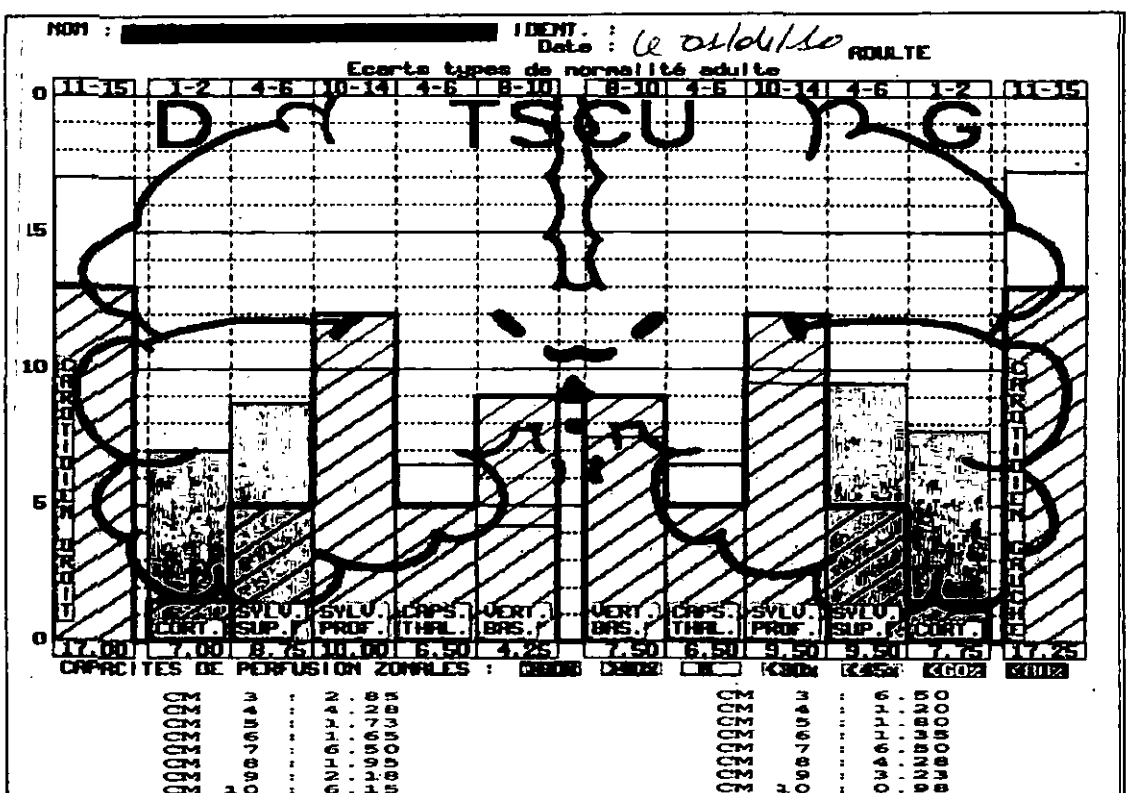


Nov 5 2009

CENTRE D'EXPLORATION DE LA FONCTION CÉRÉBRALE PARIS

Diagram 1 represents the encephaloscan of Philippe EHS before his arrival in the Forêt de Saoû. ***It is clear that after living for several years in an average town and being exposed to its artificial*** **electromagnetic microwave pollution, he is in a weakened state. In this first diagram the circulation levels in several areas of both hemispheres are seen to be seriously affected.**

Effect of Electrosmog on Brain Perfusion



Feb 1 2010

CENTRE D'EXPLORATION DE LA FONCTION CÉRÉBRALE PARIS

Diagram 2 represents the encephaloscan of Philippe EHS after living 3 months in the Forêt de Saoû (an area with very low artificial EM radiation). A spectacular improvement can be seen in the circulation in the 2 hemispheres of the brain. Visible physical consequence: Philippe was no longer in a weakened state.

900 MHz Microwaves penetrate the Brains of Children more than Adults

5 year old child | 10 year old child | adult

Electromagnetic fields from cell phones are estimated to penetrate the brain, especially in children. Model estimate of the absorption of electromagnetic radiation from a cell phone based on age (Frequency GSM 900 Mhz).

Research of O. Gandhi, University of Utah

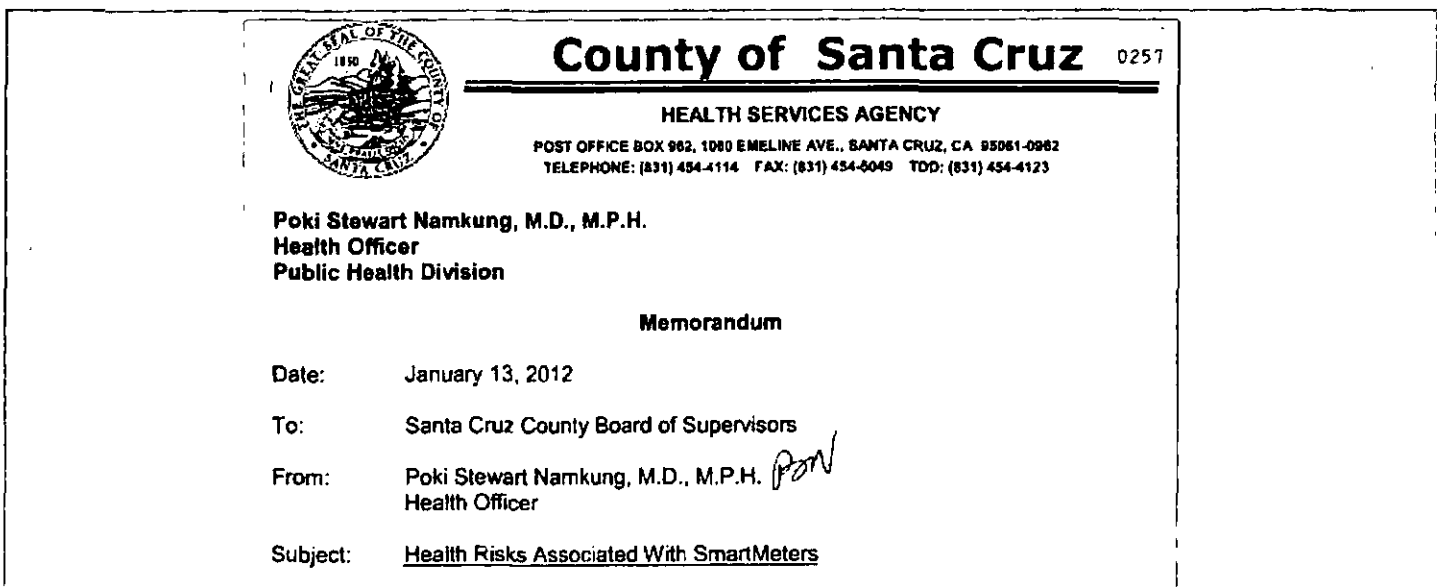
5 year old 10 year old Adult

These are Cell Phone Studies but Smart Meters use same Frequencies

American Academy of Environmental Medicine
6505 E Central • Ste 296 • Wichita, KS 67206
Tel: (316) 684-5500 • Fax: (316) 684-5709
www.aaemonline.org

American Academy of Environmental Medicine Recommendations Regarding Electromagnetic and Radiofrequency Exposure

- The AAEM recommends that:
- Patients with (certain) medical conditions and disabilities be accommodated to protect their health.
- No Smart Meters be on these patients' homes;
- Smart Meters be removed within a reasonable distance of patients' homes depending on the patients' perception and/or symptoms;



County of Santa Cruz 0257

HEALTH SERVICES AGENCY

POST OFFICE BOX 962, 1080 EMELINE AVE., SANTA CRUZ, CA 95061-0962
TELEPHONE: (831) 454-4114 FAX: (831) 454-6049 TDD: (831) 454-4123

Poki Stewart Namkung, M.D., M.P.H.
Health Officer
Public Health Division

Memorandum

Date: January 13, 2012

To: Santa Cruz County Board of Supervisors

From: Poki Stewart Namkung, M.D., M.P.H.
Health Officer

Subject: Health Risks Associated With SmartMeters

- Santa Cruz Public health officer found real health risks associated with Smart meters
- Concerned about non-thermal effects and lack of safety of long-term use of Smart meters
- Supported adoption of installation moratorium
- Concerned about 3.2% of California Electrically Hypersensitive population (Levallios 2002 study)

Moratorium against Smart Meter Installation passed by California Local Governments

- These were passed due to Health concerns, billing accuracy and privacy concerns
- Municipalities included Berkeley, Bolinas, Camp Meeker, Capitola, Fairfax, Cotati, Marin county, Mendocino county, Novato, Ojai, San Anselmo, Santa Cruz, Santa Rosa, Sebastopol, Watsonville, to name a few
- 43 CA government entities passed similar ordinances
- The utilities have blatantly ignored the wishes of these municipalities and installed them anyway.

Biological versus Health Effects

One really needs to distinguish between biological effects and health effects.

There are definite biological effects, but do they constite health hazards?

2009 paper: RF-EMFs harm our Genes

ER Pathophysiology xxx (2009) xxx–xxx

www.elsevier.com/locate/pathophys

Genotoxic effects of radiofrequency electromagnetic fields

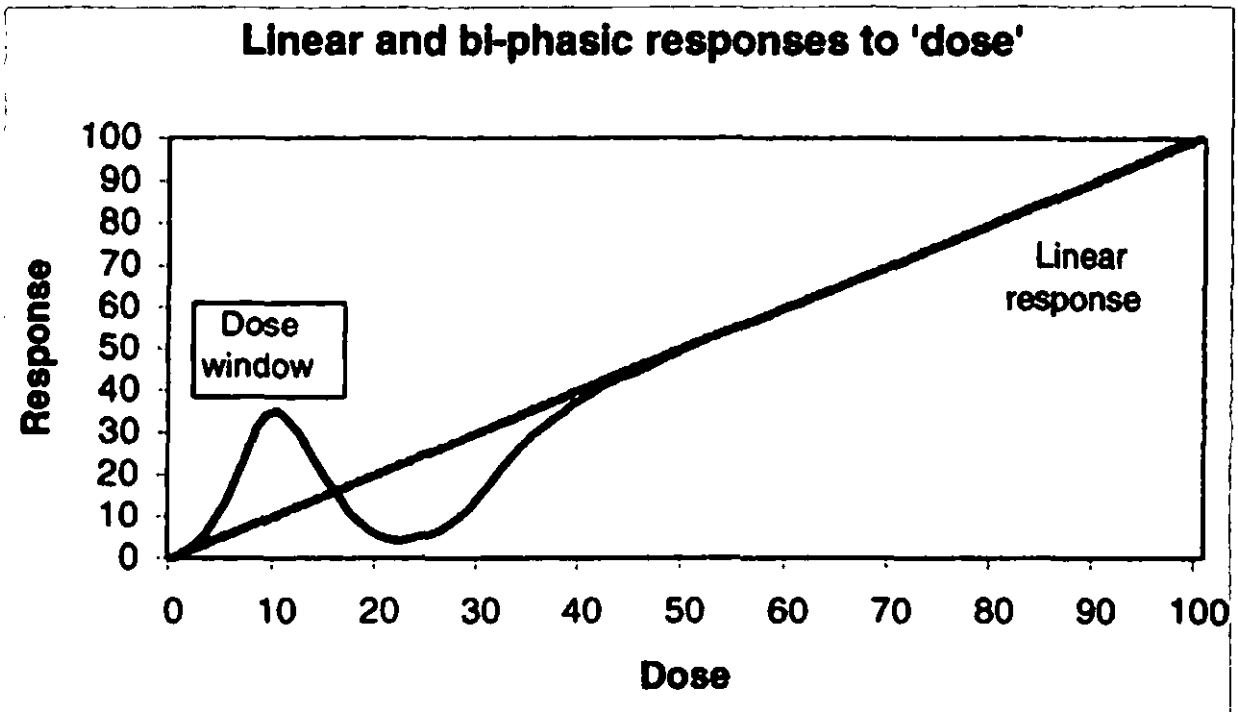
Hugo W. Ruediger*

Division of Occupational Medicine, Medical University of Vienna, Waehringer Guertel 18-20, Berggasse 4/33, 1090 Vienna, Austria

Received 24 October 2008; received in revised form 16 November 2008; accepted 16 November 2008

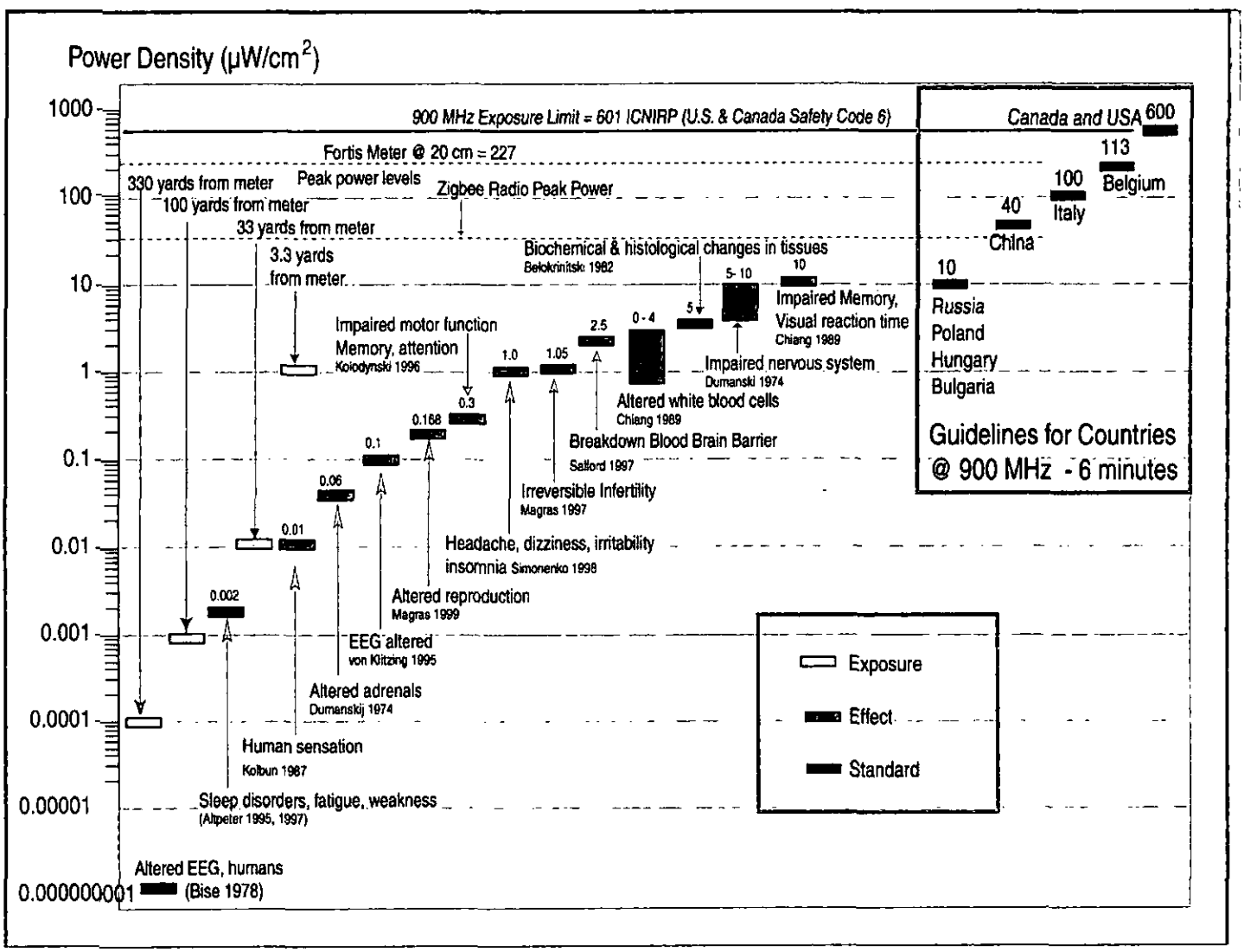
- Review paper of 101 studies: 49 reported genotoxic effects from Radiofrequency EMFs, 42 did not
- 8 studies showed an enhancement of genotoxic effects from chemicals when RF radiation was also present

EMFs can show a Non-linear Response



Lower EMF non-thermal exposures may lead to greater physiological responses or potential adverse health effects

Source: A. Philips in Electromagnetic Environments and Health in Buildings

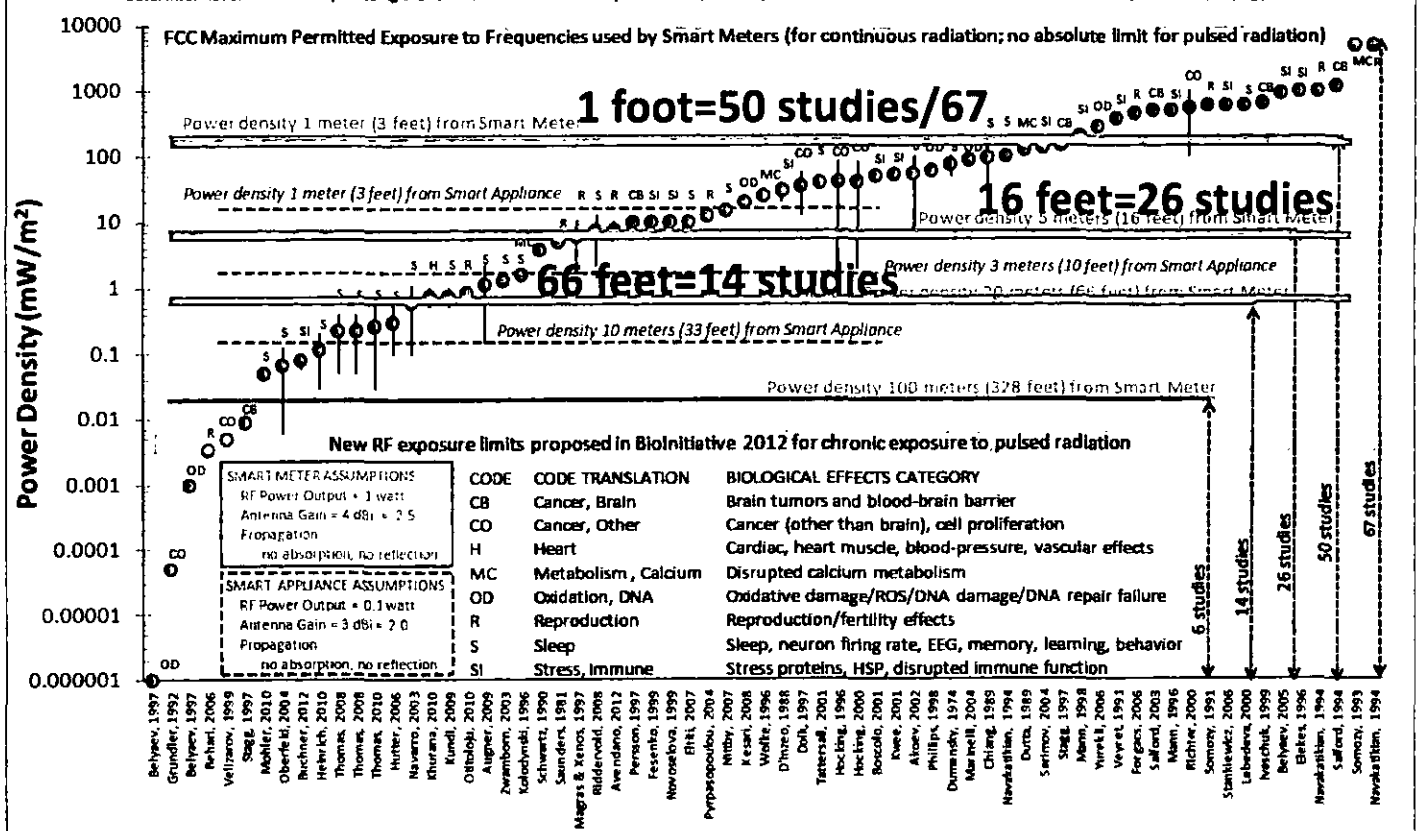

Power Density (μW/cm²)
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000000001
900 MHz Exposure Limit = 601 ICNIRP (U.S. & Canada Safety Code 6)
Fortis Meter @ 20 cm = 227
330 yards from meter
100 yards from meter
33 yards from meter
3.3 yards from meter.
Peak power levels
Zigbee Radio Peak Power
Biochemical & histological changes in tissues
Belokrinitski 1982
Impaired motor function
Memory, attention
Kolodynski 1996
Impaired Memory,
Visual reaction time
Chiang 1989
Impaired nervous system
Dumanski 1974
Altered white blood cells
Chiang 1989
Breakdown Blood Brain Barrier
Salford 1997
Irreversible Infertility
Magras 1997
Headache, dizziness, irritability
insomnia Simonenko 1998
Altered reproduction
Magras 1999
EEG altered
von Klitzing 1995
Altered adrenals
Dumanskij 1974
Human sensation
Kolbun 1987
Sleep disorders, fatigue, weakness
(Altpeter 1995, 1997)
Altered EEG, humans
(Bise 1978)
0.002
0.01
0.06
0.1
0.168
0.3
1.0
1.05
2.5
0 - 4
5
5- 10
10
Canada and USA 600
113 Belgium
100 Italy
40 China
10 Russia
Poland
Hungary
Bulgaria
Guidelines for Countries
@ 900 MHz - 6 minutes
Exposure
Effect
Standard

June 11, 2013

Reported Biological Effects from RF Radiation at Low-Intensity Exposure in Each of the 67 Studies Referenced in the "BioInitiative 2012" Report (Cell Tower, Wi-Fi, Wireless Laptop, and Smart Meter Power Densities)

Ronald M. Powell, Ph.D.

Reference for data dots (red), data range indicators (vertical black lines through red dots), biological effects categories for the red dots, and new proposed limits (yellow line): BioInitiative Working Group, Cindy Sage and David O. Carpenter, Editors. BioInitiative Report: A Rationale for Biologically-based Public Exposure Standards for Electromagnetic Radiation at www.bioinitiative.org, December 31, 2012. For references for other information on this chart, including the FCC Maximum Permitted Exposure limits, and the power densities of Smart Meters and Smart Appliances, see accompanying paper.

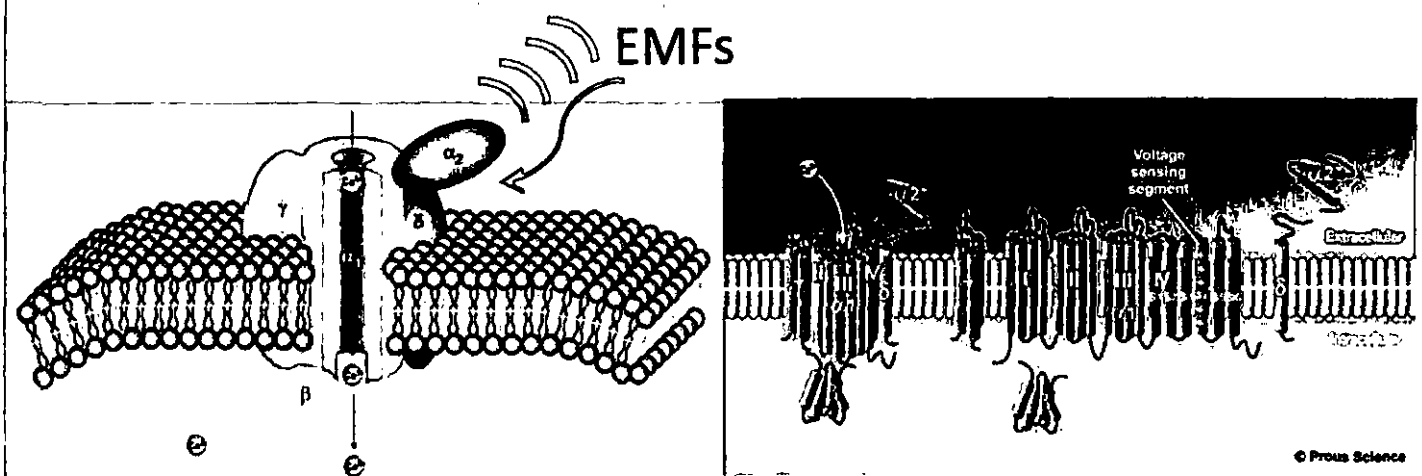


Principal Investigator of Study, and Year of Publication

Reported Mechanisms of EMF Damage by Non-Thermal Fields

- Activation of Voltage-Gated Calcium Channels
- Microwave Absorbing Magnetite in Brain Tissue
- Free Radicals causing Oxidative Stress
- Enzyme System Alteration (cellular kinases) e.g ERK, MAPK
- DNA single strand and double strand breaks → mutations can lead to serious diseases (cancer)

EMFs affect Voltage-Gated Calcium Channels on Cell Membranes



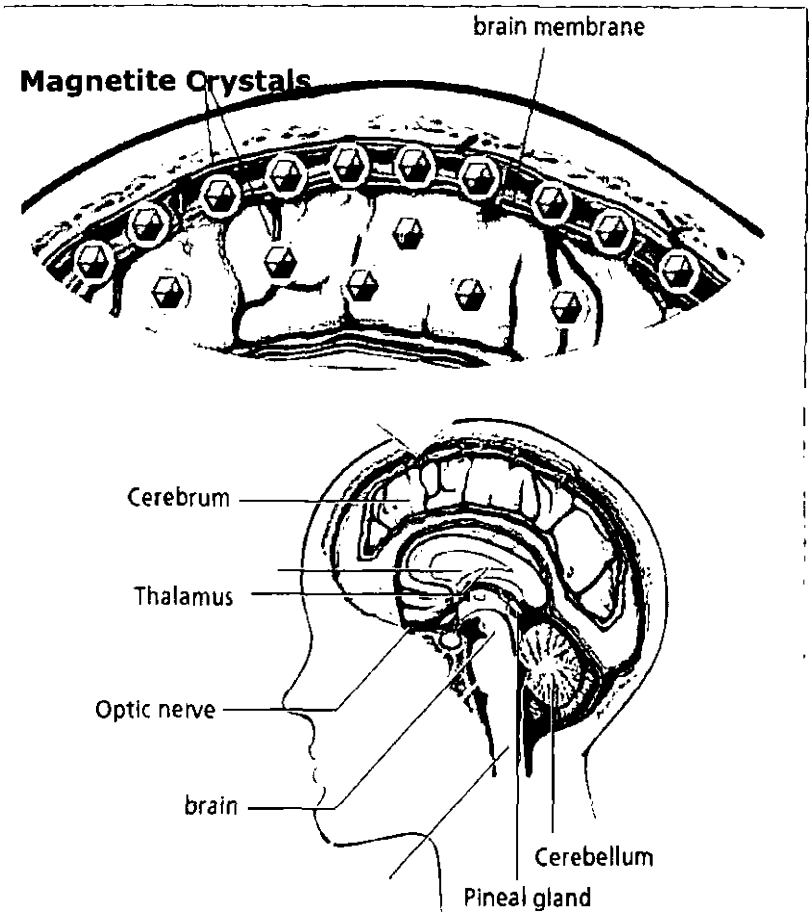
- Various types are present in every Cell Membrane
- Respond to Low Level Electromagnetic Fields (EMFs)
- Causes changes in Calcium ion release in cell
- Response of Calcium channels to EMFs is real since they can be blocked by Ca++ Channel Blocker Drugs

Magnetite Crystals in Human Brain

5 million crystals/gram
In Brain tissue

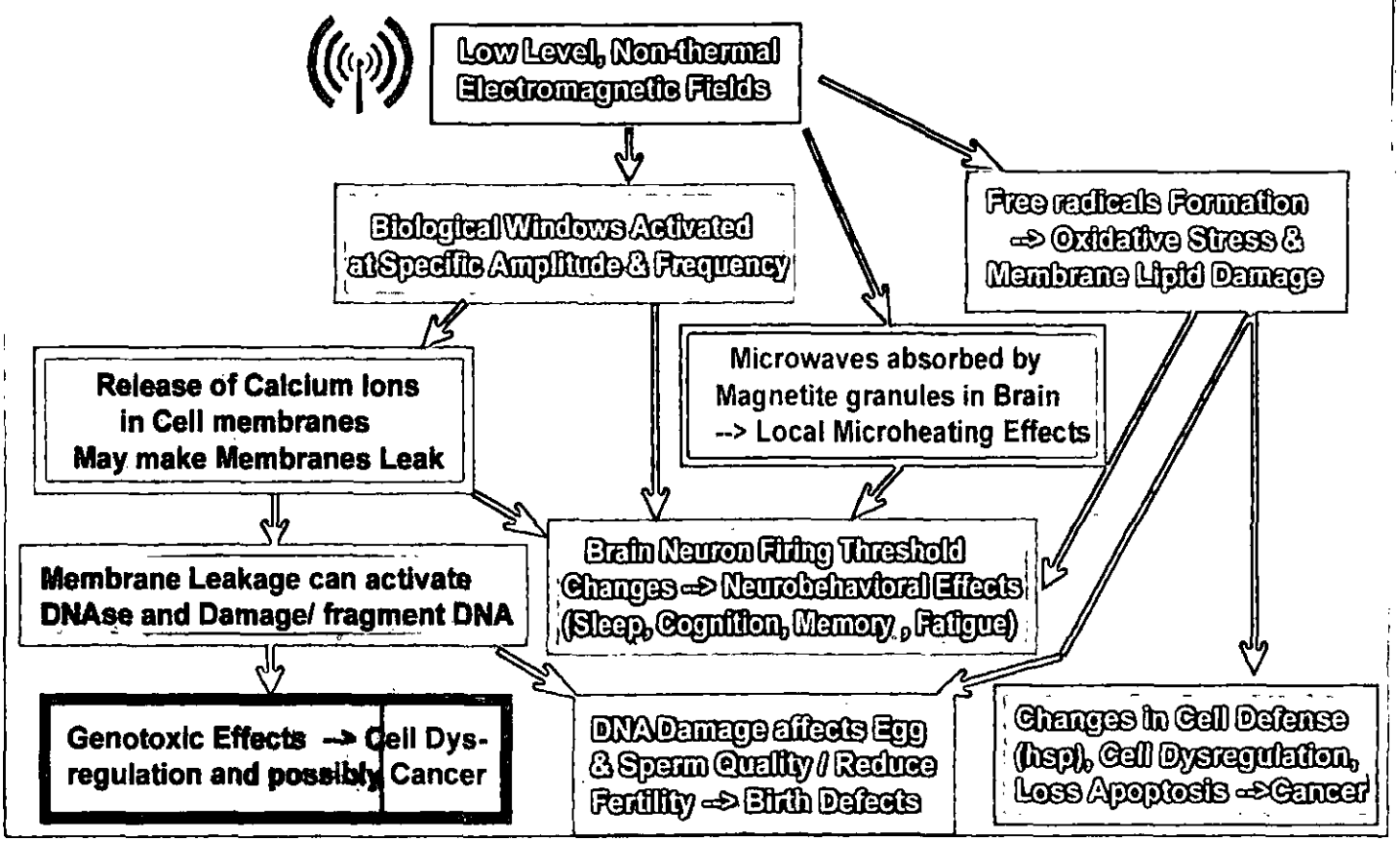
100 million crystals/gram
in brain membranes

Magnetite <u>absorbs wide range of Microwave Radiation</u> with Frequency Absorption Spectrum from 0.5 – 10 GigaHertz



Source: Kirschvink JL: Bioelectromagnetics 17(3):187-194, 1996

Mechanisms of Non-thermal EMFs



Reproductive Biology and Endocrinology

BioMed Central

Open Access

2009 Paper

Review

Pathophysiology of cell phone radiation: oxidative stress and carcinogenesis with focus on male reproductive system

Nisarg R Desai[1,2], Kavindra K Kesari[3] and Ashok Agarwal[1]

Address: [1]Center for Reproductive Medicine, Glickman Urological and Kidney Institute and Obstetrics and Institute, Cleveland Clinic, Cleveland, Ohio, USA, [2]Department of Internal Medicine, Staten Island Univers USA and [3]School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, India

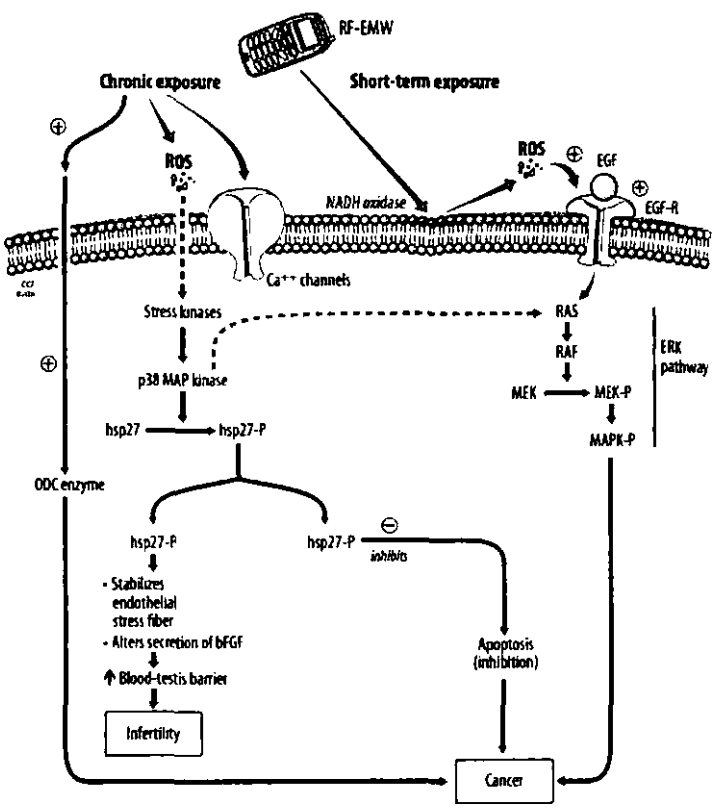
Email: Nisarg R Desai - nisargdesai@hotmail.com; Kavindra K Kesari - kavindra_biotech@yahoo.co.in; Ash

* Corresponding author

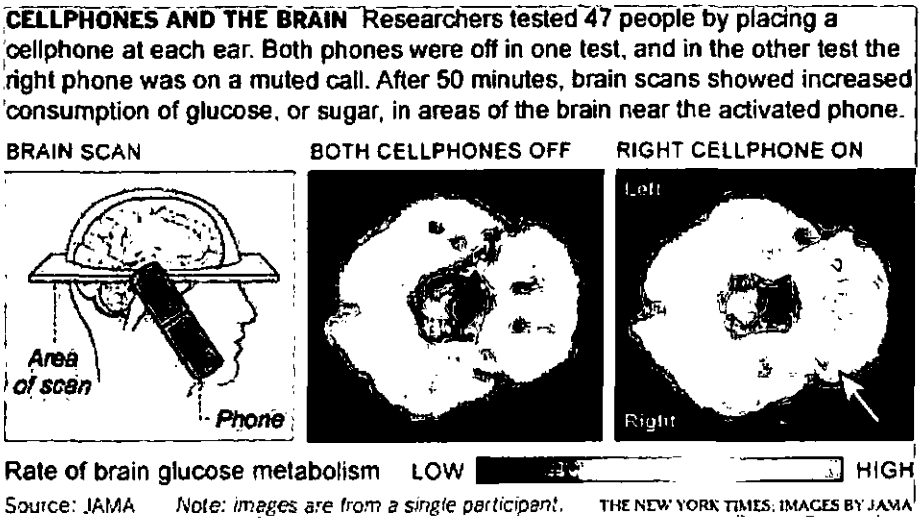
Published: 22 October 2009

Received: 13 August 2009

- Oxidative stress from cell phones causes excess free radicals that contribute to infertility, sperm changes and cancer



2011: Brain is sensitive to Non-thermal EMFs



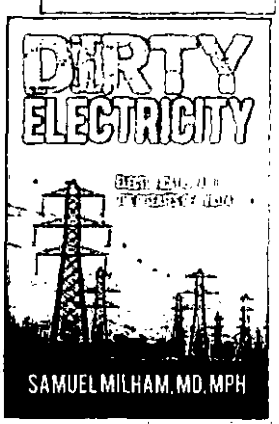
Images JAMA

- Positron Emission Tomography (PET Scan) study by Dr. Volkow at NIH and Brookhaven National Laboratory showed changes in glucose in 3 regions of brain at non-thermal EMFs.
- Metabolic effect was highest nearest to the antenna
- Source: Journal American Medical Association (JAMA) Feb 23, 2011

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 51:579–586 (2008)

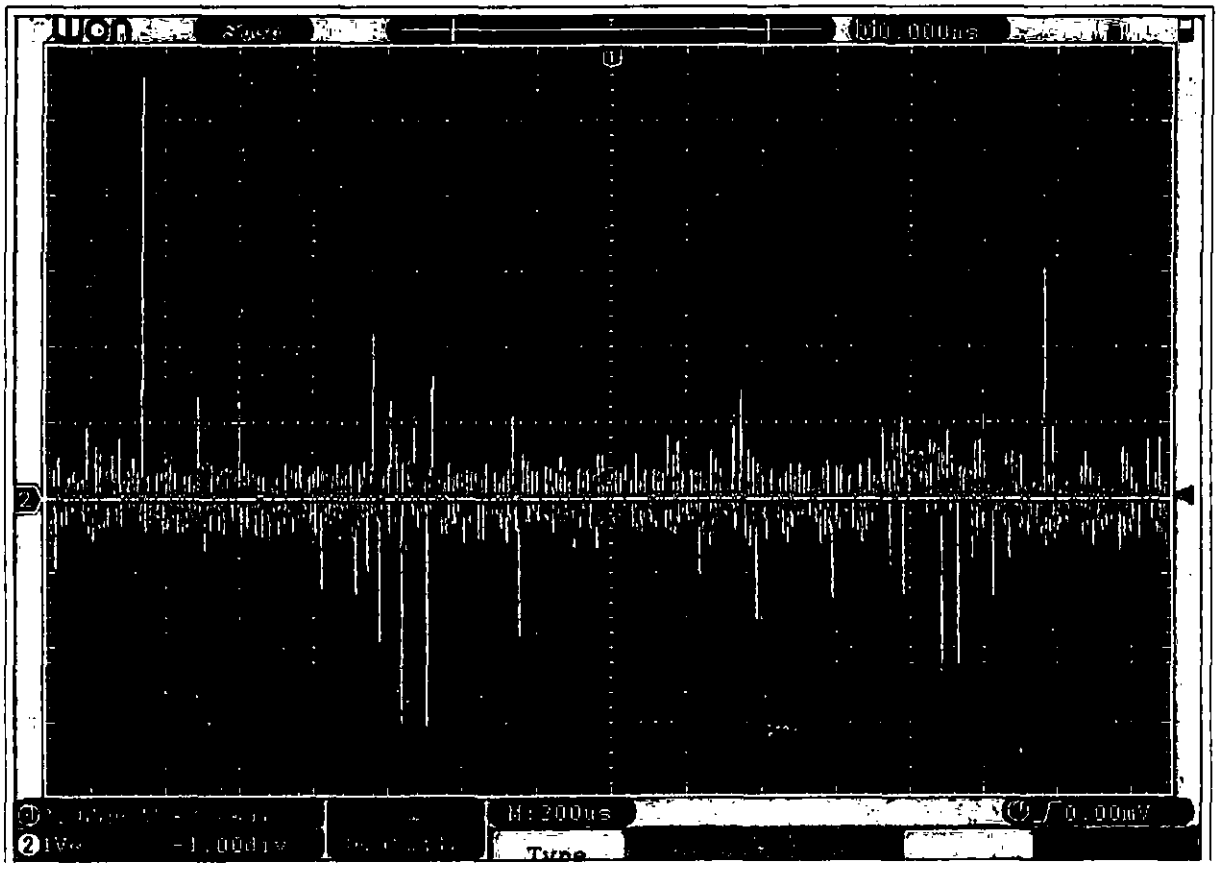
A New Electromagnetic Exposure Metric: High Frequency Voltage Transients Associated With Increased Cancer Incidence in Teachers in a California School

Samuel Milham, MD, MPH[*,1] and L. Lloyd Morgan, BS[2]

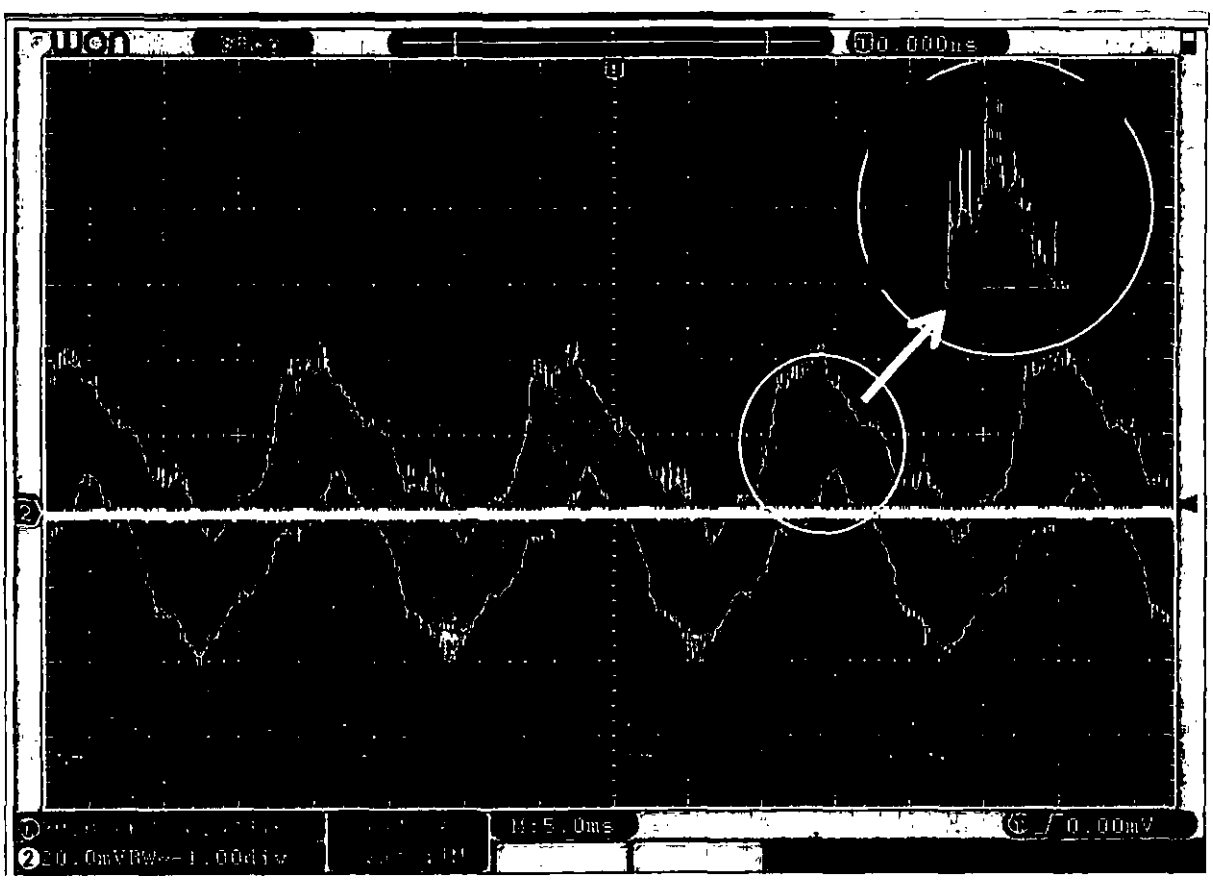


- Since 2008, concept of "Dirty Electricity" has become more widespread, especially work of Sam Milham MD
- Represents high frequency transients from digital equipment, dimmers, Smart Meter switching power supplies
- EHS people are especially adversely affected by these transients present in their house wiring
- Can be partly filtered out by power line capacitors

Digital Pulses in Ground



Digital Pulses on 60 Hz in Air

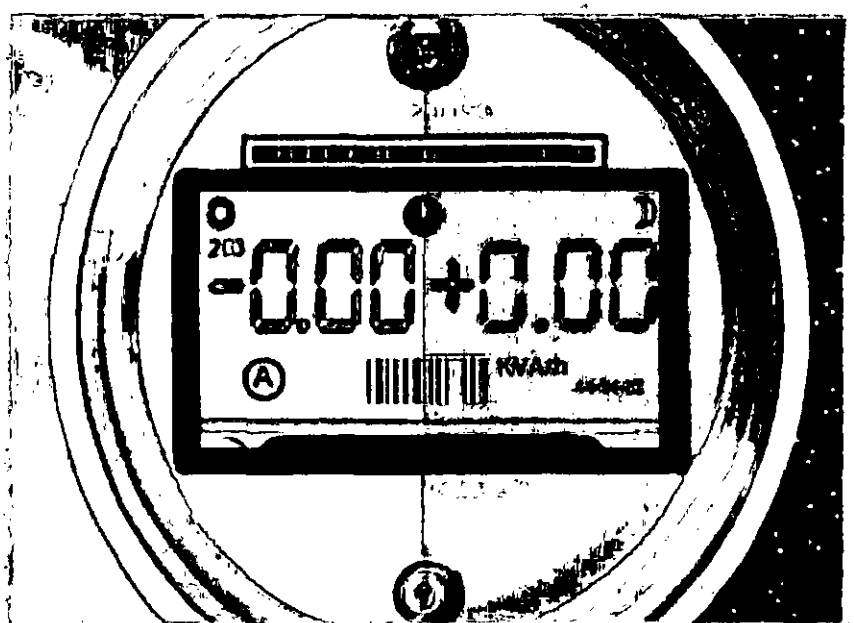


Solutions: Finding Our Way Forward

- Make Microwave Emitting Smart Meters voluntary
  - This was done in the Netherlands after customer revolt
- Ask Utilities to contribute 10 cents a month for every customer for new research on EMF effects of SM
- Fund independent studies to demonstrate unequivocally that no long-term EMF hazard from Smart Meters exists
- Educate customers on the potential hazards of EM radiation
- Create new, lower exposure guidelines
- Consider widespread filtering technologies for digital noise or "dirty electricity" on power lines
- Consider reprogramming Smart Meters for transmitting readings at specific times until a wired Ethernet or fiber-optic information system is ready (Google/Yellowstrom in Germany)
- Envision a more Direct Current based home power system including transverters and home gateways that fully support green home-based power generation and full grid integration.

Thank you for your Attention

Getting Smarter About the Smart Grid



Commonwealth Club of California - January 28, 2014

APPENDIX V

Radiofrequency fields are a probable human carcinogen

Anthony B. Miller, MD, Professor Emeritus

Dalla Lana School of Public Health, University of Toronto

IARC process to develop monograph on carcinogenicity

- Decision taken to assess carcinogenicity of an exposure
- Literature review perform
- Experts selected
- Experts assigned tasks and review (their segment of) the literature
- Experts assembled for 8 day intensive discussions
- Decision taken on level of carcinogenicity, 1, 2 a, 2b, 3, 4

Informative studies for Monograph 102

- Epidemiology studies
  - Interphone – multicountry, case control
  - Hardell case-control studies
  - Danish cohort study
- Mechanistic data
- Animal studies

Interphone – Appendix 2 for Glioma

Time since start of regular use (years)	Cases	Controls	OR	95% CI
1-1.9	93	159	1.00	
2-4	460	451	1.68	1.16-2.41
5-9	468	491	1.52	1.06-2.22
10+	190	150	2.18	1.43-3.31

Epidemiology Studies since Monograph 102

- Occupational (Cardis et al), 2013
- New Hardell, 2013, 2014
- French – Cerenat, 2014

Cerenat – 231 cases, 446 control

Brain cancer	Exposure period	OR	95% CI
Glioma	After 2 years	2.89	1.41-5.93
	After 3 years	3.03	1.47-6.26
	After 5 years	5.3	2.1-13.23
Ipsilateral glioma	All	2.11	0.73-6.08
Meningioma	All	2.57	1.02-6.08

Pending epidemiology studies

- COSMOS Cohort study in 5 European countries
- Mobi-kids case-control study (involves Canada – Montreal, Ottawa, Toronto, Vancouver)
- More are needed

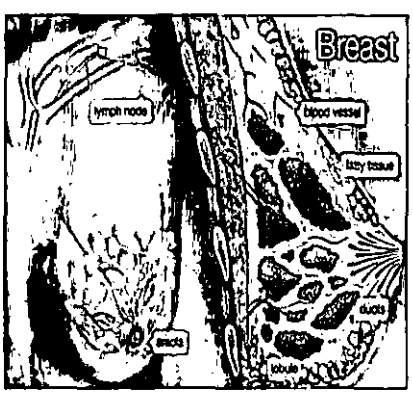
Foundation for Identifying Radiofrequency Fields as an avoidable cause of Breast Cancer

- 7 unusual clinical case reports
- Exposure modeling
- Toxicology
  - in vitro with human and animal cells
  - in vivo

Marketing for Cell Phones and Gear in Bras

Risk of Breast Cancer tied with cellphone radiation

The younger the breast the greater fluid and fat and greater microwave absorption

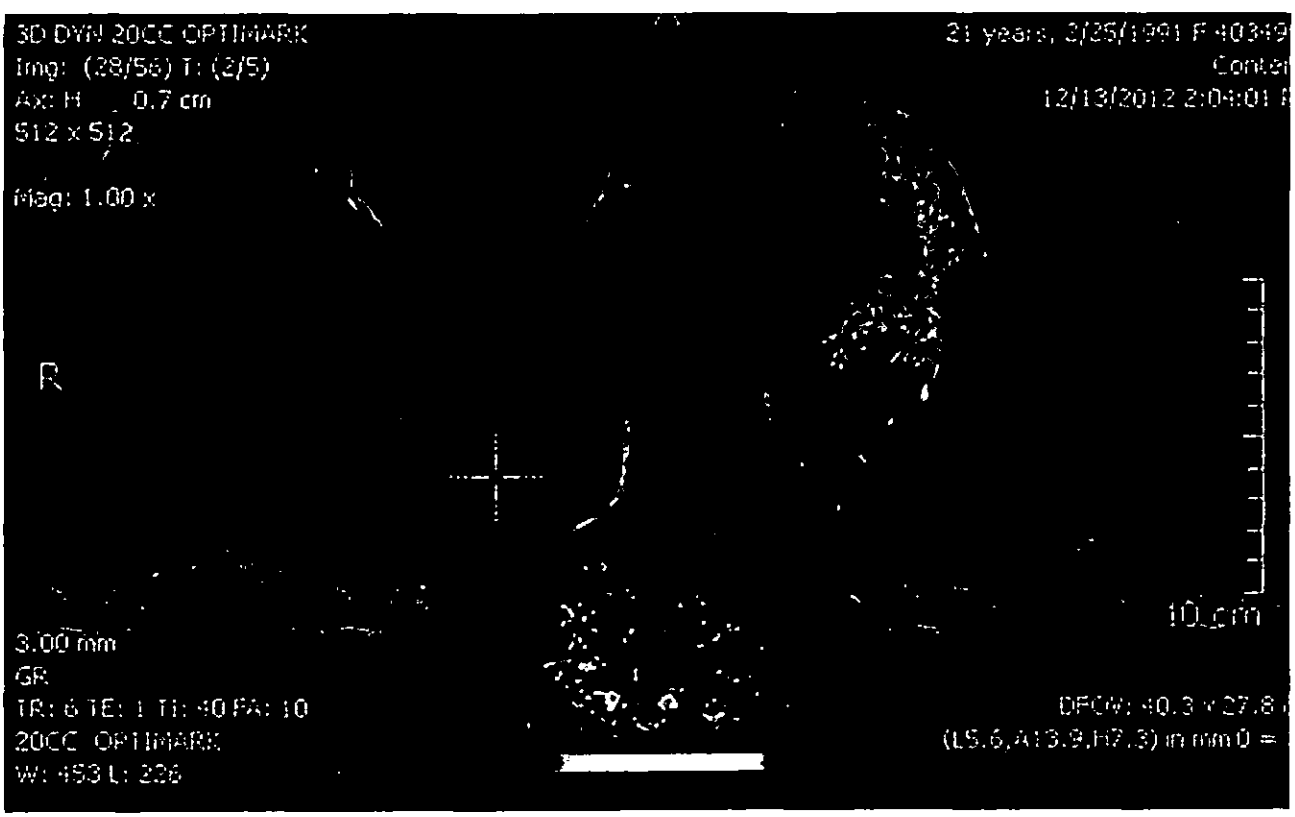


First case report, 2009

Invasive multiple primary tumors in 34 year old, avid runner Chinese-American woman who used cellphone 4 hours a day in her bra for 10 years—reported by Robert Nagourney, MD, PhD

Two cases age 21 with multi-focal tumors linked to cellphones kept in bra from age 13-21, 2012

Case Report—21 yr old multi-focal tumors linked to cellphone kept in bra



Summary of 7+ cases

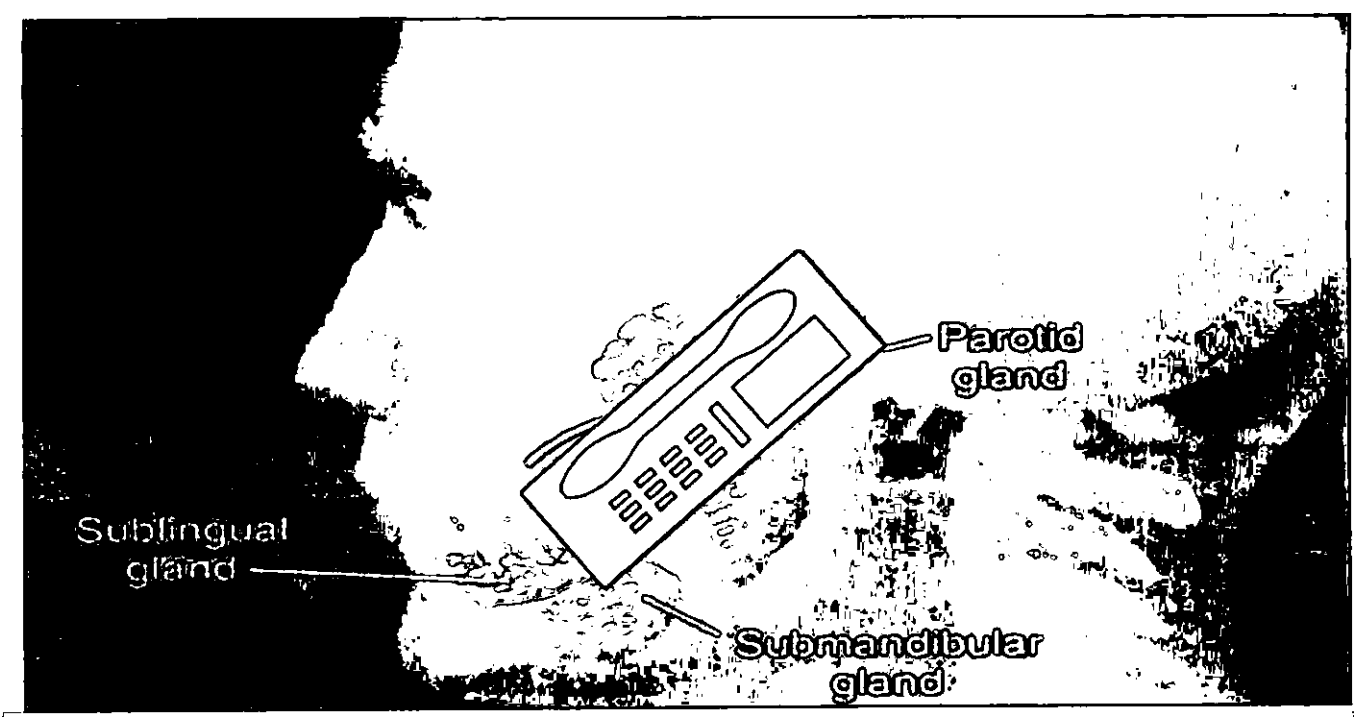
- Negative for BRCA1/2
- No family history or other risk factors
- Unusual location of multi-focal tumors where phones were kept with mix of tubular/solid patterns of identical nuclear morphology & grade
- No significant histology in ductal and lobular units away from the areas of cellular phone use
- Two with metastases

Reasons for deducing that radiofrequency fields is (an epigenetic) breast carcinogen

- Exposure Information
- In vitro toxicology
  - RFF stimulates apoptosis in normal fibroblasts
  - RFF impedes efficacy of tamoxifen
  - RFF interferes with melatonin
  - RFF is a xenoestrogen
- In vivo toxicology studies

Parotid or Salivary Gland Tumors Tripled in Israel:

1 in 5 under age 20



Increase in Parotid Gland Tumors in Israel Over the Last 30 Years

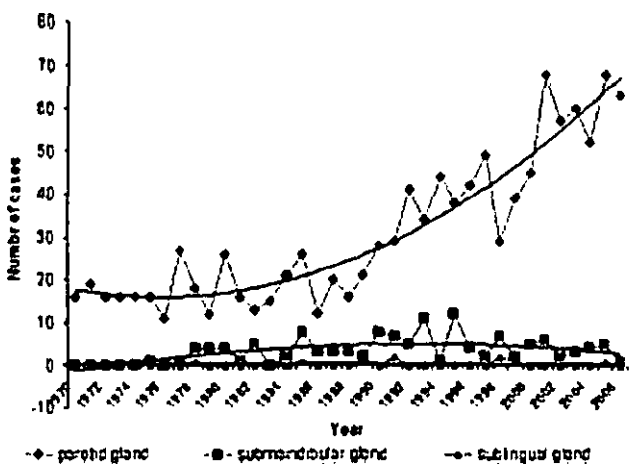


FIGURE. For trend analyses, we added regression lines and calculated R^2 values. Parotid gland cancer: $R^2 = 0.83$; Submandibular gland cancer: $R^2 = 0.36$; Sublingual gland cancer: $R^2 = 0.02$.

Source: Epidemiology, 22, p.130, *January 2011*

2007 Israeli case control finding: Association Between Tumors and Cell Phone Use

"Based on the largest number of benign [parotid gland tumors] patients reported to date, our results suggest an association between cellular phone use and PGTs."

The authors recommend continued research and implementation of precautionary measures by governments until furthers evidence becomes available.

Sadetzki et al. Am. J. Epidemiol. (2008) 167 (4): 457-467.

Israeli Dental Association Warning

- One in every five rare malignant tumors of the cheek occurs in someone under age 20
- Young people should use headsets and speakerphones and limit direct exposure of the head to microwave radiation from cell phones

Overall conclusions

- RFF are a Probable Human Carcinogen (IARC Category 2A)
- Radiofrequency fields are now ubiquitous
- Even if risk per individual is low, it is widely distributed and could become a major public health concern
- The Precautionary Principle must be applied now.

APPENDIX W

APPENDIX X

REVIEW ARTICLE

Self-Reporting of Symptom Development From Exposure to Radiofrequency Fields of Wireless Smart Meters in Victoria, Australia: A Case Series

Federica Lamech, MBBS

ABSTRACT

Context • In 2006, the government in the state of Victoria, Australia, mandated the rollout of smart meters in Victoria, which effectively removed a whole population's ability to avoid exposure to human-made high-frequency nonionizing radiation. This issue appears to constitute an unprecedented public health challenge for Victoria. By August 2013, 142 people had reported adverse health effects from wireless smart meters by submitting information on an Australian public Web site using its health and legal registers.

Objective • The study evaluated the information in the registers to determine the types of symptoms that Victorian residents were developing from exposure to wireless smart meters.

Design • In this case series, the registers' managers eliminated those cases that did not clearly identify the people providing information by name, surname, postal address, and/or e-mail to make sure that they were genuine registrants. Then they obtained consent from participants to have their deidentified data used to compile the data for the case series. The author later removed any individual from outside of Victoria.

Participants • The study included 92 residents of Victoria, Australia.

Outcome Measures • The author used her medical experience and judgment to group symptoms into clinically relevant clusters (eg, pain in the head was grouped with headache, tinnitus was grouped with ringing in the ears). The author stayed quite close to the wording used in the original entries. She then calculated total numbers and percentages for each symptom cluster. Percentages were rounded to the nearest whole number.

Results • The most frequently reported symptoms from exposure to smart meters were (1) insomnia, (2) headaches, (3) tinnitus, (4) fatigue, (5) cognitive disturbances, (6) dysesthesias (abnormal sensation), and (7) dizziness. The effects of these symptoms on people's lives were significant.

Conclusions • Review of some key studies, both recent and old (1971), reveals that the participants' symptoms were the same as those reported by people exposed to radiofrequency fields emitted by devices other than smart meters. Interestingly, the vast majority of Victorian cases did not state that they had been sufferers of electromagnetic hypersensitivity syndrome (EHS) prior to exposure to the wireless meters, which points to the possibility that smart meters may have unique characteristics that lower people's threshold for symptom development. (*Altern Ther Health Med.* 2014;20(6):28-39.)

Federica Lamech, MBBS, is a medical practitioner in Melbourne, Victoria, Australia.

Corresponding author: Federica Lamech, MBBS
E-mail address: lamech.federica@yahoo.com.au

The Victorian Auditor-General's November 2009 report[1] criticized the rollout of smart meters, which had commenced in 2009 under a previous government's mandate from 2006. As a result, a freshly elected Victorian Premier announced in 2010 that his government would review the program. Following a number of reports, including those by Deloitte,[2] EMC Technologies,[3] and Lockstep Consulting,[4] the new Victorian government announced on December 14, 2011, that it would continue with the program. Although the program would result in an overall net cost to consumers of $319 million dollars (NPV at

2008 values), Deloitte's analysis of the costs and benefits of the program had concluded that it made economic sense to continue given that a large portion of the costs had already been sunk into the project.[2] The rollout was scheduled to conclude by the end of 2013, but the deadline has been extended because of delays caused by technical difficulties, inaccessible sites, and customer refusals.

Issues Surrounding Rollout

After installation of wireless smart meters began, anecdotes of people developing symptoms started to be reported in mainstream media. For example, an article in the *Herald Sun* in Melbourne reported that Marc and Maureen Florio and their 4 children had left their home, claiming that they had been experiencing constant headaches and sleep deprivation since a neighbor's smart meter had been installed 3 weeks earlier.[5]

Public concerns over a number of issues with the compulsory rollout of smart meters have since intensified and multiplied. They have included (1) adverse health effects; (2) safety issues, such as a possible increased risk of house fires; (3) the incompatibility of the smart meter with existing wiring and appliances, possibly causing damage to electrical devices in the home; (4) privacy issues surrounding the collection and on-selling of vast amounts of data that reveal customers' energy usage patterns; (5) security issues, such as those inherent in any type of wireless communication (ie, a vulnerability to hacking and to cyber-attacks); (6) cost concerns; and (7) a perceived lack of democratic process because of the way in which the rollout had proceeded.[6] In response to these concerns, Energy Safe Victoria (ESV) released a report in July 2012, "Safety of Advanced Metering Infrastructure in Victoria," which stated that "smart meters are safe,"[7] notwithstanding the fact that ESV had mentioned in their draft in May 2012 that the issue of possible health effects was "beyond the detailed scope" of the report.[8]

Victoria's smart meters are electronic meters that are capable of measuring electricity consumption in 30-minute intervals and have a transmitter/antenna that is able to broadcast the collected data wirelessly to the base.[6] Victoria's smart meters also have a second internal antenna for the Home Area Network (HAN) radio, which can be turned on when requested by the customer.[3] The electronic meter is all that is needed to implement time-of-use tariffs (ie, charging different rates for electricity at different times); however, the remote-reading function means that meter readers are no longer required and that the power companies can disconnect and reconnect power remotely.[6] In effect, a smart grid, as opposed to deployment of electronic meters, constitutes the power companies' communication system. The bulk of Victoria's power distributors use wireless mesh networks that rely on the smart meters to act as relay stations, with households' data hopping unpredictably from meter to meter, thus forming a mesh.[6] Any reflective surface can cause a deviation in the transmission route of the radiofrequency signal. One distributor has deployed a WiMax network, which involves transmission from each meter directly to a collection tower in a star-like configuration.[6,9]

Smart meters do not have to be wireless. Italy has completed the largest smart meter rollout to date. Their smart meters are hard-wired and communicate over the existing power lines.[10] Other options have been proposed, such as communication via telephone lines, whereas fiber optic cabling has already been successfully deployed in other parts of the world.[11] Claims have been made that all types of electronic meters, including wired smart meters, can introduce dirty electricity (ie, high-frequency voltage transients and harmonics) along the wiring of a house, because of their switching-mode power supply, as well as back into the main powerline.[12] The function of the switching-mode power supply is to convert alternating current (AC) coming in from the power lines to direct current (DC), which is required to run the electronic meter. This process creates high frequency voltage spikes, which are emitted constantly, 24/7, and which travel along building wires and radiate outward from them. Critics claim that this dirty electricity can lead to short- and long-term, adverse health effects.[12,13]

Sources of Radiation

Electromagnetic fields (EMFs) is a broad term that encompasses both natural and human-made sources of radiation. The electromagnetic spectrum describes the continuum of different frequencies put together with the associated wavelength of each frequency.[14,15] The frequency is the number of oscillations or cycles per second, whereas wavelength describes the distance between successive peaks of a wave.[16] As a result, wavelength and frequency are inseparably intertwined: The higher the frequency, the shorter the wavelength is.[14] The electromagnetic spectrum is divided into 2 main types: (1) ionizing radiation, which comprises cosmic and gamma rays, X-rays, and ultraviolet rays; and (2) nonionizing radiation.[14,15,17]

Ionizing radiation has so much energy per quantum that it is able to break chemical bonds between molecules.[14] The negative effect on health of ionizing radiation is well recognized.[17] In this report, however, the term *radiation* will be used to describe nonionizing radiation, which does not carry sufficient energy to break molecular bonds.[14]

Nonionizing radiation includes (1) extremely low-frequency fields, such as those emitted by electrical appliances and power lines; (2) intermediate-frequency fields, such as those used in some antitheft and security systems; and (3) high-frequency radiation, which includes radiofrequency fields, such as those produced by mobile telephones, television and radio transmitters, and radar, as well as microwaves, a subset of radiofrequency radiation, which have frequencies in the 300 MHz to 300 GHz range.[16] The last are used in microwave ovens and for wireless Internet.[14,15]

These definitions are arbitrary but represent a useful way of describing different parts of the nonionizing component of the spectrum. Discussions of and research on the effects of nonionizing radiation revolve around thermal and

nonthermal effects.[17] According to the main regulatory agencies in Australia and the United States, only thermal effects are capable of affecting human health[17]; however, this article will deal exclusively with the nonthermal, or biological, effects on humans of nonionizing radiation. For this reason, the author has used the terms *radiation*, *radiofrequency*, and *microwaves* interchangeably in this article.

As societies industrialize, an unprecedented increase in the number and diversity of EMF sources occurs.[18] These sources include (1) video display units (VDUs) associated with computers and mobile phones and their base stations,[18] (2) wireless Internet, (3) digital television and radio, and—more recently—(4) wireless utility meters and their associated infrastructure. For some time, individuals have reported a variety of health problems that they relate to exposure to EMF.[18]

Electromagnetic Hypersensitivity Syndrome

Electromagnetic hypersensitivity syndrome (EHS) is characterized by a variety of nonspecific symptoms. The most common ones include dermatological symptoms—redness, tingling, and burning sensations—as well as neurasthenic and vegetative symptoms—fatigue, tiredness, concentration difficulties, dizziness, nausea, heart palpitations, and digestive disturbances.[18] This syndrome was first described by Russian researchers in the 1950s, who called it microwave sickness.[17]

Although the range of estimates of the EHS prevalence in the general population is broad, a survey of self-help groups has indicated that approximately 10% of reported cases have been considered severe.[18] The World Health Organization (WHO) has expressed a willingness to consider professional and public input on evidence supporting the inclusion of EHS into the 11th version of the International Classification of Diseases (ICD), to be released in 2015.[15] Various national governments have also recognized EHS as an emerging public problem. Sweden classifies EHS as a functional impairment,[15] whereas the Council of Europe Resolution 1815 calls for particular attention to be paid to the needs of electrosensitive people and for the introduction of special measures to protect them, including the creation of wave-free areas not covered by the wireless network.[19]

In May 2013, the author of the current study became aware that people were registering adverse health effects from smart meters on a public Web site. Two ways existed for people to register: (1) a health register and (2) a legal register. The health register requested that people send their data to a specific e-mail address if they believed that their health had been affected following installation of smart meters, asking 2 questions: (1) "Are you hypersensitive to electromagnetic radiation from sources such as smart meters and mobile phones?" and (2) "Has your health been affected following the installation of smart meters?" The legal register contained 1 similarly worded open-ended question: "Do you believe your health has been affected by the installation of smart meters?" If the answer was "yes," people were asked to state the symptoms from which they were suffering that they believed had resulted from exposure to electromagnetic radiation (EMR) that had been emitted from smart meters. The information could be submitted online or the form could be printed and filled in by hand, then sent to a designated postal address. Neither form of registration posed direct questions about types of symptoms or offered any form of tick-a-box questionnaire, thereby avoiding the suggestion of various symptoms, and both steered clear of a recruitment-style approach to the collection of information.

The author subsequently approached the managers of the Web site and the registers, and based on her status as a medical practitioner, she received permission to view people's deidentified data in both registers in hard-copy form. It was immediately apparent to the author that people from disparate parts of Victoria were listing the same or similar symptoms from exposure to smart meters. The majority of people could not possibly have known each other, and they certainly had no access to information that had been registered by others, as data sent to the registers had been kept strictly private and confidential. Because the information appeared to point to a new and ongoing public health problem for Victoria, the author decided that a case series report, based on the cases in the registers, was warranted.

METHODOLOGY

The author began by enlisting the agreement and cooperation of the managers of the public Web site and registers and by instructing them on her planned methodology. The managers were given the task of selecting appropriate cases from both their health register and legal register. The cases were included when the managers could clearly identify the person by name, surname, postal address, and/or e-mail address to make sure that they were genuine registrants. In the case of children, name and surname, together with postal address and/or e-mail address of at least 1 parent, were considered sufficient for identification of the child.

The managers then proceeded to print or photocopy each qualifying individual's entry and to deidentify each case, providing the author with each person's gender, date of birth, and the name of his or her residential suburb. The author considered these details important for statistical purposes. Children's symptoms were reported by their parents. E-mail addresses and phone numbers were hidden by the registers' managers, and the author made no attempt to contact any person to obtain additional details or ask for clarification(s). This practice was judged by the author to be appropriate, not only for the maintenance of anonymity but also because any further questioning would have had the potential to introduce biases in reporting and interfere with its spontaneous and unsolicited nature. What was not written or written clearly was simply omitted from the report. This fact must be kept in mind when reading the case series.

The Web site's managers then proceeded to seek signed written consent to use people's deidentified data to compile a report. This request was done by sending a letter to each

individual, mainly via post, but in a few cases in which postal addresses were not available, via e-mail. In the case of children, consent had to be signed by 1 of the parents. One case was drawn directly from the public side of the earlier-mentioned Web site, and for this reason, consent was not sought for that case because it was already available in the public domain. The Web site contained a significant number of publicly available cases of symptoms from smart meters; however, the chosen case was included because it was the only one that provided fully identifiable details: name, surname, residential address, and phone number. The author subsequently removed 1 case from outside the state of Victoria and 1 from a resident of New Zealand.

Of 142 fully identifiable cases before this removal, 91 consented, with the 1 additional case being in the public domain and not requiring consent. Therefore, the sample size was 92, and the author received all deidentified submissions in hard-copy form only. They were stored in her home office under lock and key. The author intends to keep all documents for a period of 5 years after publication of this article. At the end of this period, the documents will be destroyed.

For the results, the author has used her medical experience and judgment to group symptoms into clinically relevant clusters (eg, pain in the head was grouped with headache; tinnitus was grouped with ringing in the ears). The author has stayed quite close to the wording used in the original entries. Total numbers and percentages were calculated for each symptom cluster. Percentage values were rounded to the nearest whole number.

RESULTS

Of the 92 participants reporting symptoms from exposure to wireless smart meters, 87 were adults and 5 were children. Of the adults, the youngest person was 23 years of age and the oldest was 74; 55 (63%) were female and 32 (37%) were male. The children were aged 6, 10, and 14 years, with the ages of the remaining 2 children unknown. The children's group was composed of 2 females and 3 males. Therefore, for the total group, 57 (62%) were female and 35 (38%) were male.

Of all the individuals, 39 (42%) did not specify whether their symptoms were caused by their neighbors' or their own smart meters. This lack of information was not surprising, because that kind of information was not sought in either the health or the legal registers. Therefore, it is of note that a total of 53 people (58%) volunteered this data: (1) 27 (29%) claimed that their symptoms were from exposure to their neighbors' smart meters, (2) 20 (22%) thought the adverse health effects were from a smart meter at their own homes, and (3) 2 wrote that their symptoms were from both their neighbors' and their own smart meters. It is also interesting that 3 people stated that they experienced symptoms when visiting friends or relatives who had a smart meter, and 1 person became ill after exposure to a smart meter at work.

Only 7 people (8%) stated that they considered themselves to have been suffering from EHS prior to smart meter exposure. Of these, 2 felt that radiation from smart meters had aggravated their conditions. The place of residence of the person representing each case study was important, because the locations illustrate that individuals reporting symptoms were not concentrated in 1 geographical area but were from different and varied parts of metropolitan and rural Victoria. Figure 1 shows the residential locations of the current study's cases marked with red dots; 67% of the Victorians in this study lived within Melbourne's metropolitan area (ie, Melbourne's suburbs), which is shaded a darker green on the map. This correlates almost perfectly with current demographics for the state, which show more than 70% of all Victorians living in Melbourne's suburbs.

As Figure 2 shows, the most common symptoms were (1) insomnia, sleep disturbance, or sleep disruption—44 people (48%); (2) headaches, head pain, or dull head—41 people (45%); (3) tinnitus, ringing in the ears, or buzzing/noises in the ears—30 people (33%); (4) tiredness, lethargy, or fatigue, including chronic fatigue, exhaustion, or weakness—29 people (32%); and (5) cognitive disturbances, inability to concentrate or think, disorientation, or memory loss—28 people (30%). Table 1 identifies the symptoms that were experienced by participants, other than the 5 most common, with their incidence.

Figure 1. Map of Victoria and Places of Residence of the People in the Study's Cases

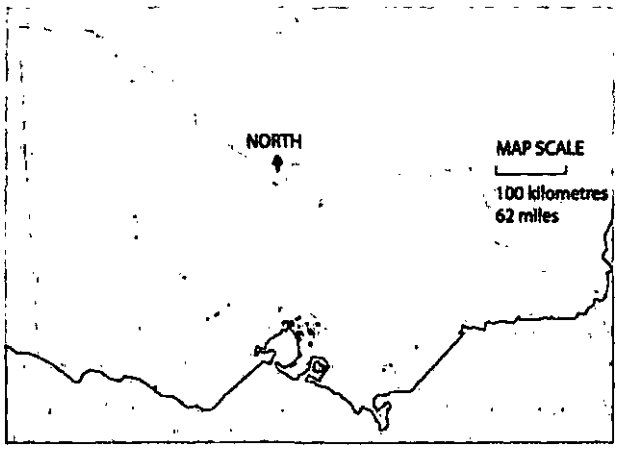


Figure 2. Five Most Common Symptoms

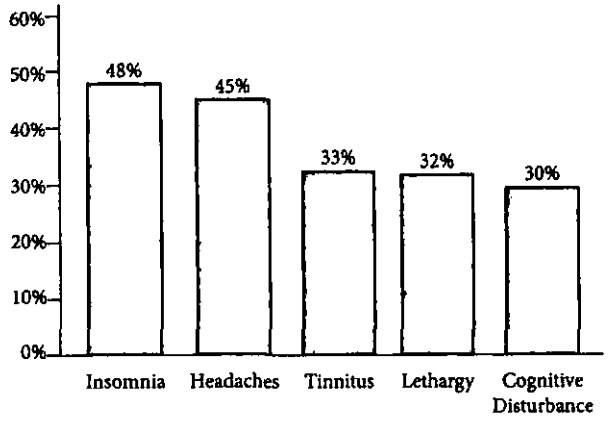


Table 1. Other Symptoms

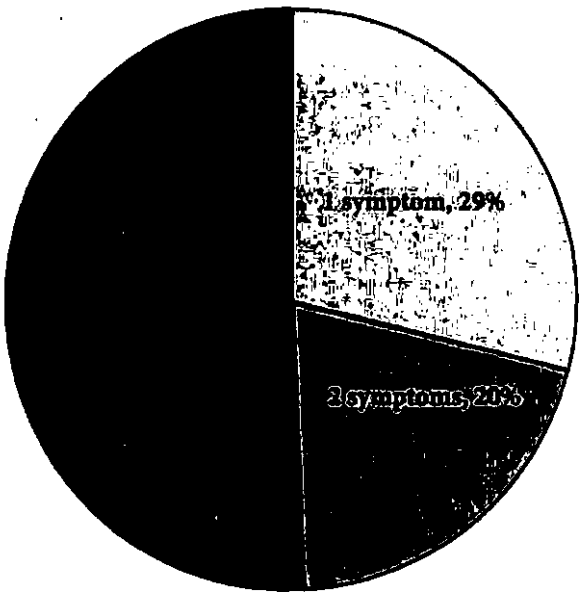
Symptom/Symptom Cluster	n (%)
Dysesthesias, including nerve pain, neuropathy, burning sensations, tremors, cold extremities, and poor circulation	20 (22%)
Dizziness/loss of balance	19 (21%)
Heart palpitations	16 (17%)
Nausea	15 (16%)
Onset of EHS	14 (15%)
Pain (in joints, bones, muscles, other and including arthritic changes)	13 (14%)
Pressure/heat/weird feeling in or on head	12 (13%)
Anxiety/agitation/irritability/restlessness	12 (13%)
Adverse health effects not otherwise specified	11 (12%)
Problems with eyes or eyesight/blurred vision	10 (11%)
Chest pain/pain in the heart	9 (10%)
Rashes/skin irritation/skin discoloration/dry skin	7 (8%)
Aggravation of pre-existing medical condition	6 (7%)
Digestive problems/bowel irritability/stomach pain	5 (5%)
Muscle spasms/cramps/twitches	5 (5%)
Nose bleeds	4 (4%)
Ear problems (ear pain, loss of hearing)	3 (3%)
Depression/loss of motivation	3 (3%)
Increased rate of infections/colds	3 (3%)
Allergies/food sensitivities	3 (3%)
Aggravation of EHS	2 (2%)
Sinus problems	2 (2%)
Lump in throat/sore throat	2 (2%)
Weight loss/loss of appetite	2 (2%)
Swollen face/lips	2 (2%)
Bladder infections/strains	2 (2%)
Flu-like symptoms	1 (1%)
Dehydration/thirst	1 (1%)
Weight gain	1 (1%)
Inability to talk	1 (1%)
Loss of motor skills	1 (1%)
Loss of feeling and movement from waist down	1 (1%)

Abbreviations: EHS = electromagnetic hypersensitivity syndrome.

It is concerning that 40% of all participants reported 4 or more symptoms, as this finding is very likely to be predictive of a greater level of disability (Figure 3). Eleven percent had developed only 3 symptoms, 20% only 2 symptoms, and 29% only 1 symptom. Note that the author counted "adverse health effect(s) not otherwise specified" as 1 symptom. She is of the opinion that even 1 symptom, depending on its type and severity, could result in significant disruption for an individual. An example of this result is the experience of the person in Case 82, an adult male who developed only 1 symptom—chronic, severe nerve pain—and had to go on a disability pension as a result.

It may reasonably be expected that a random sample of the population would also report a number of symptoms at any one time, but the difference in these cases is that all people in this study self-reported symptoms that they attributed directly to smart meters. Because EHS is a self-reported syndrome and given the current absence of a reliable assessment tool for identifying EHS in individuals, Eltiti et al[20] concluded that researchers have to rely on the

Figure 3. Number of Symptoms per Person



individual's self-diagnosis of their symptoms as caused by exposure to EMF. The researchers proposed an EHS screening tool that is centered on the fact that an individual explicitly attributes his or her symptoms to exposure to EMF-producing object(s).[20]

Similarly, a survey conducted by the Dutch Electrohypersensitivity Foundation in 2007 argues that EMF-affected individuals simply know, often by experimentation, that certain pieces of electrical equipment, installations, or facilities make them sick and that most of the problems are solved when these items are switched off or the EMF exposure is lowered by shielding or increasing the distance from a device.[21] This statement mirrors the experience of the majority of the Victorian cohort, who were specific in their description of their health problems as being directly related to smart meter exposure. A chronological relationship existed between the onset of exposure and symptom development.

A chronological relationship between length of exposure and an increase in the number or severity of symptoms, however, did not necessarily exist. This finding suggested a possible all-or-nothing mechanism, whereby smart meter exposure leads people to reach a personal threshold beyond which adverse health effects are consciously perceived. More than one-half (58%) of all the current participants also volunteered a statement with regard to the location of the smart meter(s) that they had identified as causing their symptom(s) and described clear alleviation of symptom(s) when they moved away from the smart meter(s) or when shielded from the smart meter(s).

As a consequence, a large number of people self-helped either by using shielding measures or by putting distance between themselves and the smart meter(s), which meant either relocating their bedrooms, moving to another residence, ceasing employment, restricting their movement in general, or moving out of the state of Victoria (Table 2).

Table 2. Effect on People's Lives

Effect
1. Having to go on a disability pension
2. Not being able to use part of one's house
3. Restricting freedom of movement
4. Spending a lot of money on shielding products
5. Causing financial problems
6. Causing relationship problems
7. Having to undergo otherwise unnecessary medical investigations
8. Needing to see a psychologist and doctors
9. Producing general deterioration in quality of life
10. Needing to restrict time spent using a computer
11. Needing to avoid all EMR-emitting devices
12. Being unable to drive
13. Causing secondary stress
14. Having to temporarily move out of one's home while it was being shielded
15. Developing concerns about long-term effects of exposure
16. Relocating bedroom
17. Decreased performance at work
18. Being unable to work
19. Being able to feel normal only when away from home
20. Causing several issues, such as lethargy or cognitive impairment, secondary to sleep disturbances
21. Needing to move into a caravan 25 km out of town
22. Sleeping in a van for 6 months
23. Relocating to another state

Abbreviation: EMR = electromagnetic radiation.

Figure 1 shows that people in this study were from disparate parts of the state of Victoria. They were from metropolitan as well as regional and rural areas and were not concentrated in any geographical area, which makes possible causes of symptoms related to a specific location unlikely (eg, proximity to airports, wind farms, open-cut coal mines, or chemicals used in agriculture). It is also unlikely for the reported symptoms to be associated with any seasonal factor (eg, extremes of temperatures, degree of humidity, bushfire smoke, or a high pollen count), because the reporting period stretched between September 2012 and August 2013, which meant that symptoms were reported during all 4 seasons.

Smart meters represent an ubiquitous presence throughout the state of Victoria, having been rolled out across the entire state. Their presence is not subject to seasonal variation. Therefore, they are a credible possible cause of the symptoms reported in this study, although a case series cannot prove causality. It can and does, however, offer a new hypothesis, one that will have to be tested by further research.

More than one-half (55) of all the cases did not state what effect the symptoms had had on their lives. This lack is possibly caused by the fact that the registration of their symptoms occurred in an open-ended style that did not

directly ask questions other than whether they thought that smart meters had affected their health. Moreover, participants had consented for their deidentified data to be used to compile a report at a time after their initial submission to the Web site's registers. This situation had the benefit of eliminating the likelihood of a real or perceived secondary gain for registrants but also led to the writing of short, simple statements that did not elaborate on how the symptoms had affected their lives. Table 2 provides details about the effect on the lives of the 37 people who made a statement about those effects..

DISCUSSION

Biological Effects of Radiation

With regard to the reported symptomatology related to wireless smart meters, it is interesting to look back at a research report by Dr Zorach R. Glaser for the Naval Medical Research Institute (NMRI) in the United States, completed in 1971 and revised in 1972.[22] The report lists in excess of 2300 references on the biological responses to radiofrequency and microwave radiation in its bibliography. What is immediately apparent is the fact that most of the symptoms reported in the current case series were also present in the NMRI report. This fact indicates that biological effects from nonionizing radiation are the same irrespective of the device that emits them—accounting for frequency, intensity, and duration—and that such biological effects were already known and reported to the public in 1971. In fact, Glaser mentions 2 even earlier studies that were both published in 1969.[22] The value of Glaser's report lies particularly in its lack of bias and conflict of interest because the sponsoring department was the Bureau of Medicine and Surgery (Navy) in Washington, DC.

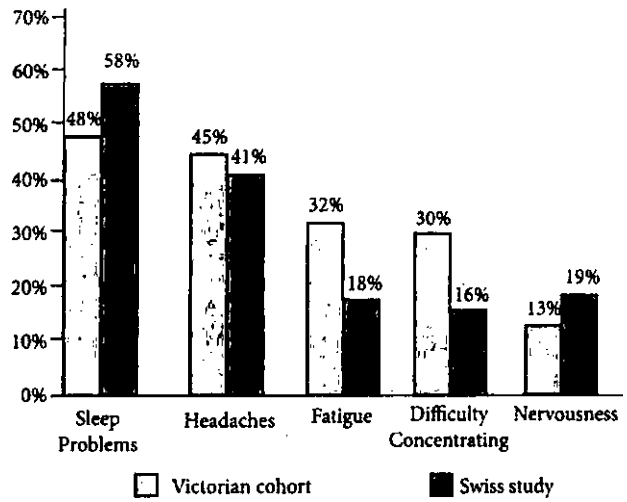
In terms of the biological symptoms listed, an almost complete overlap exists with symptoms reported in the current case series. All commonly reported symptoms in the current case series, such as insomnia, headaches, tinnitus (described as buzzing about the ears in the NMRI document), fatigue, cognitive disturbances, memory problems, dizziness, buzzing in the head, heart rate problems, eye problems, chest pain, dysesthesias, anxiety, and restlessness are very clearly biological symptoms that were listed in Glaser's report,[22] together with less common symptoms, such as heat/weird feeling in/on the head, skin problems, digestive problems, muscle cramps, sinus problems, depression, loss of appetite, and dehydration.[22]

The symptoms reported by Victorians but not mentioned in the 1971 report are (1) nausea; (2) pressure in the head; (3) pain other than head or chest pain, although the pain could be caused by changes in oxidative processes in tissues as listed by Glaser, and consequent tissue inflammation; (4) shortness of breath; (5) ear problems—pain and decreased hearing; (6) allergies and food sensitivities; (7) nose bleeds; (8) increased rate of infections/colds; (9) bladder infections/strains (10) flu-like symptoms; (11) lumps in the throat (the NMRI report instead mentions a peculiar metallic taste in the mouth); (12) swollen face or swollen lips; (13) weight gain; (14) inability to talk, which could be caused by electroencephalogram (EEG) changes and/or pyramidal tract lesions as mentioned in the 1971 report; and (15) loss of motor skills or loss of feeling and movement from the waist down, which are both consistent with pyramidal tract lesions and effects on locomotor nerves that are listed in the NMRI paper. In looking at these symptoms that were not obviously listed in the NMRI report, it is important to keep in mind that the language of that report was more technical and clinical compared with the current case series, in which the author has purposely stayed true to the wording and terms used by participants and which is, therefore, less technical and less interpretive.

In 1990, a study was commissioned in response to a petition that had been signed by a group of residents in Schwarzenburg, Switzerland, who claimed to be experiencing ill health from a shortwave-radio transmitter present in their small town. The Federal Office of Energy was charged with setting up a study group, which was chaired by Dr J. Cattin, head of the Section Energy Management, and which included the University of Berne and Swiss Telecom, among others.[23] The study was criticized, particularly because of Swiss Telecom's involvement and because of its 5-year duration, which was too short a time for any conclusive findings on long-term health effects, including cancer, to emerge.[24] It nevertheless revealed some impressive understandings on short-term effects from exposure to radiofrequency fields. The most important of these effects was that of sleep disruption, which was very common, affecting 55% of those older than 45 years, and which was directly associated with the electromagnetic-field strength of the transmitter.[23] Other symptoms reported by residents included headaches, tiredness, general weakness, irritability, nervousness, limb pain, lower-back pain, and palpitations. Most important, personality studies were carried out that showed that symptoms were not related to a health-worrying personality but displayed a dose-response relationship with logistic regression. The strong correlation between the type of symptoms experienced by the Victorian cohort and by the residents of Schwarzenburg, together with the shared high prevalence of sleep disruptions in both groups, should further inform assessment of the significance of the findings of the current case series.

A consensus paper of the Austrian Medical Association's EMF Working Group, adopted on March 3, 2012, in Vienna and titled "Guideline of the Austrian Medical Association for the Diagnosis and Treatment of EMF-related Health Problems and Illnesses (EMF Syndrome)," mentions a survey carried out in Switzerland in 2001.[25] In it, 394 respondents attributed specific health problems to EMF exposure. The following symptoms were reported: (1) sleep problems (58%), (2) headaches (41%), (3) nervousness (19%), (4) fatigue (18%), and (5) difficulty concentrating (16%). It is apparent at first glance that the first 2 symptoms are of the same order of frequency as for the Victorians in the current case series (Figure 4). A very similar percentage of people complained of headaches in both the current study (45%) and the Swiss one (41%). A similar, albeit slightly lower, number of participants reported sleep problems, such as insomnia and frequent waking, in Victoria (48%) versus those reported in the Swiss study (58%). All 5 symptoms

Figure 4. Victorian Cohort Versus Swiss Study



reported in the Swiss survey corresponded to symptoms experienced by the Victorian cohort, with fatigue (32%) and difficulty concentrating (30%) being more common in Victoria and nervousness (anxiety/agitation) (13%) being less common.

The Austrian Guidelines also list a number of what their authors consider to be EMF-related symptoms: sleep problems, fatigue, exhaustion, lack of energy, restlessness, heart palpitations, muscle and joint pain, headaches, depression, difficulty concentrating, forgetfulness, anxiety, urinary urgency, anomia, dizziness, tinnitus, and a sensation of pressure in the head and the ears.[25] All listed symptoms were experienced by Victorians in the current study, if the reader accepts that anomia corresponds with inability to talk and urinary urgency to bladder infections/strains.

Short-term effects from exposure to radiofrequency fields are also mentioned in another recent publication, the BioInitiative 2012 report prepared by 29 independent scientists and health experts from around the world. It documents bioeffects (ie, adverse health effects) and public health conclusions about effects of nonionizing radiation, including radiofrequency microwave fields. It replaces the BioInitiative 2007 report.[26] These effects involve cognition; memory and learning; behavior; reaction time; attention and concentration; and altered brainwave activity (altered EEG), as well as insomnia; discomfort; loss of well-being; sleep disruption; aberrant immune, allergic, and inflammatory responses in tissues; interference with normal cardiac function; alteration of circadian rhythms; and desynchronization of neural activity that regulates critical functions in the brain, gut, and heart. Radiofrequencies can act as disrupters of synchronized neural activity.

The BioInitiative report offers a detailed explanation on how environmental exposures to artificial EMFs can interact with fundamental biological processes in the human body.[26] This finding should not be unexpected because "human beings are bioelectrical systems."[26] In addition to short-term effects, the report dwells on the long-term sequelae (pathological conditions) from chronic exposure to nonionizing radiation, which include genotoxicity and DNA breakages among others.[26] It is not strictly within the scope of this case series to explain the biophysical mechanisms that may account for acute symptoms or effects or to discuss the long-term serious health endpoints associated with radiofrequency radiation; however, a summary of the nonthermal biological effects of nonionizing radiation is contained in Table 3. It is distilled from the BioInitiative report and intends to be a basic guide for clinicians.

It also needs to be mentioned that in 2011, the International Agency for Research on Cancer (IARC), which is part of the WHO, classified radiofrequency fields as a Group 2B Possible Human Carcinogen, based on an increased risk of glioma after 10 years or longer of cell phone use.[27] The IARC clarified that the evidence for carcinogenicity applies to exposures to radiofrequency radiation from all sources, not only cell phones (ie, it is not device-specific).[28] This finding has implications for the continued massive rollout of wireless technologies, in particular the wireless smart utility

Table 3. Summary of Biological Effects of Nonionizing Radiation

Effects

1. Pathological leakage of the blood-brain barrier, which allows toxins into brain tissues
2. Pathological leakage of the blood-gut barrier
3. Altered immune function, including increased allergic and inflammatory responses
4. Cardiovascular effects, particularly on blood pressure and heart rate
5. Disregulation of circadian rhythms and reduced melatonin production, which may account for insomnia
6. Nervous system effects, which include altered brainwave activity, changes in neuronal functioning and changes in autonomic nervous system electrophysiology
7. Desynchronization of neural activity that regulates critical functions in brain, gut, and heart
8. Lipid peroxidation of cell membranes
9. Elevated intracellular calcium with consequent disruption of cell metabolism
10. Poorly functioning mitochondria
11. Production of stress proteins as a result of the direct interaction of EMF with the DNA molecule, whereby DNA acts as a fractal antenna (because of its coiled-coil configuration)
12. Altered biochemical functions and production of hormones
13. Increased production of free radicals and deficiencies of antioxidants such as glutathione and melatonin leading to oxidative stress

Abbreviation: EMF = electromagnetic field.

meter, which was described in a recent statement to the UK Parliament as having triggered thousands of complaints of ill health and disabling symptoms worldwide.[29]

Mandated, Involuntary Exposure

With regard to smart meters, 2 unique features should be considered: (1) exposure may be involuntary and (2) exposure can be universal. In Victoria, smart meters were mandated, thereby removing the individual's choice to avoid exposure in his or her own home, and involuntary exposure also occurred to meters in neighboring homes. Each smart meter in the mesh networks transmits an unknown and variable number of burst transmissions per day, which typically reach into many thousands in number.[30] Meters on the WiMax network,[9] although not communicating with each other and deploying only bidirectional communication between a meter and the base station, nevertheless send hourly time synchronization signals in addition to their daily session transmissions.[3]

A submission by the Public Utilities Commission of California shows that only 45.3 seconds of transmissions per day (<0.1% duty cycle) still equates to 9600 transmissions.[30] Exposures are likely to be physiologically additive in nature.[25,26,31] Moreover, belief is increasing in the concept that intermittent pulses of radiofrequencies, such as those used in the smart grid, are more biologically significant compared with constant-type exposures, even when the time-averaged exposure is miniscule.[26,31] This kind of signal is biologically active and *not* invisible to the human body and its proper biological functioning, because the unpredictable pulses disrupt the synchronized biological oscillations within cells.[26] The Austrian Medical Association recommends that such periodic signals should be critically evaluated, whereas nonperiodic signals may be considered more leniently.[25]

In a 2012 memorandum titled "Health Risks Associated with SmartMeters," Dr Poki Namkung, public health officer of the County of Santa Cruz (CA, USA) stated that no scientific literature exists on the health risks of smart meters because they are a new technology.[31] This statement parallels the Austrian EMF Working Group's statement that "new technologies and applications have been introduced without certainty about their health effects."[25] Dr Namkung also explains that research on the potential health risks from radiofrequencies has been funded largely by industry because little funding is available for basic scientific research.[31]

The report indicates:

> ... exposure is additive and consumers may have already increased their exposures to radiofrequency radiation in the home through the voluntary use of wireless devices such as cell and cordless phones, personal digital assistants (PDAs), routers for internet access, home security systems, wireless baby surveillance monitors (baby monitors), and other emerging devices. It would be impossible to know how close a consumer might be to his or her limit, making safety a uncertainty if SmartMeters are mandatorily installed.[31]

Again, this statement correlates with the conclusion in the Austrian Guidelines that "multiple exposures to different EMF sources must be taken into account."[25] Dr Namkung's conclusion that "... governmental agencies are the only defense against such involuntary exposure" to mandated smart meters' nonionizing radiation emissions[31] applies in a particularly relevant way to the Victorian experience.

A similar view is also shared by Dr David O. Carpenter and 53 other scientists and doctors, who, in an article published in 2012, outline some of the effects of EMF exposure with the intent to correct some of the gross misinformation regarding wireless smart meters and advocate for the application of a precautionary principle, such as using wired meters.[32]

Although some of the studies discussed in this report offer recommendations regarding wireless smart meter deployment (Table 4), virtually no published studies are available with respect to smart meters and human health, and no long-term studies exist because of the newness of the technology.

Notably, an early voice of concern on this issue was that of Don Maisch, PhD, from Tasmania, who posed the question of whether smart meters would end up creating a public health nightmare in an article published in September 2012.[33] In it, he explained how current exposure standards are outdated and no longer relevant and warned that, given the sheer number of people exposed, simply dismissing anecdotal evidence of symptoms from smart meters as a nocebo (harmless) effect without a serious research effort would be inexcusable.

Incidence of Effects

This article has discussed the fact that people from various regional and metropolitan areas in the state of Victoria, of all ages and during all seasons, have reported symptoms from exposure to the radiofrequency fields of wireless smart meters as well as the onset or aggravation of EHS and the aggravation of pre-existing medical conditions after installation of the meters. Interestingly, only 8% of the participants in the current study stated that they had suffered from EHS prior to exposure to smart meters, which suggests that the threshold for symptom development appears to be significantly lower when it comes to wireless meters compared with that for other wireless devices.

Of an initial 142 people who had formally registered their adverse health effects from smart meters related to the current study, 92 consented to participation. The author considers this number to be significant and most likely to represent the tip of the iceberg in terms of total numbers. Underestimation could be caused by the fact that people do not associate their symptoms with smart meter exposure when the symptoms are not severe or do not occur concurrently. In addition, this underdiagnosis may be caused by a lack of knowledge about the effects of wireless technologies on the part of the general population and the majority of the medical fraternity. The ongoing campaign of

Table 4. Summary of Scientific Reports

Title	Author(s)	Country	Year	Subject Matter and Findings	Recommendations
"Bibliography of Reported Biological Phenomena and Clinical Manifestations Attributed to Microwave and Radio-frequency Radiation"	Glaser[22]	United States	1971	Provides more than 2000 references on the biological responses to radiofrequency radiation	No specific recommendation; prepared for the Naval Medical Research Institute, Bethesda, Maryland; approved for unlimited public release
"Study on Health Effects of the *Shortwave Transmitter Station of* Schwarzenburg, Berne, Switzerland"	Altpeter, *Krebs, Pfluger,* et al[23]	Switzerland	1995	Notes marked *deterioration of sleep* quality in persons exposed to radio transmitter	No urgent protection measures; *review of current exposure* guidelines; further research
"Guideline of the Austrian Medical Association for the Diagnosis and Treatment of EMF-related Health Problems and Illnesses (EMF Syndrome)"	Austrian Medical Association's EMF Working Group[25]	Austria	2012	Discusses EMF-related problems and outlines clinical-management approach	Primary method of treatment of EMF-related health problems to consist of prevention or reduction of EMF exposure
"BioInitiative 2012–A Rationale for Biologically-based Exposure Standards for Low-Intensity Electromagnetic Radiation"	Prepared by 29 experts, edited by Sage & Carpenter[26]	Experts from more than 10 countries	2012	Reviews more than 1800 new scientific studies added to the BioInitiative Report 2007, which cited 2000 studies on adverse health effects from extremely low frequencies and radiofrequencies	New, biologically based public-exposure standard; precautionary approach to RF exposure levels
"Health Risks Associated with SmartMeters"	Namkung[31]	United States	2012	Indicates objective evidence supports EHS diagnosis; no scientific literature on health risks of smart meters	All available, peer-reviewed research data on EMF applicable to smart meters; governmental agencies to protect public health from involuntary exposure
"Smart Meters: Correcting the Gross Misinformation"	Carpenter et al[32]	Authors from a number of countries; published in Canada	2012	Summarizes long-term and short-term health effects of EMF exposure, in particular from smart meters	Application of Precautionary Principle, such as using wired meters
"Electromagnetic and Radiofrequency Fields Effect on Human Health"	Dean, Rea, Smith, Barrier (American Academy of Environmental Medicine)[17]	United States	2012	Discusses different types of radiation and effect of the increasing use of wireless technology on human health	Immediate caution on smart-meter installation; further research on effects of EMF and RF exposure; use of safer technology, including for smart meters

Abbreviations: EMF = electromagnetic field; RF = radiofrequency; EHS = electromagnetic hypersensitivity syndrome.

the state government and power distributors to portray smart meters as safe has also contributed to this lack of knowledge. Even when people believe that their new symptom(s) are caused by smart meters, some are not able to report or register their symptoms because they have no Internet access, and of those who do, not all are aware of Web sites or ways to make reports.

Limitations of Current Study

The main limitation of the current study is that, being a case series, it is a descriptive, retrospective study that does not have a control arm and can therefore help formulate a new hypothesis, but can only make limited statements on the causality of correlations observed.

Another limitation, which is specific to this type of noninterventional analysis of existing nonidentifiable data, is that the author was not able to contact individual case studies and was therefore unable to clarify or add to the information given by them. For the same reason, the author was also unable to follow up these cases longitudinally, which is something that could have potentially yielded valuable information.

CONCLUSIONS

This case series has discussed the most commonly reported symptoms from wireless smart meters. Although some of these symptoms are also reported in relationship to other environmental exposures, such as proximity to airports

or wind turbines, Victorians in this report claimed a direct chronological association between exposure to wireless smart meters and symptom development. A look at the place of residence of people reporting symptoms does not suggest a link to any possible environmental factors that are geographically specific. Seasonal factors are also excluded, because the reporting period stretched over all 4 seasons. The effect of these symptoms on people's lives is far-ranging, from stress, financial problems, and unnecessary investigations to needing to move out of one's home and even to another state.

The author of the current study offers the hypothesis that some people can develop symptoms from exposure to the radiofrequency fields of wireless smart meters. This hypothesis cannot be disproven without further assessment of the affected individuals and the electromagnetic fields in which they live. An evidence-based approach, such as the one used in all other areas of medicine, must be applied, which would mean the establishment of a postrollout surveillance study and funding for further research into the particular effects of wireless smart meters, in conjunction with research into the short-term and long-term consequences of EMR exposure. Until more knowledge is accumulated and until this type of wireless technology can be proven safe, the author believes that communities should use a cautionary approach, asking for a moratorium on deployment of wireless smart meters and smart grids and for the use of safer technologies for smart meters, such as hard-wiring, fiber optics, or other nonharmful methods of data transmission, including reading of meters by meter readers. Living in a wireless smart grid makes the Austrian Medical Association's recommendation to "take all reasonable measures to reduce exposure to electromagnetic fields" impossible to implement.

Dr Maisch's article title, "Smart Meter Health Concerns: Just a Nocebo (Harmless) Effect or an Emerging Public Health Nightmare?", resonates strongly with the Victorian experience so far. This question is very pertinent and one that must be urgently answered.

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APPENDIX Y

Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms

Martin L. Pall

CONTENTS

1 INTRODUCTION TO MULTIPLE CHEMICAL SENSITIVITY (MCS)

Multiple chemical sensitivity (MCS) is a complex disorder with cases often apparently initiated by chemical exposure. Following initiation of illness, people with MCS report sensitivity or intolerance to low levels of a wide spectrum of chemicals. The reported symptoms of chemical exposure are diverse and variable from one patient to another, but include pain, especially headache pain, muscle and joint pain, confusion, cognitive dysfunction, asthma-type symptoms, rhinitis, sleep disturbances, fatigue and even such psychiatric symptoms as anxiety and depression and infrequently rage. In the Sorg (1999) review, a total of 41 different symptoms are listed, many of which occur only in a minority of sufferers. Among the more common symptoms following chemical exposure in MCS patients are extreme fatigue, headache, gastrointestinal problems, dizziness, anxiety, depression, upper airways irritation, muscle and joint pain, and memory and concentration difficulties (Sorg, 1999). It should be noted that six out of nine of these symptoms can probably be ascribed to central nervous system (CNS) changes. Changes in brain function have been shown in brain positron emission tomography (PET) scan studies of MCS patients (Heuser and Wu, 2001; Hillert *et al.*, 2007), single photon emission computed tomography (SPECT) scan studies (Simon *et al.*, 1994; Heuser *et al.*, 1994; Fincher *et al.*, 1997a; 1997b) and electroencephalography (EEG) studies (Bell *et al.*, 1999b; Muttray *et al.*, 1995; Ross *et al.*, 1999; Schwartz *et al.*, 1994; Fernandez *et al.*, 1999; Lorig *et al.*, 1991; Lorig, 1994). Miller (2001) listed 74 such symptoms that she divided into neuromuscular, head-related, musculoskeletal, gastrointestinal, cardiac, affective, airway, cognitive and other. It is likely, as is discussed below, that the profound variation in symptoms, both qualitative and quantitive among sufferers, may be due to a local mechanism whose tissue distribution may vary among different sufferers.

MCS has been given a number of different names, including chemical sensitivity, multiple chemical sensitivities, chemical intolerance and toxicant-induced loss of tolerance (TILT). The TILT name (Miller, 2001) emphasizes the observation that most cases of MCS follow exposure to one or more chemicals and the basic hypothesis that dominates much of this literature is that chemical exposure initiates cases of illness (Ashford and Miller, 1998). The Cullen case definition requires such an initiating exposure for a case to be considered to be MCS (Cullen, 1987). Furthermore, the spectrum of chemicals reported to initiate cases of MCS is similar or identical to the spectrum of chemicals to which people with MCS appear to be sensitive, suggesting that the mechanism of action of both initiating chemicals and those eliciting sensitivity responses may be similar or identical. Some researchers, mainly those who have advocated some type of psychogenic cause for MCS, have advocated calling it idiopathic environmental intolerance (IEI) and have questioned whether chemicals are in fact initiators of MCS cases.

The phenomenon of MCS has been often ignored in the toxicological literature, largely because up until recently, a series of challenging questions about MCS have been unanswered. From a toxicological perspective, the most relevant such questions include the following:

- How can such diverse chemicals be implicated in initiating cases of MCS and, having initiated sensitivity, subsequently produce responses at very low exposures?
- How can one produce high-level sensitivities to such a broad range of chemicals, with many MCS patients being estimated as being on the order of 1000-fold more sensitive than normal?
- Are there plausible physiological mechanisms that may be expected to produce the above-described pattern of sensitization?
- If so, is there any evidence supporting these mechanisms in MCS?

I will discuss each of these four questions in this review, as well as at least eight other, perhaps equally puzzling, questions about MCS.

2 DIVERSE CHEMICALS ARE REPORTED TO APPARENTLY INITIATE CASES OF MCS

There have been dozens of papers reporting a pattern of chemical exposure preceding development of cases of MCS, typically one high-level exposure or multiple

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lower-level exposures (Ashford and Miller, 1998; Sorg, 1999). Pall (2007a, Chapter 13) cited 24 distinct studies reporting chemical exposure preceding development of many cases of MCS and Miller (2000) cited 12 additional such studies and still additional studies are cited below in this section. The types of chemicals most commonly involved are the volatile organic solvents (sometimes described as volatile organic compounds (VOCs)) and pesticides, especially organophosphorus and carbamate pesticides (Ashford and Miller, 1998; Sorg, 1999; Rea, 1992; Ziem and McTamney, 1997). There are a number of additional papers reporting that exposure to organic solvent chemicals that outgas in 'sick building syndrome' situations also appear to initiate cases of MCS (Welch and Sokas, 1992; Davidoff and Keyl, 1996; Miller *et al.*, 1999; Hodgson, 2000; Arnold-Llamosas *et al.*, 2006; Redlich *et al.*, 1997; Ross, 1997). Berglund *et al.* (1984) reported that apparently chemically sensitive individuals reacted to air piped in from such a 'sick building' in blinded fashion, but did not react to uncontaminated air, suggesting that chemicals in the 'sick building' air were causal in generating the reactions. Many of the chronic symptoms of the surviving victims of the Bhopal disaster may be ascribed to MCS (Ross, 2000; Nemery, 1996).

When Miller and Mitzel (1995) wanted to compare cases of MCS apparently initiated by two different classes of chemicals, they chose cases from recently remodelled sick buildings (volatile organic solvent exposure) and compared those with cases apparently initiated by organophosphorus pesticides. In their highly cited paper, Miller and Mitzel (1995) found these two groups of MCS patients were similar, but not identical to each other, with some differences in symptom patterns and some differences in average severity between the two groups. Because MCS cases apparently initiated in these two ways are so common, it was relatively easy for Miller and Mitzel to find substantial numbers of patients of the two types to study.

Two of the most interesting sick-building cases occurred in the then recently remodelled Environmental Protection Agency building in Washington DC, in which approximately 200 people were apparently sickened with cases of MCS (Miller, 2001) and in Brigham and Women's Hospital in Boston, part of the Harvard Medical School complex. The latter case was described in detail in a US government publication (Kawamoto *et al.*, 1997), where subsequent decreases in chemical usage and increases in air flow led to substantial decreases in new cases of chemical sensitivity and related illnesses, suggesting a causal relationship between chemical exposure and illness initiation. Ashford and Miller (1998) suggested that the decreases in required air flow in buildings in the USA, as a response to the energy crises of the 1970s, led to major increases in the incidence of MCS. In an important study, occupational medicine patients differed from general patients in responses to the Toronto MCS questionnaire in much the same way that self-identified MCS patients did, albeit to a lesser extent (McKeown-Eyssen *et al.*, 2001), suggesting that chemical exposure in the occupational environment may initiate substantial numbers of MCS cases. Zibrowski and Robertson (2006) reported increased prevalence of MCS-like symptoms among laboratory technicians exposed to organic solvents, as compared with similar laboratory technicians with no apparent exposure. An epidemiological study, estimating the prevalence of MCS in various occupations, including those expected to have substantial chemical exposure to classes of chemicals implicated in MCS as a consequence of the occupation, reported increased prevalence of MCS in several occupations involving such chemical exposure, again suggesting a causal role of chemical exposure (Maschewsky, 1996; 2002). Yu *et al.* (2004) found high prevalences of MCS-like symptoms among solvent-exposed printing workers, as compared with non-chemically exposed controls. There are at least a dozen studies reporting high prevalences of reactive airways disease, a common aspect of MCS, among workers occupationally exposed to organic solvents.

In addition to organic solvents and related compounds and the organophosphorus and carbamate pesticides, there are additional classes of chemicals that are reported to apparently initiate cases of MCS. These include the organochlorine pesticides chlordane, lindane, dieldrin and aldrin (Corrigan *et al.*, 1994; Ziem and McTamney, 1997; Lohmann *et al.*, 1996; Wallace, 1995; Pröhl *et al.*, 1997) and also a variety of pyrethroid pesticides (Corrigan *et al.*, 1994; Lohmann *et al.*, 1996; Altenkirch, 1995; Altenkirch *et al.*, 1996). Lindane has been shown to initiate animal models of MCS (Gilbert, 2001; Cloutier *et al.*, 2006) as has another $GABA_A$ (γ-aminobutyric acid A receptor) antagonist (Adamec, 1994). There are reports that hydrogen sulfide exposure can initiate cases of MCS-like illnesses (Kilburn, 1997; 2003). Donnay (1999; 2000) has reviewed evidence suggesting that carbon monoxide exposure may be able to initiate cases of MCS. Furthermore, mercury and mercurial compounds are also reported to apparently initiate some cases of MCS (Eneström and Hultman, 1995; Latini *et al.*, 2005; Brent, 2001; Stejskal *et al.*, 1999) and dental assistants working with mercury amalgams were reported to have higher prevalences of neurological symptoms including MCS-like symptoms (Moen *et al.*, 2008).

Mould exposure is also suggested to initiate cases of MCS in sick-building situations characterized by mould-infested buildings (Redlich *et al.*, 1997; Claeson *et al.*, 2002; Lee, 2003; Mahmoudi and Gershwin, 2000; Straus *et al.*, 2003). Here, we cannot say much about what mycotoxins may be involved, although there is some evidence that *Stachybotrys* moulds may be often involved (Mahmoudi and Gershwin, 2000; Hintikka, 2004; Straus *et al.*, 2003; Pestka *et al.*, 2008). Hirvonen *et al.* (1999) reported that mouldy 'sick' buildings produced increases

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in nitric oxide (NO) and inflammatory cytokines in nasal passages of exposed people and similar responses were also reported in the lungs of similarly exposed people (Akpinar-Elci *et al.*, 2008). NO and inflammatory cytokines are important aspects of the MCS mechanism developed in this review.

3 A COMMON RESPONSE TO INITIATING CHEMICALS: INCREASED NMDA ACTIVITY

One of the great puzzles about MCS is how can such a diverse group of chemicals produce a common biological response? In fact, one of the MCS skeptics, Ronald Gots (1996) has argued that MCS cannot possibly be a physiological response to chemicals because the diverse chemicals implicated in MCS cannot possibly produce a common response in the human body. Clearly one needs to find such a common physiological response in order to develop a compelling model of the mechanism of MCS. An important role for excessive NMDA (*N*-methyl-D-aspartate) receptor activity in MCS was first suggested by Thomas (1998) and by Dudley (1998). Pall (2002) argued that elevated NMDA[a] receptor activity is likely to have a key role in MCS and that chemicals were likely to act, in most cases indirectly, to increase such activity. There were several types of evidence reviewed in that paper suggesting a role of elevated NMDA activity:

1. MCS patients are hypersensitive to monosodium glutamate and glutamate is the common physiological agonist of the NMDA receptors.
2. In studies of the genetic polymorphism of the CCK-B gene, the allele of the gene that acts indirectly to produce higher NMDA activity was associated with increased prevalence of MCS (Binkley *et al.*, 2001; see Pall, 2002 for discussion).
3. The NMDA antagonist, dextromethorphan was reported from both clinical observations and anecdotal reports to lower reactions to chemicals in MCS patients.
4. Bell and others have proposed that neural sensitization has a key role in MCS and the probable mechanism for such neural sensitization, called long-term potentiation (LTP), is known to involve increased NMDA activity.
5. Elevated NMDA activity has been shown to play an essential role in several animal models of MCS.
6. Elevated NMDA activity appears to play a role in such related illnesses as fibromyalgia (FM), chronic fatigue syndrome (CFS) and post-traumatic stress disorder (PTSD), with the most extensive evidence for such a role being found in FM (Pall, 2006; Pall, 2007a).

It should be noted that numbers 2 and 5 above suggest that chemicals initiating cases of MCS may act to increase NMDA activity and number 3 suggests that chemicals acting in those already sensitive may also act to increase NMDA activity. In fact, these two sets of chemicals are similar or identical to each other (Ashford and Miller, 1998) so it should not be surprising if they both may act via the same mechanism(s). All of these considerations raise the question about whether there are known mechanisms by which the several classes of chemicals implicated in MCS may act to increase NMDA activity?

3.1 Pesticides and NMDA Stimulation

In that Pall (2002) review, evidence was discussed showing that organophosphorus and carbamate toxicants (including pesticides) can act to produce increases in NMDA activity via the following pathway: these toxicants are acetylcholinesterase inhibitors, producing an increase in acetylcholine, which stimulates the muscarinic receptors, which produce, in turn, increased glutamate release leading to increased NMDA receptor stimulation, as well as stimulating other glutamate receptors (see diagram in **Figure 1**). There are a large number of studies showing that toxic effects of organophosphorus toxicants in mammals can be greatly lowered by using NMDA antagonists (Dekundy *et al.*, 2007; Lallement *et al.*, 1998; Martin and Kapur, 2008), showing that such increased NMDA activity has a substantial role in producing the response to these toxicants.

What about other pesticides and other groups of implicated chemicals? Let us take the different classes of chemicals one at a time. The organochlorine pesticides, chlordane, lindane, dieldrin and aldrin have all been shown to lower $GABA_A$ receptor activity (Gant *et al.*, 1987; Corrigan *et al.*, 1994; Cassidy *et al.*, 1994; Brannen *et al.*, 1998; Narahashi *et al.*, 1995) and this, in turn is well known to produce elevated NMDA activity (Blaszczak and Turski, 1998; Watanabe *et al.*, 1995; Tusell *et al.*, 1992), see **Figure 1**. In fact these same citations show that seizure activity produced by these $GABA_A$ antagonists, including these pesticides, is lowered or blocked by NMDA antagonists, showing that the elevated NMDA activity produced by such toxicants has a key causal role in the mechanism of seizure generation. Because MCS involves the action of short-term stressors producing chronic illness, it may be of special interest that this pathway produces chronic changes in brain function that can be blocked by short-term interruption of the pathway (Kaindl *et al.*, 2008).

Pyrethroid pesticides, which also initiate cases of MCS, act to produce long-term sodium-channel opening (Narahashi *et al.*, 1995; Valentine, 1990; Wu and Liu, 2003;

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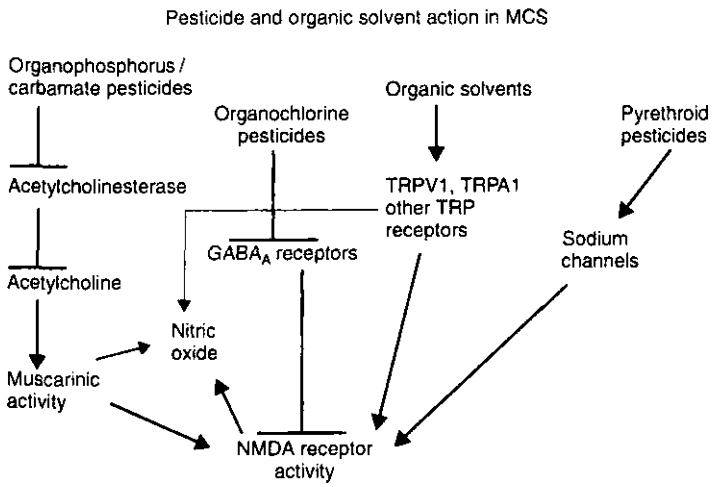

Figure 1 Pathways for action of pesticides and organic solvents. Each chemical class implicated in the initiation of cases of MCS can act along a distinct pathway to generate increases in NMDA activity, as shown in the figure. Each arrow represents a mechanism by which one parameter stimulates another. Some inhibitory (negative) interactions are also indicated. Both the organophosphorus/carbamate toxicants and the organochlorine pesticides have double-negative interactions. Such negative interactions, together with the arrows in the figure, indicate that the each of the four classes of compounds acts along one of these pathways, leading to an increase in NMDA activity.

Bradberry *et al.*, 2005; Proudfoot, 2005). This in turn, produces increased NMDA stimulation (Wu and Liu, 2003; Yu, 2006; Doble, 1996), see **Figure 1**. Type II pyrethroids also act as $GABA_A$antagonists (Valentine, 1990) and may be expected, therefore, to also act along the same pathway impacted by the organochlorine pesticides, and thus lead to increased NMDA activity along that pathway as well.

3.2 Organic Solvents, TRP Receptors and NMDA Stimulation

Clearly the greatest puzzle of chemical activity in MCS is how does the huge family of organic solvents act to initiate cases of MCS or elicit sensitivity symptoms in those who have become sensitive? These chemicals are the predominant set of chemicals that trigger reactions on a day-to-day basis in MCS patients. They have also been referred to as volatile organic chemicals and yet it is clear that nonvolatile chemicals ingested or absorbed through the skin can produce reactions, so the volatility is important due to the most common mode of exposure, inhalation, rather than being an essential part of the mechanism of sensitivity. I will refer to this extremely large group of chemicals as organic solvents, even though that does not cover this entire spectrum of chemicals.

Pall and Anderson (2004) argued that the probable target for such organic solvents in MCS is the vanilloid (transfer receptor potential) TRPV1 receptor, and presented 12 distinct types of evidence arguing for such a TRPV1 role in MCS. That paper was extensively documented with 222 citations and while specific references are provided some of this discussion, for the rest the reader is referred back to that paper. One type of evidence that we presented is that some solvents well known to be involved in MCS, such as formaldehyde and other aldehydes, were quite active TRPV1 agonists, and a variety of alcohols are vanilloid agonists and may be converted into still more active aldehydes via alcohol dehydrogenases in the body. It is known that capsaicin, the classic TRPV1 agonist, requires both hydrophobic regions and a hydrogen-bonding group in order to act as an agonist, suggesting that strictly hydrophobic solvents might require cytochrome P450 metabolism in order to act as a vanilloid agonist, or might act synergistically with a solvent that does have a hydrogen-bonding group. There is evidence from animal models of MCS, which are also animal models of Gulf War illness, for such synergistic interactions of organic solvents and related compounds (Research Advisory Committee on Gulf War Veterans Illnesses., 2004): fully 28 studies of synergistically acting stressors, most, but not all, of which were organic compounds, were reviewed in that document.

Some mycotoxins are known TRPV1 agonists, so it is possible that the role of moulds in MCS may be explained through the role of the TRPV1 receptor. Chemical sensitizers, including toluene diisocyanate (TDI) and eugenol, which produce local sensitivity to a wide range of chemicals, are known TRPV1 agonists. MCS patients often report sensitivity to chlorine gas from swimming pools or from drinking water, and chlorine acts as a TRPV1 agonist *in vivo* (Morris *et al.*, 2005), producing

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an irritant response. TRPV1 stimulation produces neurogenic inflammation and also reactive airways disease (Geppetti *et al.*, 2008; Jia and Lee, 2007; Planells-Cases *et al.*, 2005; Costa *et al.*, 2008), often called reactive airways dysfunction syndrome (RADS), a form of asthma showing reaction to a spectrum of chemicals similar or identical to those involved in MCS. Both RADS and neurogenic inflammation are often aspects of MCS cases (Meggs, 1994; 1997).

Millqvist and her colleagues have published a series of papers showing that MCS patients are hypersensitive to capsaicin, the classic TRPV1 agonist, again providing support for a TRPV1 role in MCS (Johansson *et al.*, 2002; Millqvist, 2000; Ternesten-Hasséus *et al.*, 2002; Millqvist *et al.*, 2005; 2008). Many studies have shown that capsaicin treatment leads the TRPV1-stimulated cells in several regions of the body to release glutamate neurotransmitter, leading in turn to NMDA stimulation (10 such studies are cited in Pall and Anderson, 2004). These studies provide further support for the contention that each class of chemicals involved in MCS leads to increased NMDA stimulation.

There is an additional parallel between MCS and TRPV1 stimulation. MCS patients have a phenomenon known as desensitization or masking, such that low-level chronic or repeated chemical exposure leads to decreased reactivity to chemical exposure (Ashford and Miller, 1998). This may be the basis of using low-level chemical exposure to treat MCS patients (Weaver, 1996; Rea, 1997). Low-level chronic or repeated exposure to many TRPV1 agonists leads to lowered TRPV1 activity through a complex series of changes involving increased intracellular calcium levels, complex protein phosphorylation control and probably receptor internalization (Szallasi and Blumberg, 1999; Itagaki *et al.*, 2004). Thus the desensitization/masking phenomenon found in MCS may be produced, to part or in whole, by this lowered TRPV1 activity.

While there are many properties suggesting a TRPV1 role in MCS, it is clear now that some of the interpretations given by Pall and Anderson (2004) to some of the relevant data were too narrow. It was argued, for example, that TRPV1 was primarily responsible for the sensory irritation (SI) response, a response elicited by chemicals including alkanes, alkyl benzenes, halogenated benzenes, halogenated alkylbenzenes, alcohols, ketones, ethers, aldehydes, formaldehyde, isocyanates and chlorine (Nielsen, 1991; Alarie *et al.*, 1998; Inoue and Bryant, 2005; Cometto-Muñiz and Abraham, 2008), a broad range of chemicals also implicated in MCS. It is now clear that this SI response involves as major players, other members of the TRP family of receptors, not just TRPV1. Specifically Bíró *et al.* (2007) discuss evidence for a role of TRPA1, TRPM8 and TRPV2, 3 and 4 receptors in this response, as well as TRPV1. Bautista *et al.* (2006) implicated specifically the TRPA1 receptor in the response to several environmental irritants. Many of the TRP receptors have roles in responding to xenobiotics (Nilius, 2007) and while our knowledge of such roles has been expanding rapidly in recent years, it is still, no doubt, incomplete. Neurogenic inflammation and reactive airways disease aspects of MCS, discussed above and below, are produced, not only through TRPV1 stimulation, but also through the action of other TRP receptors (Geppetti *et al.*, 2008; Jia and Lee, 2007). Whereas some chemical sensitizers act as TRPV1 agonists, sensitizers can also act as TRPV3 agonists (Xu *et al.*, 2006).

Others have argued for a central role for the SI response and the receptors involved in that response in MCS (Skov and Valbjorn, 1987; Meggs, 1993; 1997; Anderson and Anderson, 1999a; 1999b; 2003; Millqvist *et al.*, 1999; Millqvist, 2000; 2008; Nordin *et al.*, 2005).

In Pall and Anderson (2004), we used the desensitization response produced by low-level chronic exposure to capsaicin or other bona fide TRPV1 agonists to assess whether some solvents that had never been tested as possible TRPV1 agonists might have such activity. The reasoning was that if responses to a chemical were reported to be substantially reduced after low-level capsaicin treatment, that chemical should be labelled as a probable TRPV1 agonist, because the response to it was lowered along with TRPV1 desensitization. It is clear now that desensitization of one TRP receptor is often accompanied by desensitization of others. For example, TRPV1 and TRPA1 can undergo cross-desensitization (Rohacs *et al.*, 2008; Ruparel *et al.*, 2008) and TRPM8 and TRPA1 desensitization can also be produced in parallel (Zanotto *et al.*, 2008). In another study, a series of TRPC receptors were desensitized together by a receptor internalization process (Itagaki *et al.*, 2004). It seems likely, therefore, that some organic solvents that were argued to be probable TRPV1 agonists, as suggested earlier in this paragraph, may well be agonists of other TRP family receptors.

Of the other TRP family receptors, the one most likely to have a substantial role in MCS, based on current evidence, is TRPA1. TRPA1 is responsible for the activity of a number of different sensory irritants (Bautista *et al.*, 2006; Gerhold and Bautista, 2008), with TRPV1 being responsible for others. For a number of such irritants, the chemicals react by reversible covalent modification with the TRPA1 receptor (Hinman *et al.*, 2006). Among the TRPA1 agonists are certain aldehydes, including acrolein and aldehydic components of cigarette smoke (Andrè *et al.*, 2008; Simon and Liedtke, 2008) and MCS patients are commonly known to be sensitive to cigarette smoke. Formaldehyde which is commonly involved in initiating cases of MCS was shown in a recent study to act via the TRPA1 receptor in a model of inflammatory pain, rather than acting via the TRPV1 receptor (McNamara *et al.*, 2007).

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Activation of the TRPA1 receptor has been reported to lead to the release of the neurotransmitter glutamate, leading in turn, to increased NMDA activity (Kosugi *et al.*, 2007; Ding *et al.*, 2008). Given that such increased NMDA activity is also produced by TRPV1 receptor stimulation, as discussed above, it should not be surprising that organic solvent-produced changes in the nervous system can, in many cases, be blocked or lowered by using NMDA antagonists. For example, there are a number of responses to formaldehyde exposure that have been shown to be greatly lowered by NMDA antagonists (Coderre and Melzack, 1992; McMahon *et al.*, 1993; Wiertelak *et al.*, 1994; Wang *et al.*, 1999).

In conclusion, there are compelling similarities between the diverse organic solvents and related chemicals involved in MCS and the diverse organic chemicals involved in the SI response. It seems likely that the TRP receptors are involved in both, with the two most likely members of this receptor family to be involved in chemical responses in MCS and in SI, based on current evidence, being the TRPV1 and TRPA1 receptors, both of which can produce an increase in glutamate release and consequent NMDA stimulation. These various data suggest, therefore, that the proposed pattern of chemical involvement in MCS acting through increased NMDA activity is likely to be sustained for the organic solvent group of chemicals.

Before leaving this issue of the apparent roles of TRP receptors in MCS, I need to discuss the TRPM2 receptor that may have a role in amplifying responses in MCS. The TRPM2 receptor is known to be stimulated by oxidants, including hydrogen peroxide, with much of the stimulation being produced by adenosine diphosphate (ADP)-ribose, a signalling molecule whose levels can be greatly increased by oxidants (Kühn *et al.*, 2005; Fonfria *et al.*, 2004; Wilkinson *et al.*, 2008; Naziroglu, 2007; Buelow *et al.*, 2008; Lange *et al.*, 2008). The pathway of synthesis of poly(ADP)-ribose is as follows: oxidants produce nicks in DNA strands in the nucleus of cells which can lead, in turn, to a massive stimulation of poly(ADP)-ribose polymerase activity, producing poly(ADP)-ribosylation of chromosomal proteins. When this poly(ADP)-ribose becomes subsequently hydrolysed, it produces free ADP-ribose which acts as a signalling molecule. One oxidant that is very active in this process is peroxynitrite ($ONOO^-$) (Pacher and Szabo, 2008), a molecule that the author has argued (see below) has a key role in MCS and related illnesses, and whose synthesis is greatly increased by NMDA stimulation (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003). Consequently, TRPM2 activity is predicted to be elevated in MCS and to be stimulated by chemical exposure. TRPM2 may both directly and indirectly leading to increases in NO and $ONOO^-$ production, thus amplifying the already elevated levels of these compounds (see Yamamoto *et al.*, 2008 for discussion). There is some evidence that another TRP receptor, TRPM7, may also have a role in this process (Miller, 2006). The role of TRPM2 and possibly 7 may be one of several interacting mechanisms that may lead to the extraordinary chemical sensitivity reported in MCS patients.

There is evidence that other TRP receptors are elevated in response to oxidants and products of oxidative stress biochemistry, including TRPV1 and TRPA1 (Taylor-Clark *et al.*, 2008; Bessac *et al.*, 2008; Andersson *et al.*, 2008; Trevisani *et al.*, 2007; Puntambekar *et al.*, 2005; Schultz and Ustinova, 1998; Ustinova and Schultz, 1994), but these effects may be more modest than those on TRPM2. The effects on TRPV1 receptors makes them more susceptible to stimulation by their effectors, whereas with TRPM2, oxidative stress acts to open the receptor channel independently of any effector and so may produce a greater physiological response under many circumstances.

3.3 Other Apparent Initiators and Summary of NMDA Role

Three other apparent initiators of cases of MCS were discussed above, carbon monoxide, hydrogen sulfide and mercury. Do any of these act to increase NMDA activity?

Carbon monoxide has been reported to produce such increased NMDA activity and NMDA antagonists block or lower the toxic responses to carbon monoxide exposure (Thom *et al.*, 2004; Liu and Fechter, 1995; Penney and Chen, 1996; Ishimaru *et al.*, 1992). Hydrogen sulfide can also produce increased NMDA activity and again its toxic effects are lowered by NMDA antagonists (Cheung *et al.*, 2007; Qu *et al.*, 2008; Kamoun, 2004). Mercury, acting through its metabolic product methylmercury, also acts to produce increases in NMDA activity, and again methylmercury toxicity is lowered by NMDA antagonists (Juárez *et al.*, 2005; Allen *et al.*, 2002; Faro *et al.*, 2002; Miyamoto *et al.*, 2001; Zhang *et al.*, 2003; Rossi *et al.*, 1997). Methylmercury acts to produce such increased NMDA activity, at least in part, by lowering the transport of glutamate, the most important physiological NMDA agonist (Juárez *et al.*, 2005; Allen *et al.*, 2002).

In summary, then, we have evidence that all seven classes of compounds reported to initiate cases of MCS can each act to increase NMDA activity (**Figure 1**). At least for some members of each class under some conditions, NMDA antagonists can lower the toxic responses to each of them. While evidence linking any one of these to increased NMDA activity may be coincidental, the pattern of evidence for all seven strengthens the argument that increased NMDA activity is not likely to be coincidental. When coupled to the six types of additional evidence, discussed at the beginning of this section, on the apparent NMDA role in MCS, one can argue that there is very substantial evidence, not only that increased

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NMDA activity has a role in MCS, but also that chemicals are likely to act indirectly by increasing such NMDA activity.

There is extensive evidence that increased NMDA activity produces increases in NO and also its oxidant product $ONOO^-$ (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003), and it will be argued below that all three of these, NMDA activity, *NO* and *$ONOO^-$*, are likely to have key roles in MCS.

4 GENETIC EVIDENCE FOR CHEMICAL EXPOSURE BEING CAUSAL IN MCS

The pattern of chemical exposure preceding cases of MCS and the common mode of action of these chemicals in increasing NMDA activity strongly suggests causality of those exposures. However, one would like to have independent confirmation of causality. Such independent confirmation has come from genetic studies of susceptibility to MCS. There have been three such studies, each providing evidence that chemicals have causal roles in initiating cases of MCS (summarized in **Table 1**).

The first of these to be published was a study by Haley *et al.* (1999) on Gulf War veterans, including those suffering from what some have called Gulf War syndrome. There are several reports that the Gulf War syndrome veterans suffer from MCS or an MCS-like illness (Proctor *et al.*, 2001; Reid *et al.*, 2001; Miller and Prihoda, 1999; Thomas *et al.*, 2006) and there is also evidence that they suffer from such related illnesses as CFS and FM (Chapter 10 in Pall, 2001a; 2007a). The Gulf War veterans were exposed to over a dozen stressors that may have had a role in initiating their illnesses (Chapter 10 in Pall, 2007a), one of which was exposure to the organophosphorus toxicants, sarin and cyclosarin, which are both potent inhibitors of acetylcholinesterases. What Haley *et al.* (1999) report is that those carrying a form of the gene for PON1 that makes them less able to metabolize these neurotoxicants, were more susceptible to developing the neurological symptoms that comprise Gulf War syndrome. This provides substantial evidence that sarin/cyclosarin had a causal role in initiating cases of Gulf War syndrome and that those less able to detoxify these toxicants were therefore more susceptible to it. Mackness *et al.* (2000) showed that British Gulf War veterans with self-reported Gulf War syndrome tended to have lowered activity for the enzyme encoded by the PON1 gene, the paraoxonase enzyme, suggesting again a link to the organophosphorus toxicants. However, in this case, the low activity was not shown to be caused by the genetic polymorphisms of the PON1 gene, so the argument for causality is weaker than in the Haley *et al.* (1999) study. Another study from the same group (Mackness *et al.*, 2003), showed that among farmers using sheep dip containing an organophosphorus pesticide, farmers reporting chronic ill health tended to carry the the PON1 allele that produces lowered metabolism of that pesticide, as compared with farmers reporting good health. Unfortunately, MCS prevalence in these two groups of farmers was not studied.

Two studies somewhat similar to the Haley *et al.* (1999) study have been done, comparing a large number of civilian MCS sufferers with unaffected controls (**Table 1**). One was the Canadian study by McKeown-Eyssen *et al.* (2004) and the second, the German study by Schnakenberg *et al.* (2007). Each of these showed that three distinct polymorphic genes involved in the metabolism of chemicals otherwise implicated in initiation of MCS cases have a statistically significant influence on susceptibility (**Table 1**). In the Schnakenberg *et al.* (2007) study, there was an extremely high level of statistical significance for each of these three genes, so that the probability of getting these results by chance if there is no true correlation is less than one in 10^{11}. In total, in these three studies (Haley *et al.*, 1999; McKeown-Eyssen *et al.*, 2004; Schnakenberg *et al.*, 2007), five genes which help determine the rate of metabolism of chemicals previously implicated in MCS have been found to have statistically significant association with the prevalence of MCS; a sixth genetic polymorphism, for the gene *GSTT1* had a statistically significant effect only in conjunction with specific alleles of other implicated genes (**Table 1**). A recent similar, but much smaller study, roughly one quarter of the size of the McKeown-Eyssen *et al.* (2004) study and one ninth the size of the Schnakenberg *et al.* (2007) study, failed to find any statistically significant differences between apparent cases and controls (Wiesmüller *et al.*, 2008). Of the three larger studies, we have a pattern of evidence showing that genes that metabolize chemicals otherwise implicated in MCS initiation, have substantial influence on the susceptibility to develop MCS. These results support the inference that chemicals acting as toxicants cause many cases of MCS and that those chemicals must be in their toxic form in order to so act. Therefore, alleles of polymorphic genes that either decrease or increase the metabolism of these chemicals will influence the susceptibility to MCS.

One point that should be emphasized is that genetic studies of this type may well give different results with different populations, because populations may differ in either chemical exposure or in the frequencies of the polymorphic alleles in their gene pools. The genetic roles presumably involved here are what are often described as environment X gene interactions. An apparent example of this comes from studies of autism susceptibility where the susceptibility to autism in the USA and Romania, but not in Italy was apparently influenced by the PON1 gene (Pasca *et al.*, 2006; D'Amelio *et al.*, 2005). The differences were ascribed to the much higher use of organophosphorus pesticides in the USA and Romania than in Italy (Deth *et al.*, 2008).

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Table 1 Genetic polymorphisms influencing MCS susceptibility

Gene	Study	Function—chemical metabolism	Comments
PON1	H, M	Detoxification of organophosphorus toxicants	—
CYP2D6	M	Hydroxylation of hydrophobic compounds	Hydroxylation of compounds without hydrogen binding group may be expected to lead to greater activity as a TRPV1 agonist
NAT2	M, S	Acetylation	May produce more or less activity depending on the specific compound involved
GSTM1	S	Provide reduced glutathione for conjugation	Should increase detoxification and excretion
GSTT1	S	Glutathione conjugation	Should increase detoxification and excretion
GSTP1	S	Glutathione conjugation	Should increase detoxification and excretion; only statistically significant role was in conjunction with specific alleles of other genes

H, Haley *et al.* (1999); M, McKeown-Eyssen *et al.* (2004); S, Schnakenberg *et al.* (2007).

Are there any alternative interpretations to these genetic data, other than that the metabolism of these chemicals influences their role as toxicants in initiating cases of MCS? There is an alternative for two of the five genes, but not for the other three (**Table 1**). The gene for glutathione reductase has a very important role in the body's protective response to oxidants and oxidative stress, and the PON1 gene has a role in dealing with some of the lipid oxidation products produced by oxidative stress (Draganov and La Du, 2004), at least in lipoproteins in the blood. It follows that the roles of these two genes may be interpreted in an alternative way, but those of the other three genes cannot. The only consistent interpretation for these studies, taken as a whole, is that chemicals act as toxicants in the initiation of cases of MCS. By determining the rate of the metabolism of these chemicals, the genes help determine the incidence and prevalence of MCS.

There is strong, I would argue compelling, evidence that chemical exposure is causal in the initiation of many cases of MCS. What we need to do is to determine what physiological mechanisms are likely to be involved in such initiation. Furthermore, because low levels of similar, if not identical chemicals, trigger sensitivity responses in those already sensitive, similar pathways of action are likely to be involved in such low-level chemical responses.

5 MCS DOES NOT CENTRE ON AN OLFACTORY RESPONSE

The receptors that are implicated in the response to chemicals that are discussed above are not the olfactory receptors (Axel, 2005; Buck, 2005), and yet there have been many descriptions of MCS calling it a reaction to 'odours'. There is no evidence that the olfactory system has a central role here and there is considerable evidence against such a role. Ashford and Miller (1998) reviewed a number of studies where people with severe nasal congestion still reacted to chemical exposures. There are cases of MCS in people with no sense of smell, that is people suffering from anosmia (Doty, 1994). Many MCS patients report reacting at times when they could not smell any chemical odour. There have been three studies of patients where a nose clip was used to block off access of odourants to the nasal epithelia and those MCS patients still reacted to chemical exposure (Joffres *et al.*, 2005; Millqvist and Löwhagen, 1996; Millqvist *et al.*, 1999). In a recent study, regions of the brain that respond to odours were found to have lowered responses to odourants in MCS patients as compared with controls, not elevated responses (Hillert *et al.*, 2007). The author is not arguing that the olfactory mechanism is never impacted in MCS cases, but rather that it does not have any essential role in the chemical sensitivity process and should not be the focus of studies, when trying to assess responses of MCS patients to chemicals. We are looking at a response to chemicals, many of which have odours, not a response to odours.

6 PREVALENCE ESTIMATES

Sorg (1999) reviewed prevalence studies of MCS by concluding that 'prevalence of severe MCS in the United States is approximately 4%'. She also concludes that those with milder chemical sensitivity are about 15–30% of the US population. Several more recent studies of MCS prevalence provide additional information on this issue (Kreutzer *et al.*, 1999; Caress and Steinemann, 2003; 2004a; 2004b; 2005). Pall (2007a, Chapter 11) estimated that the prevalence of severe MCS in the USA was probably about 3.5%, with much larger numbers, perhaps 12–25% modestly affected. These

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estimates are slightly lower than the Sorg (1999) estimate. There have been few studies of MCS prevalence in other countries, but one study each from Canada (Joffres *et al.*, 2001), Germany (Hausteiner *et al.*, 2005), Sweden (Johansson *et al.*, 2005) and Denmark (Berg *et al.*, 2008) suggest prevalences of roughly 50–100% of those in the USA. All of these studies suggest that there is substantial impact of MCS on public health.

Caress and Steinemann (2003) estimated that 1.8% of the entire US population have lost their jobs due to chemical sensitivity, suggesting that many of the more severely affected may be unemployed or underemployed due to their MCS. There are no similar figures with regard to housing, but anecdotal reports suggest that the most sensitive often have great difficulty finding housing they can tolerate.

7 CASE DEFINITIONS

Probably the best review of and comparison of different case definitions for MCS was published by the Toronto group (McKeown-Eyssen *et al.*, 2001). In that review, they compared seven different proposed case definitions, those of Randolph (1965), Cullen (1987), Thomson *et al.* (1985), the National Research Council, Board on Environmental Studies and Toxicology, Commission on Life Sciences (1992), Ashford and Miller (1998), Nethercott *et al.* (1993) and the 1999 Consensus (MCS Consensus Conference, 1999). These differ from each other in various ways, most notably in whether they require that the symptoms be polysystemic, associated with multiple organs, whether cases must be chronic, whether cases must be acquired as a consequence of one or more chemical exposure events and whether sensitivity responses must be produced by multiple 'unrelated' chemicals.

McKeown-Eyssen *et al.* (2001) compared various groups of patients with each other for their fit to each of these case definitions, using the University of Toronto Questionnaire. They compared the case definitions in several ways using this data, but perhaps the most crucial comparison was how well a specific case definition was able to discriminate between environmental practice patients and general practice patients. By that criterion, the Nethercott *et al.* (1993) case definition and the 1999 Consensus were the best, giving the highest odds ratio in comparing these groups of patients, with both giving odds ratios of roughly 20. The 1999 Consensus case definition (MCS Consensus Conference, 1999) is the one currently used on the Wikipedia site discussion of MCS and may be currently the most widely accepted case definition.

It should be noted that comparing occupational medicine practice patients with general practice patients also produced high odds ratios by these two case definitions, albeit lower ones than did the previously discussed comparison, suggesting that occupational chemical exposure often causes cases of MCS, as defined by these two case definitions (McKeown-Eyssen *et al.*, 2001).

In contrast, the Cullen (1987) case definition only had an odds ratio of about eight, much lower than the Nethercott *et al.* (1993) or the 1999 Consensus case definition. The Cullen (1987) case definition has been criticized because of an additional, perhaps more important concern: it requires that 'no widely accepted test of physiologic function can be shown to correlate with symptoms'. However, as will be discussed below, there are a number of such tests that have been reported, tests of objectively measurable responses to low-level chemical exposure. This specific Cullen requirement may also be objected to, because it means, in effect, that we must stay perpetually ignorant of the aetiological mechanism of MCS. It should be discarded in the author's view, therefore, both for empirical and theoretical reasons.

There is one other issue that should be considered here, regarding what should and should not be part of an MCS case definition. Lacour *et al.* (2005) argued that only those patients who suffer from CNS-related complaints in response to chemical exposure should be considered to be true MCS patients. Such CNS-related symptoms include *headache, fatigue, confusion and cognitive dysfunction.* One possible rationale for this proposal is that Bell and others, as discussed below, have proposed a CNS mechanism for MCS involving neural sensitization in the brain, such that chemical exposure produces changes in synaptic sensitivities over substantial regions of the brain. Lacour *et al.* (2005) report that self-reported complaints of apparent MCS patients most commonly included CNS symptoms with symptoms derived from other regions of the body being less frequent. There is an argument for using a case definition for MCS that excludes patients without CNS-related symptoms.

Let us end this discussion by comparing the 1999 Consensus case definition (MCS Consensus Conference, 1999), listed immediately below with a couple of modifications that the author wishes to suggest for the reader's consideration:

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses often occur to multiple, chemically unrelated substances.
6. Symptoms involve multiple-organ symptoms.

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7.1 Suggestion #1

The main concern here is that it is not clear what chemically unrelated means. If it means that there is no relationship among these chemicals that can be challenged, because they all may act to produce increased NMDA activity. Describing them as being chemically diverse is more accurate. This should not change how the case definition is used in practice.

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses occur to multiple, chemically diverse substances.
6. Symptoms include those derived from multiple organs.

7.2 Suggestion #2

This suggestion includes the requirement for CNS involvement proposed by Lacour *et al.* (2005), and thus may correspond to what some consider to be the most classic aspect of MCS. I am sure that these two suggested case definitions will have much overlap in practice terms, because many will have symptoms derived from multiple organs, one of which is the brain.

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses occur to multiple, chemically diverse substances.
6. Symptoms include those derived from apparent CNS sensitivity, such as chemically elicited headache, fatigue, depression, anxiety, memory and concentration difficulties and confusion and cognitive dysfunction.

There are two additional issues that should be considered when deciding whether a particular patient should be allowed into a study on MCS:

- There is a huge variation in severity among different MCS patients and objective changes that may be obvious in looking at more severe MCS cases may be undiscernible when looking at more modestly affected patients. There is an argument, therefore, that one should limit admission to such studies to perhaps the most affected quarter of such patients, possibly using the Miller Quick Environmental Exposure and Sensitiviy Inventory (QEESI) questionnaire (Miller and Mitzel, 1995; Miller and Prihoda, 1999) to assess severity.
- Another issue is raised by the apparent local nature of chemical reactivity in MCS. If one is, for example, looking at responses in the lungs, one should distinguish between those patients who have asthma-type symptoms from those who do not. Similar divisions should be made for those who appear to be affected in other specific regions of the body.

8 The NO/ONOO$^-$ CYCLE MECHANISM AS THE AETIOLOGICAL MECHANISM FOR MCS AND RELATED ILLNESSES

The many puzzling features of MCS are thought to require a new disease paradigm in order to explain them. This argument has been made by Bronstein (1995), Miller (1999), Rowat (1998) and Arnetz (1999). Even the MCS skeptic Gots (1996) has argued that any physiological explanation for MCS requires such a new disease paradigm. Earlier in this review, an apparently convincing argument has been made that chemicals act as toxicants in MCS, acting via different pathways, but with each producing an increase in NMDA activity. It is well established that NMDA stimulation produces increases in NO and its oxidant product ONOO$^-$ (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003), so that any or all of these may be involved in generating the properties of MCS.

There are many puzzling features of MCS, each of which must be explained by any proposed new paradigm. One of these is the relationship between MCS and several other related chronic illnesses, including CFS and FM and even PTSD. Several research groups have argued for a common aetiological mechanism for two, three or all four of these illnesses (Miller, 1999; Ziem and Donnay, 1995; Buchwald and Garrity, 1994; Clauw and Chrousos, 1997; Bell *et al.*, 1998a; Wessely *et al.*, 1999; Yunus, 2001; Pall, 2001a; Pall and Satterlee, 2001; Cohen *et al.*, 2002; Buskila and Cohen, 2007). They are all comorbid with each other, they share a large number of symptoms and signs and they all share a common pattern of case initiation: cases of each are often initiated by a short-term stressor, exposure to which is followed by chronic illness. A fourth common

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Table 2 The stressors implicated in the initiation of these illnesses are summarized

Illness	Stressors implicated in initiation of illness
Chronic fatigue syndrome	**Viral infection, bacterial infection, organophosphorus pesticide exposure**, carbon monoxide exposure, ciguatoxin poisoning, physical trauma, severe psychological stress, toxoplasmosis (protozoan) infection, ionizing radiation exposure
Multiple chemical sensitivity	**Volatile organic solvent exposure, organophosphorus/carbamate pesticide exposure**, organochlorine pesticide exposure, pyrethroid exposure; hydrogen sulfide; carbon monoxide; mercury
Fibromyalgia	**Physical trauma (particularly head and neck trauma), viral infection**, bacterial infection, severe psychological stress, pre-existing autoimmune disease
Post-traumatic stress disorder	**Severe psychological stress**, physical (head) trauma

The stressors indicated in bold are the ones most commonly implicated for that specific disease/illness. It should be noted that the majority of such stressors are implicated in the initiation of more than one illness. Modified from the *author's web site, with permission.*

feature of these illnesses is that cases of each of them are stunningly variable from one patient to another, such that we need an explanation for this variability.

So what is needed, according to this point of view, is a common aetiological mechanism which explains both the similarities and the differences among cases of these illnesses. A detailed model of these four multisystem illnesses is presented below, focussing mainly on how it plays out in MCS, but also outlining how predicted variations may explain all four of these illnesses. Then and only then will the evidence be reviewed, supporting this model for MCS. Much of this discussion comes from the author's web site, with permission, and much of the evidence for it is provided in Pall (2007a) as well as other publications (Pall, 2000; 2002; Pall and Anderson, 2004).

Short-term stressors that are apparent initiators of these four illnesses are summarized in **Table 2**. You will note that each of these illnesses is initiated by multiple stressors and that these initiators include a variety of infections, physical trauma, severe psychological stress, ionizing-radiation exposure and neurotoxins such as ciguatoxin, in addition to the various chemical classes implicated in MCS initiation. These diverse stressors can all act to increase the levels of NO in the body (Pall, 2007a; 2007b; 2008; see above for MCS initiators). While each of these stressors implicated in initiation of one or more illnesses act to increase NO levels, several of these do *not* act via increased NMDA stimulation. Specifically, viral, bacterial and protozoan infections and also ionizing-radiation exposure act via induction of inducible nitric oxide synthase (iNOS) rather than acting via NMDA stimulation; NMDA receptor activation acts, in contrast, by increasing levels of intracellular calcium which stimulates, in turn, the two calcium-dependent nitric oxide synthases (NOSs), neuronal (nNOS) and endothelial (eNOS) (Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003). Thus it *may* be the case that MCS initiation requires increases in NMDA activity, but it is clear that CFS and FM initiation do not.

How then might short-term increases in NO produce a chronic illness? It can be argued that NO acts via its oxidant product $ONOO^-$ to initiate a complex biochemical vicious cycle that is then the cause of illness (Pall, 2000; 2001a; 2002; 2007a; 2007b), see **Figure 2**. So with each of these we have an initial cause, the short-term stressors, as well as on ongoing cause, with the ongoing cause being responsible for the properties of the chronic illness.

The vicious cycle initiated by these NO increases is shown in **Figure 2** and is centred on excessive levels of NO and its oxidant product $ONOO^-$. This vicious cycle is now being called the NO/$ONOO^-$ cycle (Pall, 2006; 2007a) (pronounced no, oh no!), based on the structures of NO and $ONOO^-$). Each of the arrows in **Figure 2** represents one or more mechanisms by which one element of the cycle acts to increase the levels of another element of the cycle. The chronic nature of these diseases is thought to be caused by the NO/$ONOO^-$ cycle, propagating itself over time through the mechanisms represented by these arrows. Most of the individual mechanisms in the cycle are based on very well-documented biochemistry (Pall, 2000; 2002; 2007a), supporting the plausibility of the cycle as a whole. Cycle elements, as shown in **Figure 2**, include not only NO and $ONOO^-$, but also superoxide, oxidative stress, the transcription factor NF-κB, the inflammatory cytokines (upper right hand corner), all three NOSs (iNOS, nNOS, eNOS), intracellular calcium levels and two types of receptors found in neuronal and non-neuronal cells, the NMDA receptor (Pall, 2007a) and the several of the TRP receptors (see above discussion; only the TRPV1 (vanilloid) receptor is shown in **Figure 2**). There are 22 distinct mechanisms that are represented by the various arrows, of which 19 are

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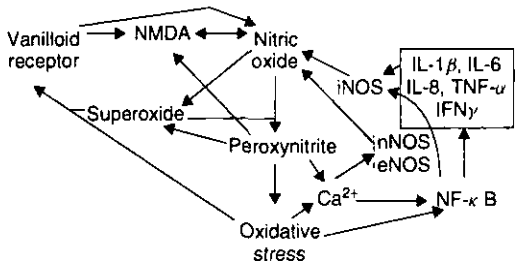

Figure 2 Vicious ($NO/ONOO^-$) cycle diagram. Each arrow represents one or more mechanisms by which the variable at the foot of the arrow can stimulate the level of the variable at the head of the arrow. It can be seen that these arrows form a series of loops that can potentially continue to stimulate each other. An example of this would be that nitric oxide can increase peroxynitrite, which can stimulate oxidative stress, which can stimulate NF-κB, which can increase the production of iNOS, which can, in turn increase nitric oxide. This loop alone constitutes a potential vicious cycle and there are a number of other loops, shown diagramatically in the figure that can collectively make up a much larger vicious cycle. The challenge in these illnesses, according to this view, is to lower this whole pattern of elevations to get back into a normal range. You will note that the cycle not only includes the compounds nitric oxide, superoxide and peroxynitrite, but a series of other elements, including the transcription factor NF-κB, oxidative stress, inflammatory cytokines (in box, upper right), the three different forms of the enzymes that make nitric oxide (the nitric oxide synthases iNOS, nNOS and eNOS), and two neurological receptors, the vanilloid (TRPV1) receptor and the NMDA receptor. (The figure and legend are taken from the author's web site with permission.)

well-established, well-accepted biochemistry and physiology (Pall, 2000; 2002; 2007a; Pall and Anderson, 2004).

Of the other three, there is substantial new evidence for each of them that was not available when that section of the Pall (2007a) book was written. The impact of NO in increasing superoxide generation from the electron-transport chain in mitochondria is now increasingly accepted (Moncada and Higgs, 2006). The effect of oxidants and oxidative stress in increasing activity of TRPV1 (vanilloid receptor) and several other the TRP receptors is also now supported by much more substantial evidence (see above discussion). And Chen *et al.* (2008) have recently provided more evidence on the impact of $ONOO^-$ on the electron-transport chain in the mitochondrion, producing increased superoxide generation. Chen *et al.* (2008) also provides important new evidence on the mechanism involved in producing this increased superoxide generation. Thus all three of the previously more weakly supported mechanisms out of the 22 are now considerably more strongly supported then they were 2.5 years ago. There is a massive amount of evidence supporting the existence of the individual mechanisms proposed to make up the $NO/ONOO^-$ cycle and the only truly original aspect to it is the simple assumption that it fits together in the way that one might assume it does, based on the individual mechanisms.

Much of the mechanism outlined in **Figure 2** is classic inflammatory biochemistry—the NF-κB actions, inflammatory cytokine induction, iNOS induction, leading to increased NO, $ONOO^-$ and oxidative stress, and consequent mitochondrial dysfunction—all of these are found in every inflammatory condition. This raises the question as to whether specific chronic inflammatory diseases, and there are dozens of them, may be $NO/ONOO^-$ cycle diseases?

There are two aspects of the $NO/ONOO^-$ cycle that are not apparent from **Figure 2**. Both add further evidence for important individual mechanisms, as well as the plausibility of the overall cycle:

1. $ONOO^-$, superoxide and NO all can act via known mechanisms to lower mitochondrial function and thus adenosine triphosphate (ATP) generation (Moncada and Bolaños, 2006; Keller *et al.*, 1998). $ONOO^-$ is known to attack a number of iron–sulphur proteins, including such proteins that have important roles in both the mitochondrial electron-transport chain and in the citric-acid cycle, and also leads to mitochondrial dysfunction through protein tyrosine nitration and other mechanisms (Radi *et al.*, 2002; Cassina and Radi, 1996; Keller *et al.*, 1998). $ONOO^-$ is also known to produce nicks in chromosomal DNA, leading in some cases to massive stimulation of poly(ADP)-ribosylation of chromosomal proteins, and because the precursor to such poly(ADP)-ribose synthesis is NAD, this can lead to massive depletion of NAD/NADH pools and consequent lowering of mitochondrial energy metabolism (Szabo, 2003; Moncada and Bolaños, 2006). Superoxide and NO also lower energy metabolism via distinct mechanisms. They both can produce lowered activity of the aconitase enzyme (Gardner *et al.*, 1997; Gardner, 1997; Castro *et al.*, 1994), as can $ONOO^-$. The cardiolipin in the inner membrane of the mitochondrion is very susceptible to lipid peroxidation and superoxide generated by the electron transport chain in the mitochondrion can indirectly produce major increases in such lipid peroxidation, leading to lowered activity of complexes I, III and IV and therefore lowered ATP generation (Paradies *et al.*, 2001; *et al.*, 2002; Musatov, 2006). NO is a competitive inhibitor of the enzyme cytochrome oxidase (complex IV) and can therefore lower the activity of the entire mitochondrial electron transport chain by lowering its terminal oxidase activity (Cassina and Radi, 1996; Galkin *et al.*, 2007). The lowered ATP generation produced by this combination of mechanisms is not only important in the generation

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of symptoms as a consequence of the NO/ONOO$^-$ cycle, but is also important as part of the proposed cycle itself: NMDA receptor activity is known to be activated by lowered availability of ATP, acting via two distinct mechanisms that are discussed below. Furthermore, the maintenance of low intracellular calcium levels involves much energy utilization via Ca^{+2}-ATPase and thus lowered ATP availability will tend to increase intracellular calcium levels, another predicted aspect of the NO/ONOO$^-$ cycle.

2. There are reciprocal interactions between ONOO$^-$ and a cofactor for the NOSs, tetrahydrobiopterin (BH4). ONOO$^-$ oxidizes BH4, leading to BH4 depletion and such depletion leads to what is called the partial uncoupling of all three NOSs (Pall, 2007b; Milstien and Katusic, 1999; Kohnen *et al.*, 2001; Kuhn and Geddes, 2003). The uncoupled NOSs generate superoxide in place of NO. Thus, in tissues and regions of cells with high NOS activity, partial uncoupling leads to adjacent enzymes generating NO and superoxide, thus leading to almost instantaneous synthesis of ONOO$^-$. In this way, partially uncoupled NOS enzymes can act collectively as ONOO$^-$ synthases (Delgado-Esteban *et al.*, 2002; Pall, 2007b). The ONOO$^-$ so generated will oxidize more BH4, thus leading to more partial uncoupling. This partial uncoupling may be central to the entire NO/ONOO$^-$ cycle leading to a shift in the ratio of NO to ONOO$^-$. That shift may be critical to the cycle in multiple ways, including generating increased activity of the transcription factor NF-κB; whereas ONOO$^-$ leads to activation of NF-κB, NO lowers NF-κB activity and thus the ratio of the two may be critical in determining the NF-κB regulatory response (Pall, 2007b).

Both of these aspects of the NO/ONOO$^-$ cycle are shown in **Figure 3**, a much more complete figure of the NO/ONOO$^-$ cycle. In it you will see the reciprocal relation between ONOO$^-$ (abbreviated PRN in the figure) and BH4 depletion. You will also see the role of ATP depletion inserted into the figure. One additional apparent aspect of the cycle is shown in the top left corner of **Figure 3**, indicated for the TRP receptors, specifically TRPV1, TRPA1 and TRPM2. TRPV1 and TRPA1 are both activated by the consequences of oxidative stress (Taylor-Clark *et al.*, 2008; Bessac *et al.*, 2008; Andersson *et al.*, 2008; Trevisani *et al.*, 2007; Puntambekar *et al.*, 2005; Schultz and Ustinova, 1998; Ustinova and Schultz, 1994), as discussed above. The transfer receptor protein TRPM2, discussed above, is strongly activated by oxidants, presumably including ONOO$^-$, with such activation producing an influx of intracellular calcium which is predicted, in turn, to increase NO synthesis. The TRPM2 role in the NO/ONOO$^-$ cycle has not been proposed prior to this publication, but it may well be an important aspect of the cycle mechanism.

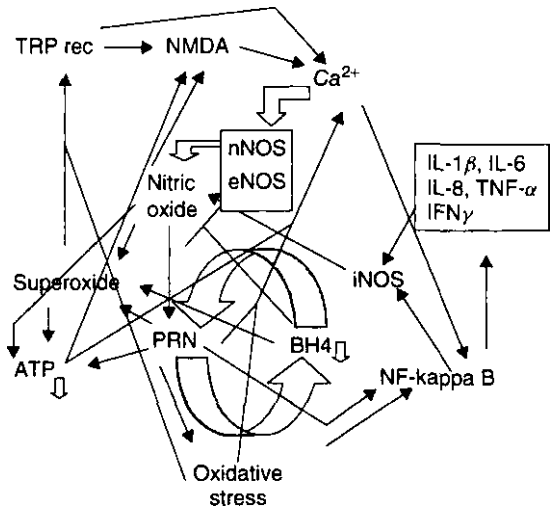

Figure 3 A more complete NO/ONOO$^-$ cycle diagram. Central to the figure are the reciprocal interactions between peroxynitrite, abbreviated as PRN and tetrahydrobiopterin (BH4) depletion. Also indicated is the ATP depletion produced by peroxynitrite, superoxide and nitric oxide. And in the upper left corner, TRP represents the three TRP receptors, TRPV1, TRPA1 and TRPM2, each of which is stimulated via distinct mechanisms by oxidative stress. Each arrow in the figure represents one or more mechanisms by which one element of the cycle stimulates another element of the cycle. (Figure and legend is taken from the author's web site with permission.)

There are three types of generic evidence that support the existence of the NO/ONOO$^-$ cycle (Pall, 2007a). By generic, I mean evidence not linked to any specific disease or illness. These are as follows:

1. Twelve studies have shown that one or both of two drugs that break down to release NO (nitroglycerine and nitroprusside) cause mammalian tissues to synthesize increased amounts of NO via all three NOSs (Chapter 1 in Pall, 2007a). These studies support the existence of a vicious cycle involving all three NOSs, as predicted by the NO/ONOO$^-$ cycle, but do not say anything about other aspects of the cycle.
2. Increased NMDA activity can increase essentially all of the NO/ONOO$^-$ cycle elements that are shown in **Figure 2** (Chapter 3 in Pall, 2007a). NMDA receptor activity directly increases intracellular calcium levels leading to increased NO levels. These studies show that most of the cycle elements can be increased simply by elevating intracellular calcium and NO, thus providing evidence for a cycle similar or identical to the NO/ONOO$^-$ cycle.
3. Hyperalgesia animal models involve all of the cycle elements shown in **Figure 2** in the generation of excessive pain in hyperalgesia (Chapter 3 in Pall,

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2007a). It is difficult to explain this involvement unless the cycle ties all of these elements together.

The NO/ONOO$^-$ cycle aetiology as an explanatory model is based on five distinct principles (Pall, 2006; 2007a; 2007b; Pall and Bedient, 2007):

1. Short-term stressors that initiate cases of multisystem illnesses act by raising NO synthesis and consequent levels of NO and/or other cycle elements.
2. Initiation is converted into a chronic illness via vicious cycle mechanisms, through which chronic elevation of NO and ONOO$^-$ and other cycle elements is produced and maintained. This principle predicts that the various elements of the NO/ONOO$^-$ cycle will be elevated in the chronic phase of illness.
3. Symptoms and signs of these illnesses are generated by elevated levels of NO and/or other important consequences of the proposed mechanism, that is, elevated levels of ONOO$^-$, NO, inflammatory cytokines, oxidative stress, elevated NMDA, TRPV1 receptor activity and/or other aspects of the cycle.
4. Because the compounds involved, NO, superoxide and ONOO$^-$ have quite limited diffusion distances in biological tissues and because the mechanisms involved in the cycle act at the level of individual cells, *the fundamental mechanisms are local*.
5. Therapy should focus on down-regulating NO/ONOO$^-$ *cycle biochemistry*.

Of these principles, we have discussed 1 and 2 above. Principle 3 predicts that the symptoms and signs of illness can be generated by elevation of one or more elements of the cycle. Some examples of how symptoms and signs of illness may be explained by the cycle are discussed below.

Principle 4 is so important that it takes up an entire chapter (Chapter 4) in my book (Pall, 2007a). Because NO, superoxide and ONOO$^-$, the three chemical compounds most central to the NO/ONOO$^-$ cycle, have relatively short half-lives in biological tissues, they don't diffuse very far from their site of origin in the body. NO has the longest such half-life and it only diffuses about 1 mm from its origin. Furthermore, most of the mechanisms implicated by the arrows act at the cellular level. The consequence of all of this is that the NO/ONOO$^-$ cycle may be elevated in one tissue of the body, but an adjacent tissue may show little elevation and therefore be little impacted by the cycle. This local nature of the cycle biochemistry means that we can have all kinds of variations in tissue impact from one patient to another, leading in turn to all kinds of variation in symptoms and signs from one individual to another. This striking variation in symptoms from one individual to another has been repeatedly been noted in these illnesses and has been one of the great puzzles about this group of illnesses. The variation can be easily explained by the local nature of the NO/ONOO$^-$ cycle mechanism. Principle 4 does *not* suggest that there are no systemic effects, but rather that much of the cycle effects are local.

Principle 5 states that the focus of therapy should be to down-regulate NO/ONOO$^-$ cycle biochemistry. In other words, therapy should focus on lowering the cause of illness, not just on treating symptoms. This is obviously an important principle for both patients suffering from these illnesses and for conscientious physicians trying to treat them. There is much stronger evidence for principle 5 in CFS and FM (discussed below) than in the related illness MCS.

These five principles are important as a group for three distinct but overlapping reasons:

- Taken together, they produce an essentially complete explanatory model.
- The fit to each of the five produces a very different type of evidence for the causality of the cycle. Are cases of the disease/illness started by agents predicted to initiate the cycle? Are cycle elements elevated in the chronic phase of illness? Can the symptoms and signs of illness be generated by one or more the elements of the cycle? Is there evidence for a local mechanism? Can the disease/illness be treated by agents predicted to down-regulate the cycle?
- Because the fit to each of the five gives a very different type of evidence for causality of the cycle, the fit to each of them provides a distinct criterion as to whether a particular disease/illness is a good candidate for being a NO/ONOO$^-$ cycle disease.

What the author has done, in his book and elsewhere, then, is to use these five criteria to ask whether each multisystem illness and also a number of other diseases are good candidates for inclusion under the NO/ONOO$^-$ cycle mechanism. It is the goal, then in a following section of this chapter to go through each of the criteria to see how good the fit is for MCS.

In summary, there are three distinct types of evidence that support the general notion that the NO/ONOO$^-$ cycle mechanism in an important paradigm of human disease.

1. The individual mechanisms of the cycle, represented by the arrows in **Figures 2** and **3**, are almost all well-documented biochemistry and physiology.
2. There are three generic types of evidence for the existence of the cycle, that is evidence not linked to any specific disease or illness.
3. There are a number of diseases/illnesses where one can argue based on the fit to the five principles outlined above, that they are good candidates for inclusion under the NO/ONOO$^-$ cycle paradigm.

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8.1 NO/ONOO$^-$ Cycle Mechanisms for the Generation of Shared Symptoms and Signs of Illness

It has been widely claimed that these multisystem illnesses and even their symptoms are unexplained. Clearly, for the NO/ONOO$^-$ cycle mechanism to be plausible for these multisystem illnesses, it must be possible to explain the symptoms and signs of illness as being generated by one or more elements of the cycle. Such explanations are needed for both the specific symptoms and signs and the shared ones, discussed here (**Table 3**). In Chapter 3 of Pall (2007a), evidence is provided on how these shared symptoms and signs may be generated by the NO/ONOO$^-$ cycle actiology. The mechanisms listed in **Table 3** are *not presented as established mechanisms in these illnesses*, but they are plausible mechanisms based on substantial scientific information. Each of these only occurs in some multisystem illness sufferers, consistent with the striking variation of symptoms and signs that are a characteristic feature of these illnesses. Indeed it may be argued that the defining symptoms and signs of CFS, MCS, FM and PTSD are found in all sufferers of each of these illnesses because we required them for the diagnosis. In other words, we appear to have a very large spectrum of illness that we have more or less arbitrarily subdivided via particular symptoms.

9 FUSION OF THE NO/ONOO$^-$ CYCLE MECHANISM WITH NEURAL SENSITIZATION AND OTHER PUTATIVE MCS MECHANISMS

While what has become the NO/ONOO$^-$ cycle has produced fairly complete explanations of such illnesses as CFS and FM and also of a number of additional, well-established diseases (Pall, 2007a; Pall and Bedient, 2007), it alone did not produce a compelling explanation for the complexities of MCS (Pall and Satterlee, 2001). It was only when fused with a previous MCS model, the neural sensitization model, that a much more complete explanation became apparent.

Bell and her collaborators (Bell *et al.*, 1992; 1999a; 2001a) and others (Antelman, 1994; Rossi, 1996; Friedman, 1994; Sorg and Prasad, 1997) proposed a neural sensitization model, where chemicals were proposed to act to greatly increase neural sensitization in the brain, particularly in the limbic system. The notion here is that if chemicals can act to produce such neural sensitization, greatly increasing the activity of synapses over large regions of the brain, that this could explain the basic mechanism of MCS. In this way, chemicals might generate changes in EEG activity (Lorig *et al.*, 1991; Bell *et al.*, 1999b; 2001b; Fernandez *et al.*, 1999; Muttray *et al.*, 1995) and also in brain PET scans (Heuser and Wu, 2001; Hillert *et al.*, 2007) and SPECT scans (Simon *et al.*, 1994; Heuser *et al.*, 1994; Fincher *et al.*, 1997a; 1997b) in MCS. There was a New York Academy of Sciences meeting in 2000 that focussed on the proposed neural sensitization mechanism for MCS (Sorg and Bell, 2001) and there is no question that at that time, this neural sensitization view was the most influential view of a possible physiological basis for MCS. Ashford and Miller (1998) listed 10 compelling similarities between MCS and neural sensitization, each of which may be considered to be evidence in favour of a neural sensitization model.

Nevertheless, the neural sensitization interpretation of MCS never generated explanations of how the various classes of chemicals may work nor how the roughly 1000-fold increase in chemical sensitivity that appears to occur in many MCS patients might be generated, nor the similarities to CFS and related illnesses. It did provide a framework for explaining the chronic nature of chemical sensitivity, namely long-term changes in synaptic sensitivity.

The most important mechanism of neural sensitization is that of long term potentiation (LTP), the main mechanism involved in learning and memory. The LTP mechanism is involved on a highly selective basis in strengthening synaptic interactions in the process of learning and memory, and the question raised by its possible role in MCS is what will be the consequences if chemical exposure leads to a massive activation of this process?

In the process of neural sensitization, changes in each synapse involve changes in both the presynaptic and the postsynaptic neurons. LTP is known to involve, as key elements in a complex overall mechanism activated in the postsynaptic neuron, several elements of the NO/ONOO$^-$ cycle, notably NMDA activity, NO and intracellular calcium (Albensi, 2001; Bliss and Collingridge, 1993; Bennett, 2000; Platenik *et al.*, 2000; Dineley *et al.*, 2001; Prast and Phillippu, 2001; Cotman *et al.*, 1988). Superoxide, another cycle element also has a role, albeit a complex one (Knapp and Klann, 2002; Hu *et al.*, 2007). Increased NMDA activity in the postsynaptic neuron has a role, as do the increases in intracellular calcium and NO produced by such NMDA stimulation of the postsynaptic neuron (Albensi, 2001; Bliss and Collingridge, 1993; Bennett, 2000; Platenik *et al.*, 2000; Dineley *et al.*, 2001; Prast and Phillippu, 2001; Cotman *et al.*, 1988). NO produced in the postsynaptic neuron, acts as what is called a retrograde messenger, diffusing back to the presynaptic neuron and causing it to be more active in neurotransmitter release, including the release of glutamate, the major physiological agonist of the NMDA

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Table 3 Explanations for symptoms and signs

Symptom/sign	Explanation based on elevated nitric oxide/peroxynitrite theory
Energy metabolism/mitochondrial dysfunction	Inactivation of several proteins in the mitochondrion by peroxynitrite; inhibition of some mitochondrial enzymes by nitric oxide and superoxide; NAD/NADH depletion; cardiolipin oxidation
Oxidative stress	Peroxynitrite, superoxide and other oxidants
PET scan changes	Energy metabolism dysfunction leading to change transport of probe; changes in perfusion by nitric oxide, peroxynitrite and isoprostanes; increased neuronal activity in short-term response to chemical exposure
SPECT scan changes	Depletion of reduced glutathione by oxidative stress; perfusion changes as under PET scan changes
Low NK (natural killer) cell function	Superoxide and other oxidants acting to lower NK cell function
Other immune dysfunction	Sensitivity to oxidative stress; chronic inflammatory cytokine elevation
Elevated cytokines	NF-κB stimulating of the activity of inflammatory cytokine genes
Anxiety	Excessive NMDA activity in the amygdala
Depression	Elevated nitric oxide leading to depression; cytokines and NMDA increases acting in part or in whole via nitric oxide.
Rage	Excessive NMDA activity in the periaqueductal grey region of the mid-brain
Cognitive/learning and memory dysfunction	Lowered energy metabolism in the brain, which is very susceptible to such changes; excessive NMDA activity and nitric oxide levels and their effects of learning and memory
Multiorgan pain	All components of cycle have a role, acting in part through nitric oxide and cyclic guanosine monophosphate (cGMP) elevation
Fatigue	Energy metabolism dysfunction
Sleep disturbance	Sleep impacted by inflammatory cytokines, NF-κB activity and nitric oxide
Orthostatic intolerance	Two mechanisms: nitric oxide-mediated vasodilation leading to blood pooling in the lower body; nitric oxide-mediated sympathetic nervous system dysfunction
Irritable bowel syndrome	Sensitivity and other changes produced by excessive vanilloid and NMDA activity, increased nitric oxide
Intestinal permeabilization leading to food allergies	Permeabilization produced by excessive nitric oxide, inflammatory cytokines, NF-κB activity and peroxynitrite; peroxynitrite acts in part by stimulating poly(ADP)-ribose polymerase activity

Taken from the author's web site with permission. It should be noted that while each of these are plausible mechanisms and, in most cases well-documented mechanisms under some pathophysiological circumstances, in most cases their role in generating these symptoms in these multisystem illnesses is *not* established. The role of reduced glutathione depletion in generating SPECT scan changes is documented in Jacquier-Sarlin *et al.*, 1996 and in Suess *et al.*, 1991.

receptors (Zhang and Snyder, 1995; Kuriyama and Ohkuma, 1995; Williams, 1996). LTP involves not only increased glutamate release, but also changes in the post-synaptic neuron, making its synapses more sensitive to stimulation.

One point that needs to be made is that we have a striking convergence between the demonstrated role of each of the chemicals implicated in MCS, producing increased NMDA activity, and the essential role of NMDA receptors in LTP. This convergence provides, therefore, for the first time, an explanation for that pattern: only chemicals leading to increased NMDA activity may be expected to produce an up-regulation of the LTP mechanism.

Whereas the normal, highly selective role of LTP in learning and memory will not be expected to involve any substantial NO/ONOO$^-$ cycle elevation, a massive stimulation of NMDA activity over substantial regions of the brain, produced by chemical exposure, will be expected to involve substantial NO/ONOO$^-$ cycle elevation. The extraordinary chemical sensitivity seen in MCS, at least in the CNS-related symptoms, may then be generated by the following multiple mechanisms:

1. Subsequent chemical exposure will stimulate regions of the brain with already existing neural sensitization, with that neural sensitization maintained both by the standard LTP mechanism *and* by the local elevation of the NO/ONOO$^-$ cycle. This combination may be exacerbated by a series of mechanisms, each involving elements of the NO/ONOO$^-$ cycle, as follows.
2. NO acting as a retrograde messenger will act to stimulate further glutamate release by the presynaptic neurons.

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3. Energy metabolism dysfunction produced by $ONOO^-$, superoxide and NO will cause NMDA receptors to be hypersensitive to stimulation. It is known that energy-metabolism dysfunction produces a decreased membrane potential which acts, in turn, to cause the NMDA receptors in such cells to be hypersensitive to stimulation (reviewed in Novelli *et al.*, 1988; Schulz *et al.*, 1997; Turski and Turski, 1993; Pall, 2002).
4. Energy-metabolism dysfunction also acts on glial cells which normally rapidly lower extracellular glutamate via energy-dependent glutamate transport. Lowered energy metabolism will then lead to *increased extracellular glutamate, leading in turn* to increased NMDA stimulation (Gadea and Lopez-Colome, 2001; Bliss *et al.*, 2004).
5. $ONOO^-$ leads to a partial breakdown of the blood–brain barrier, leading to increased chemical access to the brain (reviewed in Phares *et al.*, 2007; Pall, 2002; 2003). Kuklinski *et al.* (2003) have reported blood–brain barrier breakdown in MCS patients and there is also an animal model of MCS in which similar breakdown has been observed (Abdel-Rahman *et al.*, 2002; Abu-Qare and Abou-Donia, 2003; Abou-Donia *et al.*, 2002b).
6. Many of the chemicals implicated in MCS are metabolized via cytochrome P450 activities and these enzymes are known to be inhibited by NO, thus possibly leading to increased accumulation of the active chemical forms (reviewed in Pall, 2002).
7. Finally TRPV1, TRPA1 and some other TRP receptors are activated through the action of oxidants, as discussed above, and organic solvents and other agents that act via these TRP receptors, such as some mould toxins, may be expected to have increased activity due to such TRP receptor activation.

This combination of multiple mechanisms, each multiplying the actions of the others, is predicted to easily produce the roughly 1000-fold increase in sensitivity that appears to occur in many MCS patients. So we have, for the first time, a hypothesis that explains the last major puzzle in MCS, how one can get this stunning increase in apparent sensitivity to such wide variety of chemicals. Having said that, while each of these mechanisms are individually well-documented and we do have aspects of some of them reported to occur in MCS, there is no currently available evidence that directly and convincingly implicates any of them in producing MCS-related sensitivity. This is not surprising, given the extraordinarily low level of research support that has been available for MCS studies.

10 PERIPHERAL SENSITIVITY MECHANISMS

MCS patients typically not only have central sensitivity symptoms that can be attributed to neural sensitization/NO/$ONOO^-$ cycle mechanisms, but also peripheral sensitivities. They often have chemical sensitivity in the upper respiratory tract, leading to rhinitis symptoms on low-level chemical exposure, they have asthma-type symptoms in response to low-level chemical exposures, they have skin sensitivities, with different patterns of skin involved in different patients, they have gastrointestinal (GI) tract sensitivities and additional organ sensitivity may be seen (Ashford and Miller, 1998). These are likely to be local sensitivity mechanisms distinct from the CNS-derived sensitivity discussed in the preceding section.

Meggs (1994; 1997), Meggs *et al.* (1996) and Bascom *et al.* (1997) and others have described the initiation of cases of RADS, where a type of asthma is initiated by chemical exposure to organic solvents and other irritants and the pattern of chemicals involved is similar or identical to those involved in MCS initiation. RADS is characterized by a wide-ranging chemical sensitivity (Meggs, (1994; 1997); Meggs *et al.*, 1996; Bascom *et al.*, 1997; Krishna *et al.*, 1998), in addition to the more commonly studied sensitivities of asthma, those to allergens, exercise and cold. Not only are organic solvents involved, but several classes of pesticides as well (Proudfoot, 2005; Hernández *et al.*, 2008; Proskocil *et al.*, 2008; Fryer *et al.*, 2004). Sensitization of the bronchi in response to chemical exposure, including organic solvent and pesticide exposure and also other irritants may well be commonly involved in causing occupational asthma (Jeebhay and Quirce, 2007; Gautrin *et al.*, 1994). Interestingly, cases of asthma can also be apparently initiated, not only by organic solvents or pesticide chemicals, but also by exposure to mould toxins in mould-infested 'sick buildings', another similarity with MCS (Sahakian *et al.*, 2008; Lee, 2003; Mahmoudi and Gershwin, 2000). Thus reactive airways disease can be seen as a common aspect of MCS, with a strikingly similar pattern of chemicals involved in the initiation process.

In addition to RADS, there is also reactive upper airways dysfunction syndrome (RUDS), in which there is chemical sensitivity initiated by previous chemical exposure, producing inflammatory responses in the upper airways, leading to rhinitis symptoms as well as ultrastructural changes (Meggs, 1994; 1997; Meggs *et al.*, 1996). Similar to RADS and RUDS, there is also a reactive intestinal dysfunction syndrome (RIDS), where chemical exposure can initiate intestinal chemical sensitivity (Lieberman and Craven, 1998).

Peripheral sensitivity in the skin, lungs, upper respiratory tract, GI tract and other tissues, raises the question

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of how the mechanism of sensitivity may differ from that found in the central sensitivity discussed above? *It seems likely, given the similar spectrum of chemicals* involved at least in the RADS/airways response, that it also involves an NMDA stimulation pathway. There is evidence for an excessive NMDA role in asthma (Hirota and Lambert, 1996; Overstreet and Djuric, 1999; Dickman *et al.*, 2004; Hoang *et al.*, 2006; Said *et al.*, 2001) and also for an NMDA role in skin-sensitivity responses produced by formaldehyde (Elliott *et al.*, 1995; Coderre and Melzack, 1992). In MCS patients, the NMDA antagonist dextromethorphan seems to lower sensitivity responses, not only associated with central sensitivity, but also associated with peripheral sensitivity (Dudley, 1998). Glutamate ingestion of MCS patients appears to trigger symptoms associated with peripheral sensitivities, not just central (Miller and Prihoda, 1999; Ross, 1997). All of these observations suggest an NMDA mechanism in peripheral sensitivity, although the strength of the evidence on this is relatively weak. However, it seems reasonable, given the broad range of chemicals involved in these peripheral sensitivity responses, and the known action of these chemicals as producing NMDA stimulation, that NMDA receptor stimulation may well be involved in peripheral sensitivity, as it is in central sensitivity.

So what mechanisms may be likely to be involved in generating peripheral sensitivity? Clearly, of the seven mechanisms postulated for central sensitivity, one, the breakdown of the blood–brain barrier cannot be involved, and a second, the role of NO acting as a retrograde messenger is unlikely to be involved. The other five, however, may well have a role. And additional mechanisms may also be involved. Meggs has published biopsy studies of chemically sensitive peripheral tissues suggesting that neurogenic inflammation has an important role in generating the sensitivity of these peripheral tissues (Meggs, 1993; 1997; Bascom *et al.*, 1997). Neurogenic inflammation may be expected to be generated by elements of the NO/ONOO$^-$ cycle, including TRPV1 activity, NF-κB activity and NO (Leffler *et al.*, 2008; Kajekar *et al.*, 1995; Yonchara and Yoshimura, 1999; Ruocco *et al.*, 2001; Pall and Anderson, 2004; Lieb *et al.*, 1997; Lin *et al.*, 2007) and because of its inflammatory action, will be expected, in turn to stimulate the cycle. Mast cell activation, an aspect of neurogenic inflammation (Ruocco *et al.*, 2001; Hu *et al.*, 2008; Costa *et al.*, 2008), has been reported to be involved in MCS (Heuser, 2000; 2001), and observations providing further support for mast-cell activation in MCS have been provided by Kimata (2004) and Elberling *et al.* (2007). Such mast-cell activation by chemical exposure may also be expected to act to exacerbate the cycle, through inflammatory cytokine elevation and other mechanisms. Mast-cell activation is reported to be stimulated by TRPV1 activation and also by NF-κB (Hu *et al.*, 2008; Kempuraj *et al.*, 2003; Lee *et al.*, 2007), both NO/ONOO$^-$ cycle elements.

In summary, we have a number of locally acting mechanisms that are expected to act synergistically with each other to produce high levels of peripheral chemical sensitivity:

1. Chemical stimulation of regions of the body with elevated NO/ONOO$^-$ cycle activities.
2. Lowered mitochondrial function leading to increased NMDA receptor activity.
3. Lowered mitochondrial function leading to lowered local glutamate transport and therefore to increased NMDA stimulation.
4. NO inhibition of local cytochrome P450 activity and thus lowered metabolism of chemicals implicated in chemical sensitivity.
5. Local oxidative stress and ONOO$^-$ elevation, leading to increased activity of TRPV1, TRPA1, TRPM2 and possibly other TRP receptor activities, leading to both increased chemical sensitivity via these receptors and amplification of the inflammatory response by TRPM2.
6. Neurogenic inflammation produced, in part, by TRPV1 stimulation and NO, leading in turn to increased inflammation.
7. Mast-cell activation, generated in part by TRPV1 stimulation and NF-κB activity, leading in turn to increased inflammation.

It should be emphasized that while these individual mechanisms are well documented, their causal role in producing local peripheral chemical sensitivity in MCS is undocumented for most mechanisms and needs further substantial study in the others. At this point, they should be viewed as plausible predictions of the NO/ONOO$^-$ cycle fusion model which produce, in turn, plausible explanations of the peripheral sensitivities found in MCS.

11 THE NO/ONOO$^-$ CYCLE MECHANISM AS EXPLAINING PREVIOUSLY UNEXPLAINED MCS PROPERTIES

The title of the author's book *Explaining 'Unexplained Illnesses'* (Pall, 2007a) is obviously a challenge to those who have repeatedly claimed that this whole group of multisystem illnesses is unexplained, and there is no doubt that MCS has been the most challenging of this group of illnesses to explain. Kuhn, in his famous book *The Structure of Scientific Revolutions* makes clear that new scientific paradigms, developed from what he calls 'revolutionary science' (as opposed to 'normal

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science'), are judged in large measure by how well they explain previously unexplained properties of the scientific phenomena to which the paradigm may be expected to apply. That is, one does not only look at the available data and how well it supports the proposed new paradigm, but one needs to look carefully at how well it explains the many relevant, but previously unexplained properties.

Given the previous challenges in explaining MCS, one needs to ask how well the NO/$ONOO^-$ cycle fusion model for MCS explains its many previously puzzling properties. I will go through 12 of these one at a time, using a question-and-answer format. Citations are provided to document issues that were not documented above.

1. How can so many diverse chemicals produce a common response, namely initiating cases of MCS and also eliciting responses in those already chemically sensitive? By acting along different pathways to produce a series of common responses, notably increased NMDA activity, intracellular calcium, NO and $ONOO^-$.
2. Why is MCS chronic? Because the NO/$ONOO^-$ cycle propagates itself over time and probably, in addition, because of long-term changes in the synapses of the brain, leading to neural sensitization.
3. How can MCS patients be so exquisitely sensitive to *low-level chemical exposure, with many estimated* to be on the order to 1000 times more sensitive than normal? Possibly by a series of mechanisms in the brain predicted to lead to long-term changed neural sensitization, increased short-term sensitization, increased levels of neurotransmitter (glutamate) and increased chemical accumulation. Peripheral sensitivity may involve some of these mechanisms as well and also such mechanisms as neurogenic inflammation and mast cell activation. Two of the transient receptor potential receptors may also have roles in amplifying sensitivity responses. It is through a combination of such mechanisms, acting synergistically with each other, that such high-level sensitivity may be produced.
4. Why is MCS comorbid with such diseases/illness as CFS, FM, PTSD, tinnitus and asthma? Possibly because each of these may be NO/$ONOO^-$-cycle mechanisms and each of them certainly involves elements of the NO/$ONOO^-$ cycle in their actiology.
5. How can diverse organic solvents be involved in MCS? Probably by stimulating, either directly or through their metabolic products, several of the TRP receptors including the TRPV1 and TRPA1 receptors. This same group of receptors is involved in the SI response to a similar or identical set of organic solvents.
6. Why are symptoms so variable from one patient to another? Because the NO/$ONOO^-$ cycle is fundamentally local, such that one can have both quantitative and qualitative variable tissue impact in different patients. This same mechanism leads to similar variability in cases of CFS, FM and PTSD.
7. Several research groups have reported apparent lowered activity of the porphyrin biosynthetic pathway, leading to accumulation of compounds derived from intermediates at multiple steps in this pathway (Downey, 2001; Matthews, 1998; Morton, 1997; see also Hahn and Bonkovsky, 1997). How can such multiple steps in the pathway be lowered? *Probably because of the role of NO in regulating* this pathway (Kim *et al.*, 1995; Rafferty *et al.*, 1996) and possibly because the last step in the pathway is an iron–sulphur protein (Dailey *et al.*, 2000) and such iron–sulphur proteins are often inactivated by $ONOO^-$ or NO (Soum *et al.*, 2003).
8. How can neurogenic inflammation be involved in MCS? Probably because NO/$ONOO^-$-cycle elements, including TRPV1 receptor activity and NO, can stimulate neurogenic inflammation.
9. How can mast-cell activation be involved in MCS (Pall, 2003)? Probably because both TRPV1 receptor activity and NF-κB can stimulate mast cells.
10. It has been shown that repeated or continuous low-level exposure to organic solvents can lead to desensitization/masking of the MCS response (Ashford and Miller, 1998). What mechanism is involved here? Probably by the lowering of TRPV1 and other TRP receptor activity in response to such exposure to many TRPV1 agonists (Reviewed in Pall and Anderson, 2004; Szallasi, 2002). Interestingly, the TRPA1 receptor, also suggested above to be involved in responding to organic solvents in MCS, is also reported to be down-regulated under these conditions (Akopian *et al.*, 2007), consistent with a role for these receptors in masking/desensitization. The desensitization to very small amounts of xenobiotics applied as part of a therapeutic programme (Weaver, 1996; Rea, 1997) may also be produced by this same process.
11. How can moulds in 'sick-building situations' initiate cases of MCS? Probably because mycotoxins produce inflammatory responses and some mycotoxins can stimulate the TRPV1 receptor.
12. How should MCS be treated? Through chemical avoidance and the use of agents that lower aspects of the NO/$ONOO^-$ cycle, including antioxidants, agents that lower NO, $ONOO^-$ and superoxide production, agents that improve mitochondrial function, agents that lower inflammatory biochemistry, agents that lower excitotoxicity, including excessive NMDA activity and agents that help restore BH4.

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It can be seen from the above that there are reasonable explanations derived from the NO/ONOO$^-$ cycle mechanism, as it applies to MCS, for each of these puzzling questions. Previously, as best I can determine, only one of these had a good explanation: the chronic nature of MCS could be explained by the long-term synaptic changes produced by neural sensitization, but, even here, *this is probably only part of the explanation and additional* NO/ONOO$^-$ cycle mechanisms may be likely to be involved.

12 ANIMAL MODEL DATA ON VARIOUS ASPECTS OF THE PROPOSED NO/ONOO$^-$-CYCLE MECHANISM OF MCS

A whole series of animal models suggested as models for MCS have provided evidence for roles of various aspects of the NO/ONOO$^-$ cycle fusion model as it is proposed to apply to MCS. These include the following.

Sorg *et al.* (1998; 2001) developed a rat model showing cross-sensitization to cocaine and formaldehyde. Cocaine is known to also produce increases in NMDA activity (Laso, 2001; McGinty, 1995), as do the various initiators of cases of MCS. Her studies provide evidence for both neural sensitization and cross-sensitization. von Euler *et al.* (1994) described a similar rat model, using primarily toluene instead of formaldehyde as their main sensitizing agent, that appears to provide evidence for both neural sensitization and cross-sensitization.

Cocaine was also used in a mouse sensitization model which produced convincing evidence for cross-sensitization and increased NMDA activity, as well as an essential role of increased NO in producing the neural sensitization (Balda *et al.*, 2008; Itzhak and Martin, (1999; 2000); Itzhak *et al.*, 1998; Itzhak, 1995).

Gilbert (2001) reviewed an animal kindling model in response to repeated or high-level exposure to lindane and other similar pesticides, in which neural sensitization leads to overt seizure activity. The mechanism is essentially identical to the mechanism outlined earlier in this paper where pesticide produces decreased $GABA_A$ function, leading in turn to increased NMDA activity, increased subsequent intracellular calcium levels, acting in turn to produce LTP and consequent neural sensitization, leading in this situation to overt seizure activity. Cloutier *et al.* (2006) has also discussed the role of lindane in initiating an animal model for MCS and Adamec (1994) has discussed a different $GABA_A$ antagonist as such an initiator.

The mouse model of Anderson and Anderson (1999a, 1999b, 2003) of all MCS animal models is the one that has been shown to be at least superficially most similar to MCS in humans. It involves sensitization to a number of chemical mixtures implicated in MCS, cross-sensitization among different chemicals and chemical mixtures and also linkage to the SI response.

Willis (2001) described a primate model of central sensitization leading to secondary hyperalgesia and allodynia following repeated injections of capsaicin, the classic TRPV1 agonist. *It provides evidence for, not* only TRPV1 involvement, but also for NMDA, NO and intracellular calcium involvement, in addition, of course, to neural sensitization. Thus we have evidence of roles for five of the important elements of the model. Similar responses were reported earlier from formaldehyde injections.

Abou-Donia and his colleagues have published the most extensive studies on an animal (rat) model of MCS (Abou-Donia, 2002b). The toxicants they studied were all toxicants that the 1991 Gulf War veterans were exposed to and are therefore potentially involved in the initiation of Gulf War syndrome or illness. The Gulf War syndrome veterans suffer from MCS or an MCS-like illness (Proctor *et al.*, 2001; Reid *et al.*, 2001; Miller and Prihoda, 1999; Thomas *et al.*, 2006), along with symptoms of other multisystem illnesses, CFS, FM and PTSD (Chapter 10, Pall, 2007a). Consequently, this rat model may be considered to be a model both for MCS and for the related Gulf War syndrome.

The specific chemicals studied by Abou-Donia and his colleagues, both individually and in combination, included the carbamate acetylcholinesterase inhibitor, pyridostigmine bromide, the insect repellant and irritant DEET (*N,N*-diethyl-*m*-toluamide) (Schoenig *et al.*, 1993; Robbins and Cherniack, 1986), the pyrethroid pesticide, permethrin, depleted uranium and several organophosphorus toxicants. Of these only the depleted uranium is apparently not related to initiators of cases of MCS. In these studies, exposure to these toxicants has been found to produce chronic neurological changes, including neurobehavioural changes and sensorimotor deficits, from high-level exposures or from long-term, subclinical exposures (Abou-Donia, 2003; Abou-Donia *et al.*, 2001; 2002a; 2002b; 2004; Abdel-Rahman *et al.*, 2004a; 2004b). Even doses that show no signs of overt neurotoxicity produce these real, measurable and chronic neurological changes (Abdel-Rahman *et al.*, 2004b).

Among the important physiological changes following chemical exposure are elevation of 3-nitrotyrosine levels, a marker of ONOO$^-$ elevation, oxidative stress as measured by elevation of 8-hydroxy-2′-deoxyguanosine levels, disruption of the blood–brain barrier and elevated NO levels (Abou-Donia *et al.*, 2002b; Abu-Qare and Abou-Donia, 2001a; 2001b; 2003; Abu-Qare *et al.*, 2001; Abdel-Rahman *et al.*, 2002), all predicted consequences of the NO/ONOO$^-$ cycle mechanism.

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Abou-Donia and coworkers reported synergistic interactions of these chemicals (Abou-Donia *et al.*, 1996; Abu-Qare and Abou-Donia, 2001a; 2003; Abdel-Rahman *et al.*, 2002) and others have found such synergistic effects in animal models as well (reviewed in Research Advisory Committee on Gulf War Veterans Illnesses., 2004). They suggest at least three mechanisms for the synergistic chemical interactions: competition for a cytochrome P450 degradative enzyme (Abu-Qare and Abou-Donia, 2008); partial breakdown of the blood–brain barrier produced by one chemical, leading to increased brain sensitivity to a second chemical (Abou-Qare and Abou-Donia, 2003) and competition for cellular excretion via P-glycoprotein (El-Masry and Abou-Donia, 2006). The author suggests additional possible mechanisms for such synergism, including the synergistic action of different organic solvents, acting as TRPV1 agonists and chemical action along multiple pathways, each leading to increased NMDA activity. The synergistic interactions among chemicals produce great difficulties for toxicologists attempting to estimate the toxicity of complex mixtures of chemicals from the toxicity of the individual components.

Two chemicals and one mixture of chemicals, all implicated in cases of MCS were studied in a mouse model by Fujimaki and colleagues. They demonstrated increases in inflammatory cytokines and reactive airways disease inflammation, as well as changes in CNS neurological activity (Tin-Tin-Win-Shwe *et al.*, 2007; Fujimaki *et al.*, 2001; 2004; 2007). A causal role of the cytokine IL-6 in the generation of lung inflammation in response to diesel exhaust was demonstrated by comparing an IL-6 gene knockout mouse with the wild-type (Fujimaki *et al.*, 2006).

Low-level exposure of several noxious chemicals, including formaldehyde, to mouse skin generated progressive sensitization, leading to both neurogenic inflammation and increased inflammatory cytokine levels (Nakano, 2007).

Fukuyama *et al.* (2008) reported on an MCS mouse model, in which repeated applications of three chemical sensitizers were used to produce sensitivity, followed by a challenge with the same sensitizer. They found that the levels of several inflammatory cytokines were elevated following sensitization and that the challenge produced a much larger cytokine elevation. Thus the pattern of exposure and the response closely parallel the pattern of chemical exposure and subsequent elicitation of sensitivity responses seen in MCS. One of the sensitizers used, TDI is known to be a TRPV1 agonist.

Plitnick *et al.* (2002) showed that the chemical sensitizers, trimellitic anhydride and dinitrochlorobenzene, known to produce airway chemical sensitivity or skin chemical sensitivity, produced increases in some inflammatory cytokines in a mouse model. Harry *et al.* (2002) also showed sensitizer induction of inflammatory cytokine mRNA in glial cells in culture.

It can be seen from the above, that a surprising number of NO/ONOO$^-$ cycle MCS fusion model elements have been found to be involved in MCS animal models. These include both neural sensitization and cross-sensitization between chemicals, as well as progressive sensitization; chemical agents that are known to act by decreasing acetylcholinesterase or $GABA_A$ activity or increasing TRPV1 or sodium channel activity; chemical linkage to the SI response; increases in NMDA activity, NO, ONOO$^-$, oxidative stress, inflammatory cytokines, intracellular calcium, neurogenic inflammation, airways sensitivity and inflammation; and breakdown of the blood–brain barrier. Most, but not all, of these have been shown to have substantial causal roles in the generation of the animal model response. Although we have evidence from these animal models for roles of many features of the NO/ONOO$^-$ cycle mechanism, as it is proposed to apply to MCS, generally, two to five of these aspects have been looked at in each animal model and it is unclear whether any single animal model will involve all of these. However, given the fact that none of these studies have been done to test the NO/ONOO$^-$ cycle mechanism, and funding for such studies has been very limited, there is a surprising amount of data supporting aspects of the cycle mechanism.

13 POSSIBLE SPECIFIC BIOMARKER TESTS? OBJECTIVELY MEASURABLE RESPONSES TO LOW-LEVEL CHEMICAL EXPOSURE

One of the obvious needs in this area of medical research, is the need for one or more specific biomarker tests that can be used to objectively confirm a diagnosis of MCS. There are similar needs for such tests for CFS and FM as well. Because the aetiological mechanism of each of these is thought to be centred on the NO/ONOO$^-$ cycle and the cycle is mostly inflammatory biochemistry, looking at whole-body markers of the consequences of such inflammatory biochemistry will not be useful as a specific biomarker test. There are many dozens of inflammatory diseases, including many chronic inflammatory diseases, so prolonged elevation of such markers will be nonspecific. Furthermore, because such chronic inflammatory diseases are so common, in most cases such markers for MCS patients will often be in the normal range, because typically abnormally elevated levels are usually defined as being two standard deviations above the norm. It is only when one compares sizable groups of MCS patients with controls that one is likely to see statistically significant differences. All of these issues create difficult challenges in trying to develop specific biomarker tests.

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Given these challenges, it may be predicted that specific biomarker tests for any NO/ONOO$^-$ cycle illness must directly or indirectly measure the impact of the cycle on whatever tissue or tissues must be involved in that specific illness. In most cases of MCS, there may be many such tissues, and the obvious way to look at the impact of the cycle on those tissues is to look at the chemical sensitivity responses in one of these tissues. We need to compare the responses of MCS patients with those of controls to low-level chemical exposure, looking at one or more objectively measurable responses. The NO/ONOO$^-$-cycle mechanism predicts that such low-level chemical exposure will produce elevated responses of NO/ONOO$^-$ cycle elements in MCS patients, but little response in normal controls. Alternatively, one might look at the consequences of NO/ONOO$^-$-cycle elevation produced by low-level chemical exposure, rather than specific cycle elements themselves. There have been quite a number of studies reporting elevated responses to low-level chemical exposure in MCS patients, as compared with controls, and this section of the chapter summarizes some of these and compares those reported responses with those predicted from the NO/ONOO$^-$-cycle mechanism of MCS. Studies of neuropsychological changes following low-level chemical exposure will not be reviewed here because the author has no competence to judge such studies.

The most extensive studies of this type are the cough responses studied by Millqvist and her colleagues in response to capsaicin challenge (Johansson *et al.*, 2002; 2006; Millqvist, 2000; Ternesten-Hasséus *et al.*, 2002; Millqvist *et al.*, 2005; 2008). In these repeated studies, MCS patients show much elevated cough responses over normal controls in response to low-level capsaicin challenge. Capsaicin is the classic TRPV1 agonist and because TRPV1 receptor activity is thought, as argued above, to be involved in the responses to many organic solvents and related chemicals, this response appears to be quite consistent with what may be predicted by the NO/ONOO$^-$ cycle mechanism, as it is proposed to play out in MCS. Because the cough response produced by capsaicin is lowered by the use of dextromethorphan and other NMDA antagonists (Kamei *et al.*, 1989; Capon *et al.*, 1996; Chung, 2005), this pathway of action appears to be identical to that proposed for TRPV1 action in MCS. Millqvist *et al.* (2005) also report substantial increases in nerve growth factor (NG) activity following low-level capsaicin provocation in MCS patients, but not in controls, as predicted by two aspects of the NO/ONOO$^-$ cycle, up-regulation of TRPV1 activity and neurogenic inflammation. These responses are almost certainly local ones, as suggested by Millqvist (2000), so that the minority of MCS sufferers who do not have respiratory tract sensitivity, will not be expected to have such elevated cough responses to such capsaicin provocations.

Hillert *et al.* (2007) reported an interesting brain PET scan study, comparing MCS patients with normal controls both before and after chemical exposure. They used substantial amounts of chemicals for this study, such that both normals and MCS patients showed changes in brain PET scans after chemical exposure, but different changes. Hillert *et al.* (2007) were exploring the hypothesis that the brains of MCS patients might be particularly active in processing odour exposure information in the brain. They found that, whereas two regions of the brain have higher levels of neural activation in response to chemical exposure in MCS patients, as compared with controls, the olfactory processing regions were less responsive in MCS patients vs. controls. So the changes in olfactory processing contradicted their prediction. The two regions showing higher chemically elicited activation in MCS patients were the anterior cingulate cortex and the cuneus-precuneus. The anterior cingulate cortex is part of the limbic system, so the view presented in the current review leads us to ask whether chemical exposure might be expected to produce increased neural sensitization in this region of the brain. The TRPV1 receptor is thought, as discussed above, to often act as a receptor for various organic solvents and related chemicals in MCS, leading one to ask whether the TRPV1 receptor is located in the anterior cingulate cortex. Steenland *et al.* (2006) have found that there are quite high levels of TRPV1 activity in the anterior cingulate cortex, consistent with a local activation by chemicals in this region of the brain. While it is quite possible that this interpretation is oversimplified, it provides us with an interpretation that is compatible with the NO/ONOO$^-$-cycle–neural-sensitization model of what may be happening in the brain to generate MCS-related chemical sensitivity. In any case, the observations of Hillert *et al.* (2007) provide us with an approach to developing a specific biomarker test for MCS-related changes in the brain.

A series of EEG studies have been published in which changes of EEG patterns in MCS patients have been reported in response to low-level chemical exposure, but where normal controls show little or no similar changes (Bell *et al.*, 1999b; 2001b; Schwartz *et al.*, 1994; Fernandez *et al.*, 1999; Lorig *et al.*, 1991; Lorig, 1994). These changes, which presumably reflect changes in neural sensitization in MCS, may well provide objectively measurable changes in response to chemical exposure. My own understanding of this area is distinctly limited, so I am unable to give the reader any insights as to the pros and cons of this approach.

Joffres *et al.* (2005) reported increases in skin conductivity in MCS patients, but not in normal controls in response to low-level chemical challenge. Interestingly these skin conductivity increases were more reproducibly linked to the blinded chemical exposures in MCS patients than were there self-reported symptoms. These responses are similar to the responses measured

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in 'lie-detector tests'. The authors suggest that these responses to low-level chemical exposure may reflect a neural sensitization mechanism, indirectly influencing skin conductivity.

Kimata (2004) reported on changes in serum levels of four substances, comparing responses to low-level chemical exposures in normal controls, MCS patients and also in atopic eczema/dermatitis syndrome (AEDS) patients. The chemicals used were outgassed organic solvents in a recently painted room totalling between 3 and 3.5 mg m^{-3}. The four substances produced in response to chemical exposure were substance P (SP), vasoactive intestinal peptide (VIP), NG and histamine. The basal levels of SP, VIP and NG were elevated in MCS patients and these three, and also histamine, were elevated in the AEDS patients. These can all be viewed as inflammatory markers with SP, VIP and NG being linked to neurogenic inflammation, as suggested by Kimata (2004) and acting to increase mast-cell activation/degranulation and therefore increased histamine levels. All four of these increased in response to low-level chemical exposure in the MCS patients but *not* in either controls or in AEDS patients, although AEDS patients showed elevation of all four vs. normal controls. The increase of any of these in response to low-level chemical exposure may be useful as a possible specific biomarker test for MCS. The responses to low-level chemical exposure seem to be specific to MCS and are not produced by the inflammation seen in AEDS. Based on the data presented by Kimata, perhaps histamine may be the most interesting of these because the basal levels in MCS patients showed little, if any, elevation over normal controls, but low-level chemical exposure produced an almost doubling of these levels. These involve relatively simple serum testing, making these tests perhaps the most easily accessible in the clinical setting. One comment I have is that the data presented by Kimata (2004) show surprisingly consistent basal levels and also levels after chemical exposure from one MCS patient to another. One can't help wondering whether the patients studied here may have had MCS cases of very similar severity and it is possible that other cases with lowered severity may show lowered responsiveness.

Elberling *et al.* (2007) reported that basophils isolated from chemically sensitive patients responded to perfume exposure by releasing elevated amounts of histamine as compared with basophils isolated from normal controls. These results suggest that one can assay sensitivity even at the level of individual cells from sensitive individuals and that histamine release in response to chemical exposure may be a good assay for such sensitivity. It should be noted that the TRPV1 receptor is present on basophils (Planells-Cases *et al.*, 2005), as are some other TRP receptors. It is possible, therefore, that sensitivity to chemicals mediated by these receptors might be expressed at the cellular level.

Peden (1996) reviewed studies of nasal lavage to provide objective measurement of irritant-induced nasal inflammation, including studies of multiple chemical sensitivity or sick-building syndrome. Such nasal lavage samples can be used to measure a large number of inflammatory markers, including inflammatory cytokines, NO, eicosanoid mediators, inflammatory neuropeptides and others. Some studies of this type were reported by Koren and Devlin (1992) and Koren *et al.* (1990; 1992), in which chemically sensitive people with rhinitis responses to chemicals reacted to such chemical exposure with increased measurable inflammatory markers in nasal lavage samples. These studies did not compare their results with those of normal controls without such rhinitis responses, but it would be surprising if there would be a similar inflammatory response in such people. Such controls were performed by Hirvonen *et al.* (1999), who showed that chemically sensitive people previously sensitized in a mould-infested building responded to mould exposure with increased inflammatory cytokines and increased NO production, unlike normal subjects, using nasal lavage to measure such responses. This is a good example of how nasal lavage may be used as an objective measure of sensitivity responses in 'sick-building syndrome' situations.

Interestingly, in a series of studies, Hirvonen *et al.* (1997a; 1997b) and Ruotsalainen *et al.* (1995) showed that one could show similar inflammatory responses to mould and other microbial materials in cells in culture, suggesting that such cell-culture responses could be used as a bioassay to isolate and identify materials from these organisms that produce such an inflammatory response.

In summary, these various objectively measurable responses to chemical exposure reflect three distinct predicted aspects of the $NO/ONOO^-$ cycle mechanism. The cough responses reflect a TRPV1 stimulation leading in turn to increased NMDA activity; several of the other tests presumably reflect neural sensitization responses; still others measure inflammatory responses. Many of these are likely to reflect local sensitivity, which may occur in some MCS patients, but not others. This is expected to be the case with the cough responses and nasal lavage measurements. So their possible role as specific biomarker tests may be expected to be limited to those having lung or upper respiratory tract impact, respectively.

As tests to be used in a clinical setting, perhaps the cough response to low-level capsaicin challenge, the nasal lavage tests, and the histamine and other responses studied by Kimata (2004) may be the most easily applied. One or more of these may be used, then, in a clinical context, to provide confirmation of MCS diagnoses initially based on the fit to an accepted case definition.

It is the author's opinion that the published studies suggest that we have a number of promising possible specific biomarker tests and it is essential, in my view,

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that further research be done to establish some of these as specific biomarker tests for MCS to be used for both clinical diagnostic and experimental purposes.

14 PATTERN OF EVIDENCE: FIT TO THE FIVE PRINCIPLES

The five principles underlying the NO/$ONOO^-$ cycle mechanism show how the cycle provides explanations for the wide variety of illness/disease properties. Where there is a good fit to each of the five, one can argue that a particular disease or illness is a good candidate for being caused by the NO/$ONOO^-$ cycle mechanism. In this sense, the five principles function collectively a bit like Koch's postulates. Having described much of the evidence above that is relevant to this issue of fit, it is time to summarize how good the fit is for each of the five principles in the case of MCS. I will not, in most cases, provide citations here, as they have been provided in the preceding sections of this review.

14.1 Short-term Stressors that Initiate Cases of Multisystem Illnesses Act by Raising NO Synthesis and Consequent Levels of NO and/or Other Cycle Elements

Each of the seven classes of chemicals implicated in initiating cases of MCS are known to act to increase NMDA activity and it is known that increased NMDA activity produces, in turn, increases in intracellular calcium, NO and $ONOO^-$. Elevated NMDA activity, intracellular calcium, NO and $ONOO^-$ are all elements of the cycle. It follows that there is an excellent fit to the first principle.

14.2 Initiation is Converted into a Chronic Illness through the Action of Vicious Cycle Mechanisms, through which Chronic Elevation of NO and $ONOO^-$ and Other Cycle Elements is Produced and Maintained

This principle predicts that the various elements of the NO/$ONOO^-$ cycle will be elevated in the chronic phase of illness. Here we need to go through the various elements of the cycle to determine what evidence, if any, is available for their elevation in MCS.

There are numerous types of evidence for elevation of three closely linked elements of the cycle, NO, $ONOO^-$ and oxidative stress (Pall, 2002; 2007a; and see above):

- Several organic solvents implicated in MCS have been shown to produce increases in NO.
- Organophosphorus and carbamate pesticides, through their actions as acetylcholinesterase inactivators, can lead to increased muscarinic activity, which lead in turn to increased NO synthesis.
- Neopterin, a marker of increased iNOS induction (Pall, 2000; Pall and Satterlee, 2001), has been reported to be elevated in the more severely affected MCS patients (Bell *et al.*, 1998c).
- Elevated NO has been found in several animal models of MCS and in two of these, it clearly has an essential role in producing the biological response.
- Elevated levels of 3-nitrotyrosine were found in several studies of an MCS animal model and 3-nitrotyrosine is a marker of $ONOO^-$.
- MCS, and the related conditions CFS and FM, have been treated by methods that greatly elevate hydroxocobalamin levels *in vivo*, and hydroxocobalamin is a form of vitamin B_{12} that is known to be a potent NO scavenger. The across-the-board improvement in symptoms suggests that NO has a role, either directly or indirectly, in generating the symptoms of these illnesses.
- It is known that $ONOO^-$ can produce a breakdown of the blood–brain barrier and such breakdown has been reported in both MCS patients and in an animal models of MCS.
- Several types of evidence implicate elevated NMDA receptor activity in MCS and and in related illnesses, including FM. Such elevated NMDA activity is known to produce increases in NO and $ONOO^-$.
- Oxidative stress has been reported in MCS patients (Ionescu *et al.*, 1999; Lu *et al.*, 2007), as well as in several animal models of MCS. The notion that oxidative stress is central to the pathophysiology of MCS was first explored by Levine (1983a; 1983b) 25 years ago.

There are three types of evidence suggesting that inflammatory cytokine levels are elevated in MCS:

- Nasal lavage studies of MCS patients have reported to have elevated inflammatory cytokine levels and elevated levels of other inflammatory markers.
- Several animal models of MCS have elevated inflammatory cytokines.
- While there have not been any systemic measures of inflammatory cytokines in MCS patients, to my knowledge, there have been multiple such studies of the related illnesses CFS and FM with reported elevations.

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There are 13 distinct types of evidence implicating elevated NMDA activity in MCS; each of the seven classes of chemicals implicated in MCS can act by producing increased NMDA activity and there are also six additional types of evidence. These are all provided in Section 3 of this chapter.

Pall and Anderson (2004) listed 12 distinct types of evidence suggesting that elevated TRPV1 activity has roles in MCS. Ashford and Miller (1998) listed 10 striking similarities between MCS and neural sensitization, each of which can be viewed as evidence for neural sensitization in MCS; the animal model studies implicating neural sensitization provide an additional type of evidence. In addition, several of the putative specific biomarker tests, discussed above, provide support for a neural sensitization mechanism, providing a 12th type of such evidence.

Although there is extensive evidence for mitochondrial/energy metabolism dysfunction in CFS and FM, the only evidence for such dysfunction in MCS is from PET scan studies. Because the probe used in such PET scan studies is a glucose derivative, its transport and accumulation in the tissues is strongly impacted by mitochondrial dysfunction (Pietrini *et al.*, 1998; Holthoff *et al.*, 2004; Silverman *et al.*, 2001).

In summary, although there have been no studies on either NF-κB elevation or BH4 depletion in MCS, to my knowledge, there are a total of 51 distinct published types of evidence supporting the role of one or more aspects of the NO/ONOO$^-$ cycle in the chronic phase of MCS. Given the paucity of research support that has been available for MCS research, that is a surprising amount of evidence!

14.3 Symptoms and Signs of these Illnesses are Generated by Elevated Levels of NO and/or Other Important Consequences of the Proposed Mechanism, that is, Elevated Levels of ONOO$^-$, NO, Inflammatory Cytokines, Oxidative Stress, Elevated NMDA, TRPV1 Receptor Activity and/or Other Aspects of the Cycle

You have seen above and elsewhere (Pall, 2007a) that we can explain a wide variety of symptoms and signs of MCS through the NO/ONOO$^-$ cycle mechanism. While these proposed explanations are based on well-established mechanisms, their roles in MCS and related illnesses should be viewed as plausible, not established.

14.4 Because the Compounds Involved, NO, Superoxide and ONOO$^-$ have Quite Limited Diffusion Distances in Biological Tissues and because the Mechanisms Involved in the Cycle Act at the Level of Individual Cells, the Fundamental Mechanisms are Local

A local mechanism is supported in MCS and related illnesses basically from two distinct types of observations: The stunning variations in symptoms and signs of illness and in overall severity going from one MCS patient to another is difficult to explain without having a local mechanism that can have variable impact among the tissues of the body. Such tissue distribution can be directly visualized in the brain PET scan and SPECT scans studies, which show striking variations from one patient to another.

14.5 Therapy Should Focus on Down-Regulating NO/ONOO$^-$-Cycle Biochemistry

There have been, unfortunately, few studies of therapy for MCS and except for one, these have been at the level of clinical observation and anecdotal reports, rather than clinical trials. The data we have available to ask for possible fit to the fifth principle are limited to the following:

- Clinical trial data on the related illnesses CFS and FM, where much more extensive data is available
- Evidence on causality from animal models of MCS
- A single clinical trial on MCS patients
- A variety of clinical observations and anecdotal reports.

The last of these is discussed in Chapter 15 of Pall (2007a) and will just be referred to here briefly.

Each of these types of observations provides evidence towards a fit to the fifth principle.

The animal model data that was discussed above provides evidence for causal roles of NO, TRPV1 activity and NMDA activity. Each of these types of studies have used agents that relatively specifically lower these activities and provide evidence, in the animal models, for what are, in effect, therapeutic effects of agents that down-regulate these specific aspects of the NO/ONOO$^-$ cycle.

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There are quite a number of clinical trials with CFS and/or FM showing apparent efficacy of agents predicted to down-regulate various aspects of the NO/ONOO$^-$ cycle (**Table 4**). The citations for these clinical trials are provided in Chapter 15, Pall (2007a), except for the more recent trials. These recent trials are for pregabalin, a drug that indirectly lowers excitotoxicity, including NMDA activity (Mease *et al.*, 2008; Crofford *et al.*, 2005); D-ribose (Teitelbaum *et al.*, 2006; Gilula, 2007); and the antioxidant *Ecklonia cava* extract (Bierman, 2008, see also In Focus, 2007).

As can be seen from **Table 4**, of these 16 classes of agents, many have antioxidant properties, providing evidence that oxidative stress has an important causal role in generating these illnesses. Some of these agents either act as NMDA antagonists, or act indirectly to lower NMDA activity, thus providing strong evidence for a causal role of excessive NMDA activity. Carnitine/acetyl carnitine, coenzyme Q10 and possibly hyperbaric oxygen are likely to act to help improve mitochondrial function, thus providing evidence for a causal role of mitochondrial/energy metabolism dysfunction.

The potent NO scavenger, hydroxocobalamin is a form of vitamin B_{12}, but its role is much more likely to involve scavenging NO. In a clinical trial study (Ellis and Nasser, 1973), there was no correlation between initial B_{12} levels and the clinical response. Furthermore, higher doses are needed to get clinical responses here than are needed to treat a B_{12} deficiency. It seems unlikely, therefore, that hydroxocobalamin is acting to allay a B_{12} deficiency. The potent action of hydroxocobalamin as a NO scavenger is sufficiently well established that hydroxocobalamin has been used in experimental settings to establish a role for NO in biological processes (Pall, 2001b).

There is also weaker evidence for two other aspects of the NO/ONOO$^-$ cycle having a causal role. The long chain omega-3 fatty acids in fish oil are well known to have anti-inflammatory aspects, so that their reported efficacy provides some evidence for an inflammatory causal role, although an alternative interpretation to these observations is also possible. High-dose vitamin C and high-dose folate supplements help restore BH4 levels, suggesting a causal role of BH4 depletion, but again, there are other possible interpretations for their actions, so the evidence for BH4 depletion being causal must be viewed as relatively weak.

There are a number of clinical observations suggesting that these same agents are often helpful in MCS treatment, suggesting a possible similar aetiology. The various types of evidence supporting an NO/ONOO$^-$-cycle mechanism for all three of these illnesses (Pall, 2006; 2007a; 2007b) of course also suggest a common aetiological mechanism.

The only relevant clinical trial on MCS patients is that of Heuser and Vojdani (1997), which used high-dose vitamin C therapy and showed objectively measurable improvements in immune function in response to therapy.

In chapter 15, Pall (2007a), I discuss five different protocols that have used multiple agents predicted to down-regulate different aspects of the NO/ONOO$^-$ cycle. Each of these five uses at least 14 agents/classes of agents. Two of these protocols have been tested in clinical trials, one (Teitelbaum's) with both CFS and FM patients and the other (Nicolson's) with CFS-like patients. Each of the five protocols appears to produce substantially better clinical responses than do single agents. This approach may, then, be promising as a general approach to the treatment of these illnesses. Of these, only the Pall/Ziem protocol has been tried on chemically sensitive patients and the generally favourable response to this protocol is described by Dr. Grace Ziem in that chapter.

Subsequently, the author has developed a somewhat different approach to nutritional support of these patients through the Allergy Research Group, containing 22 different agents/classes of agents predicted to down-regulate different aspects of the NO/ONOO$^-$ cycle. Physicians and others using this approach report favourable responses with a large majority of patients with CFS, FM or MCS. In some cases, people who have been ill for two or more decades report rapid improvements within three or four weeks, improvements that are sustained for periods of six months or more, but do not, in general, clearly progress towards complete recovery. Clearly, the reader needs to maintain a high level of scepticism, at this point. These are unpublished observations, they do not constitute anything approaching a clinical trial and the author has a conflict of interest here, receiving some royalties from the Allergy Research Group.

In summary, there are a number of types of evidence that provide some support for the view that agents that down-regulate various aspects of the NO/ONOO$^-$ cycle produce clinical improvement in patients with MCS and in related illnesses. However, there is a great need for much more clinical study of these approaches. Clinical trial data from the related illnesses, CFS and FM, provide substantial support for the view that oxidative stress, excessive NMDA activity and NO all have causal roles; less convincing evidence suggests that inflammatory biochemistry and BH4 depletion also have causal roles in these illnesses. Various aspects of the cycle also are reported to have causal roles in MCS animal models.

15 PSYCHOGENIC CLAIMS

There have been a whole series of papers published arguing that MCS and/or the related multisystem illnesses are not physiological illnesses but are, rather, what has become known as psychogenic, having some often ill-defined psychological or psychiatric origin. These same authors have often argued that MCS should be called idiopathic environmental intolerance, a name that

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Table 4 Clinical trial studies of agents predicted to lower NO/ONOO$^-$ cycle elements in the related illnesses chronic fatigue syndrome and fibromyalgia

Agent or class	Mechanism	Comments
Vitamin C (ascorbic acid)	Chain-breaking antioxidant; lowers NF-κB activity; reported to scavenge peroxynitrite and also help restore tetrahydrobiopterin (BH4) levels by reducing an oxidized derivative of BH4	May require high doses to be effective with the latter two mechanisms; this may be the basis of so-called 'megadose therapy' for vitamin C; clinical trials on CFS and MCS used high-dose IV ascorbate
Magnesium	Lowers NMDA activity and may be useful in improving energy metabolism and ATP utilization	Magnesium is the agent that is most widely studied and found to be useful in the treatment of the multisystem illnesses
Fish oil (long chain omega-3 fatty acids)	Lowers iNOS induction; lowers production of inflammatory eicosonoids; important for brain function	Highly susceptible to lipid peroxidation and may, therefore be depleted; four studies reported improvements in clinical trials, three with CFS and one with FM
Flavonoids	Chain-breaking antioxidants; some scavenge peroxynitrite, some scavenge superoxide; some reported to induce superoxide dismutase (SOD); All three types are found in FlaviNox; some flavonoids may also act to help restore BH4 levels; lower NF-κB activity	Ginkgo extract tested in CFS; anthocyanidin flavonoids in FM; other flavonoids tested in CFS animal model
NMDA antagonists	Lower NMDA activity	Four different antagonists reported to be effective in the treatment of fibromyalgia; anecdotal reports of effectiveness for MCS
Agents that indirectly lower excitotoxicity *including NMDA activity*	—	Only clinical trials done with pregabalin for fibromyalgia, but other members *of this class often used clinically*
Acetyl L-carnitine/carnitine	Helps transport fatty acids into mitochondria; may be important here not only directly for energy metabolism but also to restore the oxidized fatty acid residues that may be produced in the cardiolipin of the inner membrane	May also help lower reductive stress; two trials in CFS
Ecklonia cava extract	Polyphenolic chain-breaking antioxidant; reported to help scavenge both peroxynitrite and superoxide; based on its reported properties, it may also help restore BH4 levels	Appears to stay in the body much longer than do the flavonoids, a useful property; reported to be helpful in a clinical trial study of fibromyalgia
Reductive stress relieving agents	These include S-adenosyl methionine (SAM or SAMe), trimethylglycine (betaine), carnitine and choline	SAM reported to be effective in multiple clinical trials with FM and CFS patients; betaine widely used clinically
Hydroxocobalamin form of vitamin B-12	Potent nitric oxide scavenger, lowers nitric oxide levels	Limited intestinal transport; often taken by intramuscular injection or as a nasal spray or inhalant; clinical trial with CFS-like illnesses; widely used for treatment of CFS, FM and MCS
Folic acid	Relatively high doses will lower the partial uncoupling of the nitric oxide synthases by helping to restore tetrahydrobiopterin (BH4)	Reacts with oxidants and therefore may be depleted due to the NO/ONOO$^-$ cycle

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Table 4 (*continued*)

Agent or class	Mechanism	Comments
Algal supplements	Probably act as antioxidants	—
Hyperbaric oxygen	May act to help restore cytochrome oxidase activity by competing with nitric oxide	My impression is that this approach needs to be used with substantial care—too high or prolonged dosage can cause damage
Trimethyl glycine (betaine), S-adenosyl methionine (SAM), choline, carnitine	Lower reductive stress; also helps with the generation of S-adenosyl methionine (SAM)	While lowering reductive stress may be the main concern, SAM generation may also be of concern; the enzyme methionine synthase is inhibited by nitric oxide and inactivated under conditions of oxidative stress, thus leading to lowered SAM and lowered methylation
Coenzyme Q10 (ubiquinone)	Important in mitochondrial function; important antioxidant, especially in mitochondrion; reported to scavenge peroxynitrite	Optimal dosage may vary considerably among different individuals; suggest taking early in day
D-ribose, RNA or inosine	Two important functions: Provides adenosine for restoring adenine nucleotide pools after energy metabolism dysfunction; when catabolized, the purine bases generate uric acid, a peroxynitrite scavenger	Each of these may act somewhat similarly; however only D-ribose has been tested in a clinical trial and reported to be effective; each of these agents has distinct drawbacks

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denies, in effect, that chemicals cause MCS or have a role in eliciting symptoms in people who suffer from MCS. It also denies that we have a mechanism that may explain the many puzzling features of MCS. The name implies that we have neither initiating causes nor ongoing causes of illness.

What this section does, is to briefly and superficially review this field, making many generalizations, some of which may not be adequately supported. To do a thorough review would take a paper considerably longer than this entire chapter, so there is not space nor time to do so. The reader is referred to Chapter 13 in Pall (2007a), which provides a more comprehensive discussion of this area, not just for MCS, but also for CFS and FM. The reader is also strongly encouraged to look at the papers advocating a psychogenic basis for MCS (**Table 5**) and the Davidoff and Fogarty (1994), the Davidoff *et al.* (2000) and the McCampbell (2001) reviews.

From a toxicological perspective, none of these psychogenic advocate papers considers the question of what chemicals are apparently involved in MCS and how they might act as toxicants in the human body. From a toxicological perspective, therefore, they all must be viewed as being flawed. This section outlines the main issues with regard to psychogenesis of MCS that were developed in Chapter 13 in Pall (2007a) and then discusses several of the reviews that have each been written from a psychogenic perspective.

There are, in the author's view (Pall, 2007a), 10 important issues that challenge the positions of psychogenic advocates of MCS and related multisystem diseases and we are considering these here one at a time.

Many such advocates argue that these multisystem illnesses are caused by 'belief' and that they are somatoform disorders generated by a mechanism called somatization. How well founded are these views? Let's consider the basis of somatoform disorders and somatization.

Somatoform disorders are defined (Smith, 1990) as a group of disorders with somatic symptoms that suggest a physical disorder, but for which no organic aetiology can be demonstrated. There is presumptive evidence of a psychological basis for the disorder.

Somatization is defined as a process whereby psychological distress is expressed in physical symptoms (Smith, 1990). So psychogenic advocates typically argue that MCS and the other multisystem illnesses are somatoform disorders generated by the process of somatization. According to its definition, it is incumbent on such psychogenic advocates to demonstrate that *no organic aetiology can be demonstrated*. That is, they not only need to show that no organic aetiology *has* been demonstrated but that none *can* be. This is a very difficult hurdle for them and none of them, to my knowledge, have even tried to jump it. They rarely, if ever, consider the detailed properties of the mechanism proposed here, or the neural sensitization interpretation or the neurogenic inflammation interpretation, nor have they developed a

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Table 5 Publications of MCS skeptics

Gots (1996)	Argues for a psychogenic 'mechanism' for MCS based mainly on dualistic reasoning
Barsky and Borus (1999)	Argues the multisystem illnesses are 'functional somatic syndromes'. Unclear whether this argues for psychogenesis, but paper is often cited by those advocating psychogenesis
Kellner (1994)	Argues that multisystem illnesses are somatoform disorders caused by somatization
Staudenmayer (1999)	Staudenmayer's book makes the longest argument for psychogenesis in MCS
Wessely *et al.* (1999)	Argues that the multisystem illnesses may not be distinct and may share an aetiology possibly centred on psychogenesis
Binder and Campbell (2004)	Similar arguments to Gots (1996), Kellner (1994) and Staudenmayer (1999); considers a broader group of illnesses
Staudenmayer *et al.* (2003a)	Goes through the Hill criteria, asking whether MCS (IEI) can be a physiological illness caused by chemical exposure.
Staudenmayer *et al.* (2003b)	Goes through the Hill criteria, asking whether MCS (IEI) can be a psychogenic illness
Wiesmüller *et al.* (2003)	Another proposal to the effect that these multisystem illnesses may be somatization disorders. While considering these illnesses from a predominantly psychiatric perspective and ignoring physiological, biochemical and animal model data, the authors are much more circumspect about their inferences than are the psychogenic advocates
Hausteiner *et al.* (2007)	A psychiatric interpretation of MCS or what they call IEI.
Eis *et al.* (2008)	Complex psychological study; argues against physiological interpretations while providing no data on them
Das-Munshi *et al.* (2006)	Review of provocation studies in MCS
Das-Munshi *et al.* (2007)	Review of MCS, from a group of psychogenic advocates from the Institute of Psychiatry, Kings College, London

compelling argument ruling out *any possible organic aetiology*.

While it may be argued that they have never even attempted to seriously fulfil this requirement, it is also the case that the very concepts of somatoform disorders and somatization have come under increasing attack (Janca, 2005; Epstein *et al.*, 1999; Mayou *et al.*, 2005; Dalen, 2003; Bradfield, 2006; Sykes, 2006). There are a number of reasons for this, including the issue that the concept of somatoform disorders and somatization is based on a dualistic view of human beings, where the psychological/psychiatric/mental is separate and distinct from the biological/physiological/physical. The process of somatization assumes that all of the initial causes are on one side of this dualism and somehow reach across the divide to generate physical symptoms. However this Cartesian dualism has been rejected by modern science. For example the American Psychiatric Association (1994) states that 'there is much "physical" in "mental" disorders and much "mental" in "physical" disorders'. Dualistic reasoning has been used repeatedly by advocates of psychogenesis of MCS and other multisystem illnesses and has led them astray in many circumstances. Let us consider an example: a letter published by Black (2002) on the apparent effectiveness of the drug paroxetine in the treatment of MCS. Paroxetine has been shown to lower NOS activity (reviewed in Chapter 6, Pall, 2007a) and is also a serotonin reuptake inhibitor and is a drug that has been used to treat certain psychiatric disorders. Black reports that this drug was effective in the treatment of an MCS patient and in other studies, in two other patients and concludes that, 'This case joins two others in showing *that some patients diagnosed with multiple chemical sensitivity have an underlying psychiatric disorder that, when identified, responds to medication therapy*' (italics added). Black concludes that because paroxetine has been effective in the treatment of some psychiatric diseases, it must be acting to correct a psychiatric flaw in these MCS cases. This is the same logical flaw as if one were to argue that: aspirin cures headaches; aspirin decreases blood clotting; therefore headaches cause blood clotting. The logical flaw here is obvious, but because Black is so immersed in an assumed dualism, he cannot apparently see it. I will provide some additional examples of such dualistic reasoning below.

We have discussed, thus far in this section, three weaknesses that show up in the positions of psychogenic advocates of MCS: that they base their arguments on the concepts of somatoform disorders and somatization, concepts that they have never shown to be adequately supported in MCS and concepts that have been attacked on a theoretical basis as well; that much of their position is based on a rejected dualism between the mental/psychiatric/psychological on the one hand and the physical/biological/physiological on the other; and that

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this rejected dualism has led them, in turn, to make logical flaws. These, then are three substantial flaws underlying psychogenesis—there are others.

Another important issue is that there is a long history of false psychogenic attribution in medicine. In Chapter 13 (Pall, 2007a), there is a discussion of the fact that each of the following diseases has been falsely claimed to have an aetiology that is largely or completely psychological:

1. Multiple sclerosis (MS)
2. Parkinson's disease
3. Lupus
4. Interstitial cystitis
5. Migraine
6. Rheumatoid arthritis
7. Asthma
8. Gastric and duodenal ulcers
9. Ulcerative colitis.

Each of these has been subsequently been shown to be a real physiological disease. Of that list, the psychogenic claim that has been most recently rejected by modern science is number 8, ulcers, for which two Australian physicians, Robin Warren and Barry Marshall won the 2005 Nobel prize in physiology and medicine for showing that the bacterium *Helicobacter pylori* plays a key role in the development of both types of ulcers. Ulcers are a bacterial infectious disease, with ulcers being generated when the inflammation produced by a *Helicobacter pylori* infection becomes sufficiently severe. Ulcers can be treated by a simple antibiotic regimen and this is not a psychogenic illness, as had been confidently claimed for decades.

It is essential, in the author's view, that psychogenic advocates of MCS or other multisystem illnesses show that they are not repeating the same errors that led to false psychogenic claims in the past. However, none of them has ever apparently considered this issue in their publications.

A fifth issue is the role of genetics in dealing with susceptibility to MCS or other multisystem illnesses. There is substantial published evidence for a role of genetics in determining such susceptibility, not only in MCS, but also with CFS, FM and PTSD. The role of specific genes in MCS provides strong support for the inference that chemicals are acting as toxicants in MCS and the role of the CCK-B gene also provides some evidence for a role of the NMDA receptors. Thus the genetic evidence is in very good agreement with the mechanism discussed in this review. The genetics of CFS is also consistent with a $NO/ONOO^-$ cycle mechanism (Chapter 5, Pall, 2007a). But there is a more fundamental issue with a genetic role. Genes act by influencing the structure and amounts of proteins synthesized in the body and by doing so, determine both the physical structure of the body and its biochemical activities. In a dualistic framework, they act to determine the biology and any psychological effect is indirect, produced from the biology. Staudenmayer (1999, p. 20) states that, 'The core supposition of psychogenic theory is that psychological factors are *necessary and sufficient* to account for the clinical presentations of EI [what he calls MCS] patients. Psychogenic theory emphasizes belief, somatization, psychophysiologic stress and anxiety responses, and psychogenic etiology' (italics added). Obviously if psychological factors are *necessary and sufficient*, then there is no room for a genetic role, or for any other biological role. The demonstrated genetic roles in MCS and other multisystem illnesses show that psychological factors are *not* sufficient.

A sixth issue is that psychogenic advocates rarely make clear, testable predictions. The Staudenmayer prediction discussed in the previous paragraph is a rare, perhaps unique, exception to this and as indicated immediately above, the test leads to rejection of the psychogenic hypothesis. The need to make clear, testable (and therefore potentially falsifiable) predictions is essential in science. One of the things that they do, however, is to suggest that because some (but not other) patients with multisystem illnesses clearly suffer from what are classified as psychiatric symptoms, that therefore the multisystem illnesses should be viewed as psychiatric. However, there is a large amount of literature showing that most, perhaps all, serious chronic diseases are characterized as having comorbid psychiatric symptoms, but that does not mean that these serious chronic diseases are psychiatric. The fact that cancer patients and rheumatoid arthritis patients have higher prevalences of PTSD, anxiety and depression, for example, does not make either cancer or rheumatoid arthritis a psychiatric disease.

A seventh issue is that scientists have an obligation to avoid emotion-laden rhetoric and to attempt to provide objective assessments of the scientific literature. Some examples of such emotion-laden statements from the psychogenic advocates are provided elsewhere (Chapter 13 in Pall, 2007a) and will not be repeated here. The focus here is on the need to provide an objective assessment of the literature. Let us consider some specific examples.

The Binder and Campbell (2004) review has relatively brief discussions of several illnesses, including MCS, CFS and FM with relatively few citations provided for each of them. They argue that in these illnesses, cognitive abnormalities are not caused by neurological disease, but rather are caused by 'biological and psychological factors', while concentrating their claims heavily on the psychological side. It is probably reasonable to expect that the relatively few citations on each illness will be carefully chosen to represent some relatively objective assessment of the relevant literature. Let's take a look at some of them here.

On p. 371, Binder and Campbell (2004) argue that the proposed name change from CFS to chronic fatigue and immune dysfunction syndrome was made 'despite the lack of evidence of immune dysfunction in this illness'.

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The only citation provided is that of the psychiatrist and psychogenic advocate Wessely (1997). They would apparently have us believe that the extensive evidence for immune dysfunction in CFS, reviewed, for example, by Komaroff and Buchwald (1998), by Patarca (2001) and by Klimas and Koneru (2007), does not exist because one psychogenic advocate argues that it does not.

In the MCS section of their paper, Binder and Campbell claim that the substances triggering discomfort in people with MCS are 'aromas rather than neurotoxins', citing the psychologist Bolla (2000) as their only documentation for this. They would apparently have us believe that the hundreds of citations showing that organic solvents are neurotoxicants that are cited in Kilburn (1998) or that the many citations showing that pesticides are neurotoxicants cited earlier in this chapter do not exist.

Binder and Campbell (2004) also state that sensitization 'may be initiated by aversive childhood experiences such as sexual abuse', providing Bell *et al.* (1998b) as their only documentation. What Bell *et al.* (1998b) actually report is that girls with a history of sexual abuse were at apparently greater risk for later becoming chemically sensitive, not that it directly initiated cases of MCS. But what is much more important is that they cite this one study as evidence for a possible causal role of sexual abuse in MCS, while completely ignoring the many dozens of studies showing an apparent causal role for chemical exposure in initiation of cases of MCS—and chemical exposure often leads very quickly to the development of MCS symptoms—as compared with the possible role of sexual abuse as a risk factor in the medical history of the patient. This is, unfortunately, a typical example from the psychogenic literature of only citing evidence that can be interpreted as supporting their viewpoint, while completely ignoring massive literature that contradicts it.

Binder and Campbell (2004) also dismiss a number of physiological changes found in MCS and other multisystem illnesses based on these same changes being found in what are classified as psychiatric diseases. For example they state that, 'Neuroendocrine abnormalities are associated with FM and that the illness is caused by abnormal sensory processing. *However emotional problems also are associated with neuroendocrine disorders. We know of no evidence of neuroendocrine abnormalities specific to that condition.* There was evidence of reduced cerebral blood flow in the thalamus and pontine tegmentum in patients with FM, *but similar findings are nonspecific and occur in psychiatric patients*' (italics added). It should be noted that, as discussed above, similar neuroendocrine abnormalities are also reported in FM and CFS, as well. Later in the same paper they state that, 'A fluorine [sic]-deoxyglucose PET study suggested that hypometabolism of the brain stem was found only in CFS and not in depression, *but a study using the same technique found no differences between a group with CFS and a group with somatization disorder*' (italics added). Again similar brain changes are reported in MCS and CFS, albeit with different tissue distribution. In both of these quotes, Binder and Campbell (2004) dismiss any biological significance of objectively measurable physiological changes in these multisystem illnesses, if similar changes are also reported to occur in psychiatric diseases. By their dualistic reasoning, if a physiological change occurs in a psychiatric disease it is forever dismissed as a biologically significant marker in other illnesses, based on some sort of guilt by association. The obvious inference that when these changes are seen in a psychiatric disease, they are important clues as to the pathophysiology of that disease seems to be completely lost on them.

The dualistic reasoning seen with Binder and Campbell is all too common in the psychogenic literature. The Black (2002) letter with its dualistic reasoning is discussed above. Gots' (1996) paper on MCS is essentially all based on such dualistic reasoning. In it he states, 'Stimulation of a neurotransmitter or release of a hormone occurs in response to stimulus. Evidence of response to stress or phobia, such as EEG changes or elevated cortisol levels, helps to describe part of the organic interface between stimulus and response and supplements our knowledge of how the mind produces symptoms. *These responses, however, are not indicative of organic dysfunction and do not eliminate the role of the mind in the phobic or stress response*' (italics added). The author noted (Chapter 13, Pall, 2007a) that, 'Gots would have us believe that because these are produced in response to psychological stress, cortisol or EEG changes are of no organic consequence, incapable of producing organic dysfunction. Taken to its logical conclusion, this same reasoning would have us believe that if a person responds to psychological stress by committing suicide, he or she is not "organically" dead.' Elsewhere in his paper Gots (1996) makes clear where some of his commitment to this discarded dualism comes from stating that, 'Manufacturers cannot be held responsible for responses that depend on psychological processes'. The legal issues of possible liability for the initiation of MCS cases are often discussed in the papers of psychogenic advocates and they consistently argue against any such liability. Could that be related to their roles as 'expert witnesses' in such liability trials?

In a recent MCS review, Das-Munshi *et al.* (2007), referring to a study by Baines *et al.* (2004), stated that 'a recent study suggested that people with MCS showed a nonsignificant trend towards lymphocyte depletion, but this is also known to occur in major depression, possibly as a result of hypercortisolaemia, and widespread immunological differences have also been shown in people with somatization disorders'. In that one sentence they state that the trend towards lymphocyte depletion in MCS patients was nonsignificant, whereas Baines *et al.* (2004) reported it was highly significant ($p<0.001$);

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they also discount the biological significance of this by suggesting that because similar changes occur in two apparent psychiatric diseases, major depression and somatization disorders, this aberration has no biological significance in MCS. So we see again, dualistic reasoning discounting any objective physiological changes if they occur in what are considered to be a psychiatric diseases. There is a third flaw in this sentence—that in what is *not* said. This statement, when coupled to the lack of any discussion of other objectively measurable changes in MCS, suggests that lymphocyte depletion is the only such reported change, when clearly it is not.

One of the papers that was reviewed in Chapter 13 on psychogenesis of Pall (2007a), was a paper by Staudenmayer *et al.* (2003a) raising the issue of whether chemical exposure meets the Hill (1965) criteria for initiation of cases of MCS. Hill, in his paper, stated nine criteria that were proposed to be used to help determine whether a particular environmental stressor or group of stressors might have a causal role in the initiation of some particular illness or disease. The goal here is to distinguish chance association from causation. The idea was not that all of them had to be fulfilled in order to infer probable environmental causation, but that if there was reasonably good evidence for most of them, one might infer such causation. So the question that needs to be raised in the context of MCS is whether chemical exposure is apparently causal in initiating cases of MCS, based on the Hill criteria. This seemed to be an interesting paper to analyse because Ashford and Miller (1998), themselves did an analysis of the Hill criteria as it applies to MCS (pp. 273–276), so it would be interesting to see how Staudenmayer *et al.* (2003a) might deal with these questions. Staudenmayer *et al.* (2003a) concluded (p. 244) that 'toxicogenic theory fails to meet any of the nine Hill criteria'.

The Staudenmayer *et al.* (2003a) paper is surprising in three ways: firstly they were apparently unaware of the previous Ashford and Miller (1998) treatment of this same topic in their very influential book. Secondly Staudenmayer and colleagues either did not know about or did not see the relevance of any of the cited literature that Ashford and Miller (1998) used to support their view that there was substantial evidence for fulfilling six of the nine Hill criteria with regard to chemical causation of MCS. Thirdly, in several cases, Staudenmayer failed to even ask the question that Hill requires them to ask in supposedly examining the case for the nine Hill criteria. Let's go through the first four Hill criteria one at a time to see how the Staudenmayer *et al.* (2003a) treatment compares with the scientific literature that appears to be relevant to these Hill criteria.

The first Hill criterion is strength of association. In this case, is exposure to the types of chemicals suggested to have a role in causing MCS associated with increased incidence of MCS? There are three main types of evidence suggesting such a relationship (Pall, 2007a, pp. 218–220). Firstly, there is the great increase in synthetic organic chemical production (15-fold increase from 1945 and 1980) and also a roughly similar increase in the production of pesticides, following World War II through the 1980s, paralleling the apparent incidence of MCS. One has to say apparent because we have no good epidemiological data before 1980, so we have to rely on surrogates, such as the increasing scientific and medical interest in this field around the world, as possible measures of increased MCS incidence. Secondly, we have the great increase in 'sick building syndrome' situations in the USA following the decreased requirement for indoor air flow that was put into place in 1973, after the first oil shock. By the late 1980s the US Environmental Protection Agency was reporting that fully 50% of the environmental complaints that they had to deal with were 'sick building syndrome' types of complaints (much of this information comes from Ashford and Miller, 1998 and is discussed in Pall, 2007a, pp. 218–220). So we have an apparent parallel, both with regard to increased chemical production and decreased air flow, and apparent increased MCS initiation. A third example is the genetic evidence that genes that determine the rate of metabolism of chemicals can influence the prevalence and therefore incidence of MCS. The only study that was available before Staudenmayer *et al.* (2003a) submitted their paper was the Haley *et al.* (1999) study on PON1, but there is, as discussed above, much more data available now. Staudenmayer *et al.* (2003a) state that there is no evidence for increased incidence of IEI (what they call MCS) with occupational chemical exposure: this is not accurate because Zibrowski and Robertson (2006), McKeown-Eyssen *et al.* (2001) and Maschewsky, (1996; 2002) present some data on this, as discussed above, but it is fair to state that we have very limited data. There is extensive data both on the existence of occupational asthma and the role of chemical exposure in it, and that it is part of the MCS spectrum of sensitivity, but clearly Staudenmayer *et al.* (2003a) are unable or unwilling to see that connection. Staudenmayer *et al.* (2003a) spend most of their discussion on what is supposed to be the first Hill criterion criticizing the prevalence data on MCS, rather than asking the question that must be asked for this Hill criterion—is there an association of chemical exposure with MCS incidence and prevalence, however those may be defined. In the author's judgement, the evidence for the first Hill criterion in the case of chemical causation of MCS is suggestive, but not compelling, with the exception of the more recent genetic evidence, which was not published before the Staudenmayer *et al.* (2003a) paper was submitted. However, to state, as they did, that there is no such evidence is simply incorrect.

The second Hill criterion is consistency: is there a fairly consistent illness or disease pattern that has been described in a variety of different places and circumstances? Similar observations have been made in a variety of countries around the world, including the USA, at least

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nine European countries, Canada, Australia and Japan. As stated by Miller (1997, p. 445) 'numerous investigators from different geographic regions have published strikingly similar descriptions of individuals who report disabling illnesses *after exposure to recognized environmental contaminants*' (italics added). What Staudenmayer *et al.* (2003a) discuss regarding the consistency criterion is whether or not chemical provocation studies in MCS have been properly performed, ignoring the central issue raised by the second Hill criterion.

The third Hill criterion asks whether there is some specificity to the stressors proposed to initiate a specific disease or illness. Here, Staudenmayer *et al.* (2003a) produce the strongest of their arguments with regard to any of the Hill criteria. The chemicals apparently involved have appeared to have little specificity and many of the case definitions, as seen above, discuss them as being 'unrelated' chemicals. There had been only four papers that had been published before the Staudenmayer *et al.* (2003a) paper had been submitted proposing that chemicals might act via increased NMDA activity and/or increased NO and $ONOO^-$, so perhaps it is not unreasonable that they did not consider that possibility. At this point in time, however, it should be clear that there is a substantial argument for specificity through the common response mechanism of NMDA stimulation, even though diverse chemicals are implicated in MCS initiation and in eliciting symptoms in those already sensitive.

The fourth Hill criterion, that of temporality asks, in the context of MCS, whether chemical exposure precedes or follows the initiation of illness. In Chapter 13 of Pall (2007a), the author led the reader to 30 citations that reported that chemical exposure preceded illness initiation, all apparently published before the submission of the Staudenmayer *et al.* (2003a) paper and there are a dozen additional such citations provided in Section 2 of this review; none of these 42 are cited by Staudenmayer *et al.* (2003a) in what they describe as an 'evidence-based review'. These 42 citations are not a comprehensive list of the literature and there are likely to be many other such publications as well. Among the papers ignored by Staudenmayer *et al.* (2003a) is the highly cited Miller and Mitzel (1995) paper, whose title alone implies that it is relevant to this fourth Hill criterion. How do Staudenmayer *et al.* (2003a) support their contention? They cite a single non-peer-reviewed paper by a psychogenic advocate, Terr (1993), published some 10 years earlier; the Terr paper criticizes people studying the physiological basis of MCS, based on their theoretical models and their methodology for studying the effects of chemical exposure on MCS patients. The Terr (1993) paper is, therefore, irrelevant to the issue of temporality—does chemical exposure precede or follow the initiation of illness. The Terr (1993) paper also refers to MCS as if it were an allergy, which clearly it is not.

It is difficult to see how any objective assessment of the literature can come to the conclusion that the fourth Hill criterion is not supported for MCS and the failure of Staudenmayer *et al.* (2003a) to even consider the easily accessible, extensive and obviously relevant scientific literature may be viewed as a sign of their unacceptable bias.

There is not time time nor space here to go through the other five Hill criteria as they relate to MCS, but the reader is referred to the discussion of this in Chapter 13 of Pall (2007a). The reader is also encouraged to read both the original Hill (1965) paper and also the Staudenmayer *et al.* (2003a) paper. The author's own assessment of the Hill criteria is that there is strong evidence for fulfilling six of the Hill criteria for MCS and weaker, but still suggestive, evidence for fulfilling the other three (Chapter 13, Pall, 2007a). Such evidence is not immune from criticism. It is common, as Hill (1965) suggests, that such evidence can be questioned and it is for that reason that it makes sense to weigh the evidence on nine criteria, rather than just a few, to assess the balance of evidence in the complex consideration of possible environmental causation. It is not necessary, according to Hill (1965), to find support for fulfilling all of the nine criteria in order to make a substantial case for environmental causation, but it is the author's view (Chapter 13, Pall, 2007a) that one can do just that for chemical causation of initiation of MCS cases.

Before leaving the issue of possible psychogenesis of MCS, it is essential to discuss the two masked, placebo-controlled provocation (that is controlled-exposure) studies that have been published, which together, to my knowledge, provide the only evidence that is reasonably claimed to positively argue for a psychogenic aetiology of MCS. Although there are only two such studies, given the relative paucity of direct experimental studies on MCS, it is important to look at them carefully. Both of these report on studies where they performed placebo-controlled provocation studies where the exposures were 'masked' by the presence of a presumably benign masking agent, so that the patients would be unable to tell through odour when they were exposed to the chemical. In both studies, the patients were presumably unable to distinguish the chemical exposure from the masking agent alone. One of these studies was published by Staudenmayer, Selner and Buhr (Staudenmayer *et al.*, 1993) and the other was published by Smith and Sullivan (2003). Both were reviewed favourably by Das-Munshi *et al.* (2006), a group that has argued for a psychogenic mechanism of MCS and also other multisystem illnesses (Das-Munshi *et al.*, 2006; 2007).

The Staudenmayer *et al.* (1993) study has been criticized for three reasons (Miller, 1997; Bell *et al.*, 1997; 1999a; Joffres *et al.*, 2005): the masking agent used, a heavy amount of mint, is not always benign for MCS patients (Fernandez *et al.*, 1999) and therefore may not

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be the neutral masking agent that the authors claim; MCS patients can become desensitized when exposed to various chemicals and these experimenters failed to provide the patients with a substantial period away from such exposures before the provocation challenges were performed; and the patients were not chosen using a standard case definition of MCS, so that there is some question whether they were, in fact, MCS sufferers.

Somewhat surprisingly, the more recent Smith and Sullivan (2003) study may have had somewhat similar problems. Smith and Sullivan tested CFS patients, not MCS patients, and although there is a substantial comorbidity between the two, they did not use, as one would argue they should have, MCS patients who fulfilled a well-accepted case definition for MCS. They do report that their patients had self-reported food sensitivities or chemical sensitivity or both, but food sensitivity is not specific for MCS and is common among CFS patients with no apparent chemical sensitivity. Smith and Sullivan (2003) chose the chemicals to be used as follows: chemical substances chosen by an allergist based on 'clinical criteria and patients subjective responses' were previously tested on each patient until a 'reactive substance' was identified. They give trichloroethane as an example of such a reactive substance, but provide no further information on the chemicals used in this study or their frequencies of use and very little information on dosage. The masking substance used was identified as a substance to which the participants did not react—they give vanilla essence as an example, but do not provide any further information on the masking compounds used. It has been reported that vanillin, the main odourant in vanilla essence, is more of an irritant in MCS patients than in normal controls (Hillert *et al.*, 2007), suggesting that it is not a neutral masking agent for MCS patients. Clearly if either the original test of the 'reactive substance' was a false positive or if the test of the possible masking compound was a false negative, the experimental test for that specific patient would have been flawed.

There is no description of any procedure being used in Smith and Sullivan (2003) to prevent desensitization of patients, caused by recent chemical exposures prior to provocation, another possible criticism. The choice of CFS patients rather than MCS patients can be criticized for an additional reason. Classical MCS patients have their symptoms resolve in the absence of chemical exposure, whereas CFS patients do not. Because they used neuropsychological tests to measure reactions here, CFS patients will have at best a low signal-to-noise ratio because of the high level of neuropsychological aberrations before any provocation exposure. Therefore, these patients were not well chosen, in my judgement, for use in such a test, even if they all did have comorbid MCS.

It should be clear that these provocation challenge experiments are complex and difficult to perform with anything approaching a bullet-proof protocol. The point here is *not* that these two experiments are flawed and that all of the experiments that support the conclusion that MCS patients react to low levels of chemicals acting as toxicants have no flaws. Rather it is that we need to maintain a high level of objectivity in analysing these complex experiments. When Das-Munshi *et al.* (2006) conclude that the Staudenmayer *et al.* (1993) and Smith and Sullivan (2003) studies have no flaws, but that all of the studies coming to the opposite conclusion have substantial flaws, their objectivity must be questioned.

16 SUMMARY OF THIS WHOLE AREA OF POSSIBLE PSYCHOGENESIS OF MCS AND OTHER MULTISYSTEM ILLNESSES

- Psychogenic advocates have failed to consider how chemicals implicated in MCS may impact the human body and specifically the human brain.
- They have failed to consider animal models of MCS and what lessons they may carry on the mechanisms of MCS.
- They have failed in most instances to provide anything resembling an objective assessment of the scientific literature about MCS. Given that most psychogenic advocates have clear conflicts of interest, either making large amounts of money testifying as 'expert witnesses' in MCS liability trials or as psychiatrists who may make substantial amounts providing psychiatric treatment for patients with multisystem illnesses, their ability or lack of same to provide an objective assessment of the literature must be subject to careful scrutiny.
- Their interpretation of MCS and other multisystem illnesses is dominated by the view that these illnesses are produced by the beliefs of the patients and that these are somatoform disorders generated by a process called somatization. However, they have failed to provide evidence that there cannot be a physiological explanation for MCS and the basic concepts of somatoform disorders and somatization have come under increasing attack.
- Their approach to MCS and other multisystem illnesses is based on the rejected dualism between the mental/psychological/psychiatric and the physical/biological/physiological.
- Belief in that dualism has apparently led them to make many logically flawed arguments.
- There is a long history of false psychogenic attribution in medicine, making it essential that psychogenic advocates show that they are not simply repeating the errors of the past. They have failed to consider this issue.
- Their argument that psychological factors are necessary and sufficient to explain MCS and other multisystem illnesses is falsified by the genetic data;

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both the specific genes implicated in MCS and their known function provide for such falsification, but also the general finding that genes have a role in determining susceptibility implicates biological factors because genes act by determining the structure and biochemical activities of the body.

- Psychogenic advocates rarely make clear and testable predictions. One of the rare exceptions to this is clearly falsified by the available data.
- Their papers are full of emotion-laden statements.

Each of these ten considerations creates, in my judgement, great challenges for psychogenic advocates of MCS. Clearly the combination of all ten create still more daunting challenges, completely apart from the main thesis of this review on the NO/ONOO$^-$ cycle and the physiological mechanism(s) of MCS.

17 SUMMARY AND AREAS OF GREATEST RESEARCH NEED

This chapter describes a detailed apparent mechanism for MCS, called the NO/ONOO$^-$ cycle, which explains, when fused with neural sensitization, neurogenic inflammation and other mechanisms, the many challenging aspects of this illness that have never been explained previously. Because new scientific paradigms are tested, often largely, by their ability to explain the many previously unexplained aspects of a scientific field, the power of the NO/ONOO$^-$ cycle as an explanatory model is of great importance. It is my view that the power of the NO/ONOO$^-$ cycle mechanism, when fused with the earlier neural sensitization mechanism as an explanatory model in MCS, and the various aspects of the model that are well supported experimentally, support the inference that the overall model is likely to be fundamentally correct. However, it could certainly be wrong in one or more details and is almost certainly incomplete.

This proposed mechanism is supported by well-established mechanisms of action of seven classes of chemicals implicated in initiating cases of MCS, all of which can act to elevate NMDA activity and produce toxic responses in the human body through such NMDA elevation. It provides mechanisms for the generation of symptoms in MCS patients, both symptoms that are shared with such related illnesses as CFS, FM and PTSD and also chemical sensitivity symptoms that are viewed as being specific for MCS. It is supported by observations implicating excessive NMDA activity, excessive NO levels and oxidative stress, neural sensitization, elevated TRP receptor activity, elevated ONOO$^-$ levels and elevated levels of intracellular calcium in people afflicted with MCS, in animal models or both. While there has been little in the way of published studies on therapy for MCS, clinical trial data on the related illnesses CFS and FM provide support for the inference that such aspects as excessive oxidative stress, NO, NMDA activity, mitochondrial dysfunction and possibly inflammation and BH4 depletion have important causal roles in the generation of this group of illnesses. We have some clinical observations suggesting that complex protocols designed to normalize these several parameters can produce substantial rapid improvement in many MCS patients also avoiding chemical exposure, even among patients who have been ill for decades.

Having said that, there are many aspects of this proposed MCS mechanism that need much study. That is not surprising, given the extraordinarily low level of funding that has been available for such studies. Pall (2002) estimated that although MCS has roughly the same prevalence as does diabetes in the USA, the funding available for research on MCS has been approximately 1/1000th of the funding for diabetes. This low level of funding is despite the fact that what little data we have on comorbid diseases for MCS (Baldwin and Bell, 1998; Bell *et al.*, 1995; Baldwin *et al.*, 1997; 1999) and the substantial impact on employment of MCS patients both suggest that the morbidity associated with MCS and its associated comorbid diseases may be comparable to that found as a consequence of diabetes.

The five areas that are in most need of further study, in my judgement, are:

1. Animal model studies testing various aspects of this mechanism that have never been adequately tested.
2. Studies to establish one or more low-level chemical exposure tests as specific biomarker tests for MCS.
3. Clinical trial studies on agents and groups of agents aimed at down-regulating various aspects of the proposed mechanism as potential therapeutic protocols for the treatment of MCS patients.
4. Studies of some of these same agents in placebo-controlled studies to determine if they can lower responses to low-level chemical exposure in MCS patients. These might be done in conjunction with the specific biomarker tests in item 2.
5. Use of bioassays described above to ascertain likely chemicals in the air of mould-infested 'sick buildings' to determine what mycotoxins are involved and what moulds produce them under what culture conditions. Promising methods have been developed for such bioassays (Hirvonen *et al.*, 1997a; 1997b; Ruotsalainen *et al.*, 1995), but we are still plagued by many examples of such 'sick buildings' due in part to our stunning ignorance about the mycotoxins involved and their mechanisms of action.

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NOTES

a. The most important physiological agonist for the NMDA receptors is L-glutamate; NMDA stands for *N*-methyl-D-aspartate, a nonphysiological agonist that is specific for these receptors, not acting as an agonist for other, non-NMDA glutamate receptors.

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APPENDIX Z

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ELECTROMAGNETIC FIELD SENSITIVITY

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ABSTRACT

A multiphase study was performed to find an effective method to evaluate electromagnetic field (EMF) sensitivity of patients. The first phase developed criteria for controlled testing using an environment low in chemical, particulate, and EMF pollution. Monitoring devices were used in an effort to ensure that extraneous EMF would not interfere with the tests. A second phase involved a single-blind challenge of 100 patients who complained of EMF sensitivity to a series of fields ranging from 0 to 5 MHz in frequency, plus 5 blank challenges. Twenty-five patients were found who were sensitive to the fields, but did not react to the blanks. These were compared in the third phase to 25 healthy naive volunteer controls. None of the volunteers reacted to any challenge, active or blank, but 16 of the EMF-sensitive patients (64%) had positive signs and symptoms scores, plus autonomic nervous system changes. In the fourth phase, the 16 EMF-sensitive patients were rechallenged twice to the frequencies to which they were most sensitive during the previous challenge. The active frequency was found to

be positive in 100% of the challenges, while all of the placebo tests were negative. We concluded that this study gives strong evidence that electromagnetic field sensitivity exists, and can be elicited under environmentally controlled conditions.

INTRODUCTION:

Interaction mechanisms that underlie the health and biological effects of electromagnetic fields (EMF) on humans have been studied by many authors (1,2,3,4,5,6). This subject was reviewed recently at the 1990 Spring Meeting of the American Physical Society (7). Choy *et. al.* (8) investigated individuals with multiple sensitivities who reported reactions to various types of electrical equipment, including power lines, electronic office equipment such as typewriters and computer terminals, video display terminals, household appliances (such as hair dryers), and fluorescent lights.

This paper presents preliminary data on electromagnetic field tests using a square wave generator to evaluate the EMF sensitivity of patients reporting such sensitivities under environmentally controlled and monitored conditions.

MATERIALS AND METHODS:

This study has been carried out in four phases.

I. The tests were carried out in an environmentally controlled area with porcelain-on-steel walls to minimize airborne chemical pollution which might interfere with the testing procedure. This type of construction also acted to decrease external electromagnetic fields. Portable EMF monitoring devices were used to find an area that would minimize background EMF which might disturb double-blind challenges and interfere with the testing process. The low-pollution room had a background of 0-100 V/m electric field and 20-200 nT (Tesla) magnetic field. The immediate test site of the patients had unmeasurable electrical fields and magnetic fields in the vicinity of 20 nT.

The major emphasis of this phase of the studies was the evaluation of the effects of the magnetic field generated by a coil fed from a sweep/function generator (Model 3030, B.K. Precision Dynascan Corp.). This equipment allowed us to test square wave frequencies from 0.1 Hz to 5 MHz.

The patients were tested while they were sitting comfortably upright in a chair with the generator on a desk at least 2 m away,

with its output connected to a coil 6 cm in diameter and 15 cm tall, made of 35 m of cable and positioned on the floor with its center approximately 0.3 m from the feet of the person tested. The mean values of the alternating magnetic field generated by this arrangement were approximately 2900 nT at floor level, approximately 350 nT at the level of the chair seat and patients' knees, and about 70 nT at hand level. The exposure period lasted approximately 3 minutes per challenge.

Before the EMF challenge, blood pressure, pulse rate, respiratory rate, temperature, sign and symptom scores, and autonomic nervous system functions were tested. The autonomic nervous system function was tested with a binocular iriscorder (Model C2515, Hamamatsu Photonics), which measured pupil area, time at which constriction and dilation occurred, and rate of constriction/dilation (9).

All patients had been previously evaluated and treated for biological inhalant, food and chemical sensitivities in order to minimize possible confusion from coexisting problems. The patients were stabilized on a healthy diet in a constant low-pollution environment. In addition, they had their overall body load reduced and stabilized in a controlled environment.

II. This was a single-blind screening of 100 patients who complained of being EMF-sensitive. They were challenged under low-pollution conditions using the sweep/function generator at 0.1, 0.5, 1, 2.5, 5, 10, 20, 40, 50, 60, and 100 Hz; then at 1, 5, 10, 20, 35, 50, 75, and 100 KHz; and finally at 1 and 5 MHz. There were twenty-one active challenges and five blanks (placebos) per person, giving a total of 2600 challenges. When the number and/or intensity of symptoms were 20% over baseline, the result was considered positive, and were recorded as such under the various criteria used. A change in the iriscorder readings more than two standard deviations from baseline was also recorded as a positive result.

III. Twenty-five patients, who were found to be positive in phase II challenges, and who had no more than one placebo reaction were then selected for a third phase of the study. In addition, 25 healthy naive volunteers were challenged. Double-blind EMF challenges and placebos using the aforementioned parameters were performed. There were 1300 total challenges, of which 1050 were

Table 1

Phase II -- Single-blind Challenge of 100 Patients

No. of Patients	No. of Active Challenges	No. of Blank Challenges	Pos. Reactions to Active Challenges	Pos. Reactions to Blanks
50	1050	250	750	150
25	525	125	0	0
25	525	125	325	0

active and 250 were blanks. The tests averaged 21 active frequencies and 5 blanks per subject.

IV. Sixteen patients who reacted in phase III were then rechallenged on two separate occasions in a double-blind manner, using only the frequencies to which they had responded most strongly. For each subject, the frequency of maximum sensitivity was inserted randomly into a series of 5 placebo challenges. Thus, there were a total of 32 active challenges and 160 blanks.

RESULTS:

Phase I. The EMF measurements were quite reproducible. We found that the lights and air handling equipment had to be off during the tests because of their electromagnetic field output. Baseline studies on patients were completed without remarkable result.

Phase II. Of the total of 100 patients tested in the single-blind study, 50 reacted to several of the placebos in addition to the active challenges, and were excluded from further study. Twenty-five subjects who did not react to any active challenges were also excluded. A final 25 subjects who did react to active challenges, but not to blanks, were selected for the third phase of the study (Table 1).

Phase III. The 25 subjects selected from phase II were rechallenged, and 16 (64%) reacted positively to the active challenges

(Table 2). The total number of positive reactions to the 336 active challenges in the 16 patients was 179 (53%), as compared to 6 positive reactions out of 80 blanks (7.5%). There were no reactions to any challenge, active or placebo, in the volunteer group of naive subjects (Table 2).

When evaluating frequency response, 75% of the 16 patients reacted to 1 Hz, 75% to 2.5 Hz, 69% to 5 Hz, 69 % to 10 Hz, 69% to 20 Hz, and 69% to 10 KHz (Table 3). No patient reacted to all 21 of the active frequencies in the challenges. The average was 11 reactive frequencies per patient, with a range of 1 to 19 positive responses.

The principal signs and symptoms produced were neurological (tingling, sleepiness, headache, dizziness, unconsciousness), musculoskeletal (pain, tightness, spasm, fibrillation), cardiovascular (palpitation, flushing, tachycardia, edema), oral/respiratory (pressure in ears, tooth pain, tightness in chest, dyspnea), gastrointestinal (nausea, belching), ocular (burning), and dermal (itching, burning, prickling pain) (Table 4). Most reactions were neurological.

Phase IV. In the 16 patients again rechallenged in a double-blind manner, using only the single frequency to which they were most sensitive, all reported reactions to the active frequencies when challenged. None reacted to the placebos (Table 5). Signs and symptoms in all 16 patients were positive as was the autonomic nervous system dysfunction, as measured by the Iriscorder (Table 6, Figure 1). Examples of changes were a 20% decrease in pulmonary function and a 40% increase in heart rate. In the 16 patients with positive reactions to EMF challenges, two had delayed reactions; gradually became depressed and finally became unconscious. Eventually, they awoke without treatment. Symptoms lasted from 5 hours to 3 days.

DISCUSSION:

Since it has been found that electromagnetic fields can affect health, researchers have investigated these phenomena *in vivo* and *in vitro*, in animals (10,11,12) and humans (1,2,3,4,5,6,7).

No individual had been specifically challenged in an attempt to reproduce acute symptoms until Smith and Monro (5) followed by

Table 2

Phase III - 25 Patients Previously Positive Rechallenged And Twenty-Five Controls Tested Double-blind

No. of Persons	No. of Active Challenges	No. of Blank Challenges	Positive Reactions to Challenges	Positive Reactions to Blanks
16 patients (out of 25 reacting positively)	336	80	179	6
25 controls (none of them reacting positively)	525	125	0	0

Table 3

PERCENTAGE OF 16 PATIENTS WITH POSITIVE REACTION TO DIFFERENT FREQUENCIES

Frequency (Hz)	Patients with Positive Reaction %
0.1	31
0.5	44
1	75
2.5	75
5	69
10	69
20	69
40	50
50	50
60	63
100	56
1K	56
5K	38
10K	69
20K	56
35K	31
50K	50
75K	50
100K	38
1M	50
5M	31

Table 4
Comparison of Symptoms and Signs Induced by Frequencies

Hz.	No. patients w/pos.reaction	Neurological No.of Pts. %	Musculoskeletal No.of Pts. %	Cardiovascular No.of Pts. %	Respiratory No.of Pts. %	Gastrointestinal No.of Pts. %	Eyes No.of Pts. %	Skin No.of Pts. %
0.1	5	3 60	0 0	0 0	0 0	1 20	0 0	0 0
0.5	7	4 57	0 0	0 0	0 0	0 0	0 0	0 0
1	12	4 33	3 25	0 0	1 8	1 8	0 0	0 0
2.5	12	5 42	2 17	0 0	1 8	1 8	0 0	0 0
5	11	5 46	0 0	1 9	2 18	1 9	0 0	0 0
10	11	7 64	1 9	0 0	2 18	0 0	0 0	0 0
20	11	4 36	0 0	1 9	1 9	1 9	0 0	0 0
40	8	4 50	0 0	0 0	2 25	0 0	0 0	1 13
50	8	5 63	0 0	2 25	1 13	0 0	0 0	0 0
60	10	5 50	0 0	1 10	3 30	0 0	0 0	0 0
100	9	4 44	0 0	1 11	2 22	1 11	0 0	0 0
1K	9	6 67	0 0	1 11	0 0	0 0	1 11	0 0
5K	6	2 33	1 17	0 0	1 17	0 0	0 0	0 0
10K	11	4 36	1 9	0 0	0 0	0 0	0 0	0 0
20K	9	5 56	0 0	2 22	0 0	0 0	0 0	1 11
35K	5	2 40	0 0	0 0	1 20	0 0	0 0	1 20
50K	8	2 25	0 0	1 13	2 25	0 0	0 0	1 13
75K	8	1 13	0 0	1 13	3 38	0 0	1 13	0 0
100K	6	2 33	2 33	0 0	2 33	0 0	0 0	0 0
1M	8	4 50	1 13	0 0	0 0	0 0	0 0	0 0
5M	5	2 40	1 20	0 0	0 0	0 0	0 0	0 0

179 positive reactions out of 336 individual challenges

Table 5

Phase IV --Sixteen Patients Rechallenged to One Active Frequency on Two Separate Episoded and in Addition to Five Blank Challenges on Each Episodes -- Double-blind

First Episode of Challenge

No. of patients	Total No. of frequencies	Total No. of blanks	No. of patients reacting to active challenge	No. of patients reacting to blanks
16	16	80	16	0

Second Episode of Challenge

No.4 of patients	Total No. of frequencies	Total No. of blanks	No. of patients reacting to active challenge	No. of patients reacting to blanks
16	16	80	16	0

Choy, Monro, and Smith (8), who used a series of oscillators of varying frequency to trigger symptoms in electrically sensitive patients. We modified this procedure by developing controlled environmental areas where baselines were constantly monitored for particulates, pollutants, and extraneous fields. Here, controlled EMF output was applied so that data would be more reproducible.

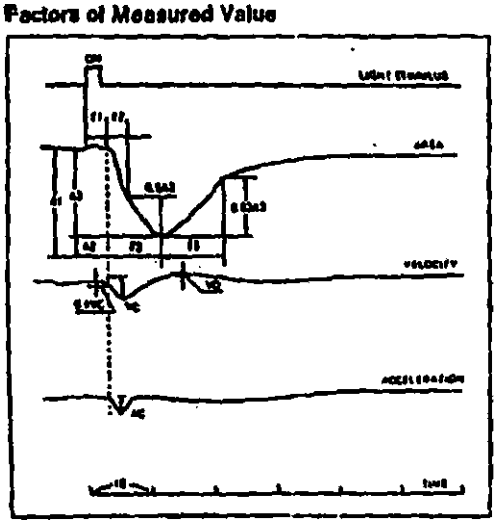
Several factors have led us to believe that we have reproducible results. Meticulous construction of environmental rooms made a great difference in the reproducibility of test results. Prior to the use of such facilities and careful monitoring, a variety of factors, such as diet, exposure to chemicals, EMF, or dust gave rise to symptoms which would have been mistaken for placebo reactions. Such effects were minimized here, as evidenced by the small number of placebo reactions. A few patients reacted to the fields generated by the monitoring devices (Iriscorder, EKG, and computers) and had to be dropped from the study as too fragile for accurate analysis. Some patients reacted to the fields generated by the fluorescent lights, and others did not present the same

Table 6

Parameters of 25 normal control's pupillary light reflex - Iriscorder - EEC-Dallas (Right and Left Eyes Combined)

Parameter	x ± SD	Percent Variation
A1	5.70 ± 3.58	10.0
CR	0.46 ± 0.048	10.4
T2	190.74 ± 18.36	9.5
VC	49.67 ± 5.86	11.8
AC	503.20 ± 75.80	15.1
T5	1520.04 ± 285.86	18.7
VD	13.65 ± 2.44	17.9

Factors of Measured Value



The C2515 Iriscordor uses some or all of the following twelve factors to measure Light Reflex, Alternate-Stimulus Reflex, and Near Reflex.

A1 : Initial pupil area (mm^2)
A2 : Minimum pupil area after light stimulus (mm^2)
A3 : Pupil area change after light stimulus (mm^2)
CR: Contraction ratio (A3/A1)
DI : Initial diameter ❶ (mm)
T1 : Time from light stimulus to start of contraction ❷ (msec)
T2 : Time to half contraction (msec)
T3 : Time to total contraction (msec)
T5 : Time to recover to 63% of A3 after dilation from minimum state (msec)
VC: Maximum velocity of contraction (mm^2/sec)
VD: Maximum velocity of dilation (mm^2/sec)
AC: Maximum acceleration of contraction (mm^2/sec^2)

❶ DI is calculated from the pupil area, assuming that the pupil is circular.

❷ T1 is measured as the time from the light stimulus until the velocity of pupil contraction VC reaches 10% of the maximum velocity VCmax.

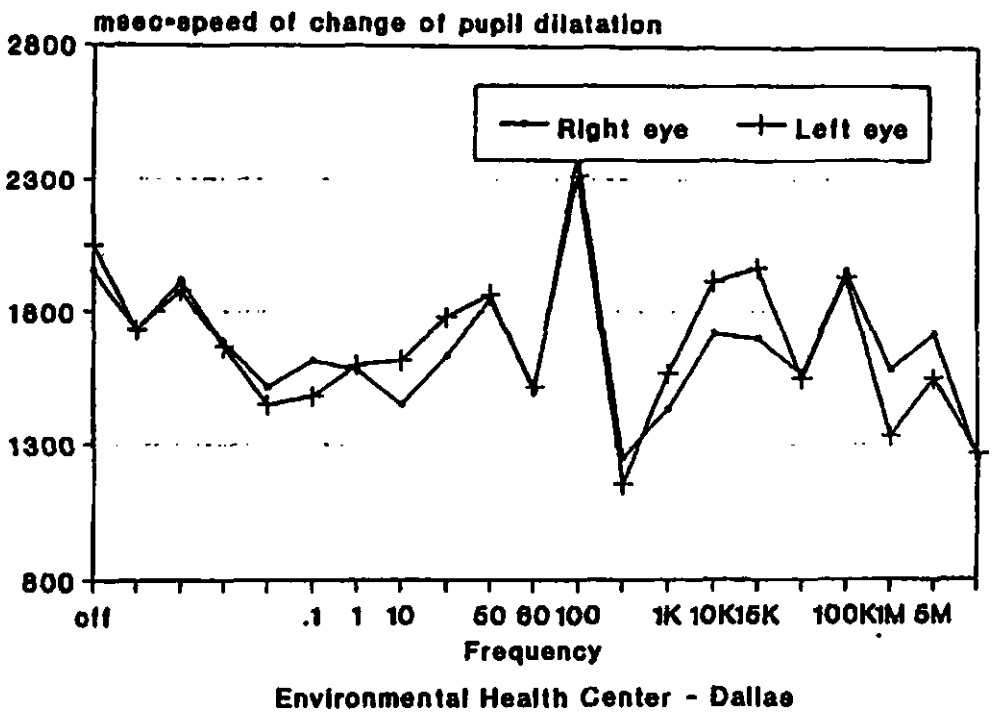


Figure 1. Speed of dilation of the pupil following EMF stimulation at various frequencies as measured by iriscorder. Note that right and left eyes respond simultaneously and to the same relative degrees at a given frequency. These results are quite reproducible (viz. text).

signs and symptoms at each challenge, even though the reactions were significant when contrasted with the blank responses. The Iriscorder data were objective, however, and were always reproducible (Figure 1).

We also noted that patients sometimes had delayed or prolonged responses. Therefore, care had to be taken to be certain that the patient had returned to baseline before the next challenge. This carry-over was first noted when evaluating responses to placebo

challenges. Such a response could usually be explained and eliminated by use of longer intervals between challenges.

In this study, of the 100 patients who expressed suspicion of EMF sensitivity, 75 actually responded to fields, whereas none of the controls did. Of the 75, 25 had no reactions to blanks, whereas 50 did, and thus were discarded from the study; even though we felt that some of the reactions to blanks might be evidence of delayed reaction to previous frequencies, or prolonged response to the previous positive challenge, as well as true placebo reactions.

We learned that challenge with 21 frequencies was impossible on many sensitive patients. They were often unwell for several hours or days, which confused the data from repeat challenges on subsequent days. Hence, we selected the one frequency of maximum sensitivity for repeat challenges in the phase IV studies.

When one compares the various groups to controls, it is clear that there is a group of patients who have unstable response systems which appear different from those of the individuals who acted as controls. These studies show that EMF sensitivity could be elicited under environmentally controlled conditions. As a result of the weak field levels and short exposure time, the responses were mild except in two patients whose symptoms were so severe (e.g. drop attack, severe itching) that they received intravenous vitamin C, magnesium, and oxygen as a result of the prolonged and delayed reactions.

Signs and symptoms appeared similar to those seen in food or chemically sensitive patients at the Environmental Health Center/ Dallas, and included neurological, musculoskeletal, cardiovascular, respiratory, gastrointestinal, dermal, and ocular changes. The neurological symptoms were most common. Similar responses have been recorded by others in the literature (5,6,7,8,13,14). In 1972, after the Soviets reported that electrical utility workers were suffering from listlessness, fatigue, and nausea, Subrohmangam and coworkers (13) investigated and reported decisive changes in cardiac function and bioamine levels when pulses of 0.01 and 0.1 Hz were used. They found significant changes in the hypothalamus in response to the EMF fields.

In these studies, the preponderance of reactions occurred at one to 10 Hz, which accords well with their observations. However, many reactions also occurred at 50 and 60 Hz, as well a some up to

5 MHz. We conclude that in any given individual, susceptibility may develop to any frequency, and produce reactions.

Static magnetic fields are known to cause increased blood pressure on some individuals (14). Choy and coworkers (8) found that EMF reactions in EMF sensitive patients were not limited to the nervous system, but occurred in the same systems as in these studies, which basically corroborate theirs, though neurological symptoms predominated in our experiments.

Over the past 30 years, numerous investigations with animals and a few epidemiological studies of human populations have been devoted to assessing the relationship of microwave exposure to cataract development. The severity and speed of formation depends not only on intensity, but also on wavelength and duration of exposure (16-21). McCally *et. al.* (22) reported damage to corneal epithelium in *Cynomolgus* monkeys after 2.45 GHz irradiation for several hours at only 20-30 mW/cm^2 (CW) or even 10-15 mW/cm^2 with pulsed fields. Therefore the results of Paz (23) strongly suggests that the potential for eye injury exists in surgery where EMF fields are present.

In our experience, the patients' clinical responses could not always be reproduced completely, but the objective Iriscorder, EKG, and respirometer could be. However, the responses were definitely different from controls or placebo challenges, In our experience over the years, we have found partial reproduction of symptoms on repeat challenge to be as significant as total reproduction. Therefore, significant differences from controls in objective measurements were deemed valid.

There are several explanations for lack of exact reproducibility. These are: a) the patients' total body loads were different at different exposure periods. For example, some patients may only respond to EMF when in a reactive hypersensitive state (5,8); b) tissue resistance could influence the effect of the EMF. Zimmerman (24) reported that electrical resistance of skin decreased with increasing temperature and increased with progressive drying, as might be expected; c) injections of antigen neutralizing substances prior to test may have reduced the response to EMF. One patient with asthma was sensitive to high voltage power lines a well as low voltage house wiring. He experienced muscle spasms in head, neck, arms, and legs. This patient was also

sensitive to dust, weeds, dust mites, and some foods. He reacted in our tests to 2.5 and 60 Hz, and to 5 and 50 KHz with tightness in the chest. He then received an antigen shot to neutralize his hypersensitivity reactions. Five months later, he was unreactive to EMF; d) weather changes might affect the results, since we know that the weather can influence the propagation of EMF, as may alterations in the geomagnetic fields. Since humidity, pollution, temperature, etc. can affect resistance and total body load, weather should perhaps affect the results. Adverse weather (inversions, for example) may increase pollution load, while good weather lessens it. There is some evidence of resonance between geomagnetic fields and an applied ac magnetic field (25), which implies that the results may depend in part at least upon the strength and orientation of the geomagnetic field in the test area; and e) different wave forms might cause different responses. In these experiments, we used only square wave inputs to the coils. Consequently, we do not know whether other wave forms (sine, sawtooth, triangular, etc.) might induce different types or intensities of reactions.

Thus far, definitive information has not been sufficient to identify a plausible mechanism for EMF interactions with biological tissue. Interactions appear to take place at the cell surface, perhaps acting on receptor sites and altering ion and molecular transport across the membranes (25). Further work remains to be done in the field.

It is clear that EMF sensitivity is a real phenomenon in some environmentally sensitive patients, because some had consistent reactions while none of the controls did. THis study must be considered as only preliminary, but the evidence clearly points to sensitivity in some people.

In conclusion, it is evident that EMF testing is at a rudimentary stage; but clearly EMF sensitivity exists and can be elicited under environmentally controlled conditions. Further studies are needed to investigate the effects of EMF fields on human health.

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APPENDIX AA

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Absence of genotoxic potential of 902 MHz (GSM) and 1747 MHz (DCS) wireless communication signals: In vivo two-year bioassay in B6C3F1 mice

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Abstract

Purpose: The aim of the present investigation was to determine the incidence of micronuclei in peripheral blood erythrocytes of B6C3F1 mice that had been chronically exposed to radiofrequencies (RF) used for mobile communication.
Materials and methods: 'Ferris wheels' were used to expose tube-restrained male and female mice to simulated environmental RF signals of the Global System for Mobile Communications (GSM, 902 MHz) or Digital Cellular System (DCS, 1747 MHz). RF signals were applied to the mice for 2 hours/day on 5 days/week for two years, at maximal whole-body-averaged specific absorption rates of 0.4, 1.3, and 4.0 W/kg body weight. Concurrent sham-exposed mice, cage controls, and positive controls injected with mitomycin C were included in this investigation. At necropsy, peripheral blood smears were prepared, and coded slides were stained using May-Grünwald-Giemsa or acridine orange. The incidence of micronuclei was recorded for each mouse in 2000 polychromatic and 2000 normochromatic erythrocytes.
Results: There were no significant differences in the frequency of micronuclei between RF-exposed, sham-exposed, and cage control mice, irrespective of the staining/counting method used. Micronuclei were, however, significantly increased in polychromatic erythrocytes of the positive control mice.
Conclusions: In conclusion, the data did not indicate RF-induced genotoxicity in mice after two years of exposure.

Keywords: *Radiofrequency radiation, mobile phones, B6C3F1 mice, genotoxicity, peripheral blood, micronuclei*

Introduction

Non-ionizing radiofrequency (RF) radiation in the frequency range used for wireless communication systems has a tremendous impact in modern society. The escalated use and the consequent exposure to RF resulted in increased concern regarding its potential adverse effects on human health, thus prompting concerted effort to investigate the issues related to RF-exposure. Some research priorities were identified: (i) Additional large-scale animal studies to test the effects of long-term exposure to RF, (ii) studies that examine effects on health other than cancer, such as memory loss and effects on the eye or inner ear, and (iii) large-scale epidemiological studies in people exposed to RF (U.S. Government Accountability Office [GAO] 2001, Valberg et al. 2007, Jauchem 2008). The above research needs have been addressed in a number of studies in several countries, some of which have been already completed, are ongoing or planned.

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The European Commission through its fifth framework program, the Swiss and Austrian governments, the Global System for Mobile Communications (GSM) Association, and the Mobile Manufacturers' Forum have been supporting research projects addressing human health-related issues of exposure to RF emitted from wireless communication systems. Among these projects, the program with the acronym PERFORM-A (EC Contract No. QLK4-CT-1999-01476 entitled: 'In vivo research on possible health effects related to mobile telephones and base stations [Carcinogenicity studies in rodents]') addressed the potential carcinogenic effects of long-term exposure to wireless mobile communication signals in experimental animals. The PERFORM-A1 study, in particular, focused on the carcinogenic potential of RF exposure in male and female B6C3F1 mice, which were exposed to 902 MHz (GSM) or 1747 MHz (Digital Cellular System, DCS) RF for 2 hours/day on 5 days/week over a period of two years. Complete histopathological examination was subsequently conducted to determine the incidence and severity of neoplastic/non-neoplastic lesions. Detailed data have been published previously (Tillmann et al. 2007). Up to now, very few investigators have examined the potential genotoxic effects of chronic exposure to RF. Observations related to genotoxicity following RF exposure are considered important, since enhanced genetic damage is very often linked to carcinogenicity. Hence, the present genotoxicity study was appended to the PERFORM-A1 carcinogenicity study in mice. This combination offered the possibility to evaluate the extent of genetic damage following chronic exposure to RF 902 MHz (GSM) and 1747 MHz (DCS) and to correlate it with carcinogenicity. In the present investigation, the rodent micronucleus (MN) assay was used to determine the genotoxic potential of RF exposure, a standard in vivo genotoxicity test used for regulatory purposes in several countries (Auletta et al. 1993, Health Protection Branch Genotoxicity Committee, Canada 1993, Kirkland 1993, Sofuni 1993). Since MN arise from broken chromosomal fragments and whole chromosomes that are not incorporated into daughter cells at the time of cell division (due to disturbances in the spindle apparatus), the MN test can identify both clastogenic and aneugenic agents. Furthermore, it has been suggested that long-term studies using peripheral blood may evaluate MN in both, or either, normochromatic (NCE, mature) or polychromatic erythrocytes (PCE, immature), in contrast to the short-term bone marrow MN tests, where scoring is limited to PCE. The incidence of micronucleated PCE provides an index of damage induced within 72 h of sampling, whereas the incidence of MN in NCE at steady state provides an index of average damage during the 30-day period preceding sampling (Witt et al. 2000). Although RF and sham exposures were conducted over a period of two years, the incidence of MN was evaluated in NCE as well as in PCE in order to detect more acute, chronic, and delayed effects of RF exposure.

Methods

Study design and guidelines

The present investigation was performed as an add-on to the PERFORM-A1 mouse carcinogenicity study reported by Tillmann et al. (2007). The animal experiment was conducted at the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM, Hannover, Germany). The protocol complied with the German Animal Welfare Act and was approved by the responsible local authority. The study considered guideline No. 453 of the Organization for Economic Co-Operation and Development (OECD) and was performed in compliance with the principles of Good Laboratory Practice (GLP, German Chemicals Law, § 19a, Appendix 1, June 28, 2002). The entire study was conducted 'blind' to all scientists involved. The staff of the Foundation for Research on Information Technologies in Society (IT'IS, Zurich, Switzerland), responsible for the technical aspects for controlling and monitoring the RF exposures, were also not aware of the identity of the exposure groups. All data were 'decoded' after completion of the histopathological examinations in the PERFORM-A1 carcinogenicity study and the MN evaluations in the present add-on investigation. The incidence of MN was analyzed by independent investigators in separate laboratories, namely, the Fraunhofer ITEM and the University of Texas Health Science Center (UTHSCSA, San Antonio, TX, USA).

Animal housing and maintenance

Young adult, specified pathogen-free B6C3F1/Crl BR male and female mice, 4–5 weeks of age, were purchased from Charles River Deutschland (Sulzfeld, Germany). They were kept in two separate rooms, one for 902 MHz (GSM) and another for 1747 MHz (DCS) experiments. The temperature in both rooms was maintained at 22 ± 2°C with a relative humidity of 30–70% and an airflow rate of 12–15 exchanges/hour. A time-controlled system provided 12-hour light and dark cycles. Mice were maintained in Makrolon® polycarbonate type II cages ($22 \times 16 \times 14$ cm, EBECO, Castrop-Rauxel, Germany) with absorbent softwood bedding throughout the study, except the daily RF-exposure

period. Male mice were caged individually, while the females were housed two per cage. Except during exposure, all animals had free access to standard diet (Altromin 1324N), supplied by Altromin International (Lage, Germany) and drinking water from the Hannover city water supplier (Hannover, Germany).

Experimental design

For details of experimental design, exposure conditions, and exposure monitoring, see Tillmann et al. (2007). A total of 1170 mice (585 males and 585 females) were randomized by weight into groups using computer-generated numbers. Exposure group identities are given in Table I. Each group initially consisted of 50 + 15 males and 50 + 15 females. Fifty animals of each sex were used for the two-year exposure study, while the other 15 animals per group were used for interim examinations (organ weights, hematology, gross pathology, and histopathology, but not MN induction) after a 12-month exposure period. The number of male and female mice per group was derived from the guidelines/bioassays that have been successfully utilized for decades in the testing of products in the chemical and pharmaceutical industries (National Toxicology Program, OECD, Environmental Protection Agency). Additionally, 30 males and 30 females were assigned as sentinel animals. All mice were acclimatized to the animal room conditions for about four weeks. A training program was initiated during this period to accustom the mice to the RF-exposure setup by gradually increasing the time during which the animals were restrained in tubes (similar to those regularly used for inhalation studies, see Figure 1).

RF exposure, 902 MHz (GSM) and 1747 MHz (DCS)

The exposure signal and system were described earlier in detail (Tillmann et al. 2007). In brief, mice restrained in tubes (supplied by IT'IS) (i.e., all animals except cage controls and sentinel) were sham-exposed or exposed to RF for 2 hours/day on 5 days/week over a period of two years. The RF signals simulated exposure from GSM (902 MHz) and DCS (1747 MHz) handsets. The exposure units were supplied by IT'IS with assurances for RF transmission, dosimetry, and continuous monitoring. The main equipment consisted of 'Ferris wheels' (see Figure 1), signal generator (Rhode & Schwarz, Munich, Germany), amplifiers (LS Electronic, Spanga, Sweden), and electronic control and monitoring devices (SPEAG, Zurich, Switzerland). The 'Ferris wheel' concept was developed by Balzano et al. (2000) and adopted and optimized by IT'IS for uniform whole-body exposure of mice. Briefly, the 'Ferris wheels' consisted of two parallel, circular, stainless steel metal plates, which were placed 117 mm apart with a conical (GSM) or bi-conical (DCS) antenna in their center and stainless steel posts forming a cylindrical cavity of 755 mm radius.

Table I. Exposure groups, dose levels, and numbers of mice evaluated for micronucleus induction after two years of RF exposure.

Exposure level[#]	Sex	Frequency	Restraint duration (daily, 5 days/week)	Max. wb-SAR [W/kg]	Number of animals[$]
-	m	Cage control	-	-	36
	f			-	37
Sham	m	902 MHz	2 h	0	44
	f			0	35
Low	m	902 MHz	2 h	0.4	40
	f			0.4	37
Medium	m	902 MHz	2 h	1.3	43
	f			1.3	40
High	m	902 MHz	2 h	4.0	42
	f			4.0	35
Sham	m	1747 MHz	2 h	0.0	44
	f			0.0	36
Low	m	1747 MHz	2 h	0.4	41
	f			0.4	36
Medium	m	1747 MHz	2 h	1.3	44
	f			1.3	36
High	m	1747 MHz	2 h	4.0	43
	f			4.0	36
				Mean number of animals ± SD:	39 ± 3.5

[#]Decoded exposure levels after completion of the study; [$]evaluation of micronuclei was performed on survivors only, after two years of exposure; *m, male; f, female; wb-SAR, whole-body specific absorption rate; SD, standard deviation.*

A 'Ferris wheel' could house up to 65 mice. The position of the animals was optimized for maximum uniform exposure by using a radius (center of wheel to center of the tubes) of 700 mm for GSM exposure and of 670 mm for DCS exposure. In order to maintain a symmetrical load, missing animals were replaced by conical plastic tubes filled with 36 ml of liquid simulating the dielectrical properties of muscle tissue in mice at the corresponding RF frequencies.

All applied signals were compliant with the definitions of the GSM or DCS signaling standards and were designed to simulate all exposure conditions (low-frequency power envelope) as they occur during the use of GSM/DCS mobile phones at maximized time-averaged exposure. Each exposure session (duration 2 h) was divided into three phases of 40 min each. Each slot was modulated with a random code. In the first phase non-discontinuous transmission (DTX) mode ('GSM Basic') was applied simulating the exposure conditions during continuous talking, i.e., one active slot per basic frame while each 26th basic frame was idle. The second phase, 'GSM Talk', simulated a conversation, i.e., by temporal switching between the non-DTX (average time active: 2/3) and DTX (average time active: 1/3) modes. The third phase, 'GSM Environment', simulated exposure during a conversation. This included GSM features such as non-DTX, DTX, power control, handovers, etc. according to their statistical occurrence. The target whole-body-averaged specific absorption rate (SAR) during 'GSM Basic' for the 'high exposure' group was 4 W/kg body weight. Since the maximum slot average power was kept constant, the exposure during 'GSM Talk' was 2.7 W/kg and during 'GSM Environment' 1.1 W/kg body weight, respectively. All exposure levels were reduced by a factor of 3 for the 'medium exposure' group and a factor of 9 for the 'low exposure' group. The rational, the signal, and the monitoring techniques were described in detail previously (Kainz et al. 2006).

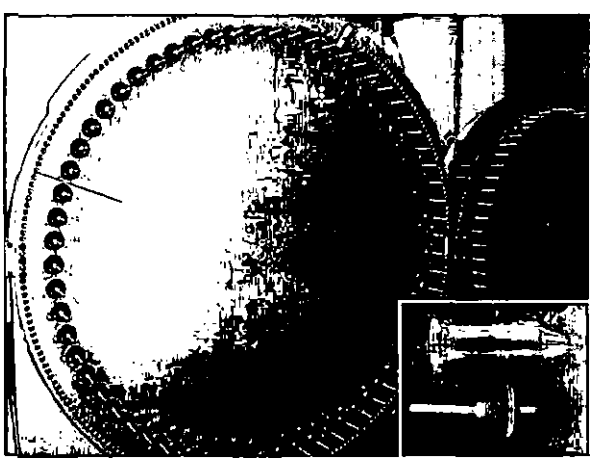

Figure 1. Mouse exposure set-up. Presented is one of the 'Ferris wheels' developed by IT'IS and a restraint tube with a dielectric stopper.

For each RF frequency, four 'Ferris wheel' exposure units were used, allowing to simultaneously expose the three power levels and shame. The thermal threshold and breakdown levels revealed that the high-dose level was close to, yet below, the thermal threshold (Ebert et al. 2005). The spatial peak and organ-averaged SAR (relative to the whole-body average values) in the mice ranged from 0.18–1.9 for 902 MHz GSM and from 0.14–3.3 for 1747 MHz DCS. A new methodology was proposed to obtain comprehensive dosimetric information for whole-body, peak spatial SAR, as well as the averaged values for the most important organs. For each of the values, the uncertainty as well as the instant and life-long variations was determined (Kuster et al. 2006). During the two-year exposure period the position of any tube on the wheel was moved clockwise by one port on a weekly basis. With this rotation scheme all mice were positioned on each of the exposure compartments for a similar duration over the course of the study. Therefore, in cumulated terms of the dose received by the mice, any differences in the exposure signal within the wheels were minimized. The whole-body exposure and the organ-specific averaged SAR were several magnitudes higher than those of humans during phone or base station exposure (Tillmann et al. 2007 and Table II). However, the tissues in the closest vicinity

Table II. Organ-averaged SAR at whole-body-averaged SAR of 4 W/kg body weight and the corresponding standard uncertainty and variations (Tillmann et al. 2007).

	SAR_{organ} (group- and lifetime-average)*		Uncertainty ($k=2$)		Variations (instant) ($k=1$)		Variations (lifetime-averaged) ($k=1$)	
Tissue	GSM (W/kg)	DCS (W/kg)	GSM (dB)	DCS (dB)	GSM (dB)	DCS (dB)	GSM (dB)	DCS (dB)
Blood	5.6	13.2	±2.7	±2.3	±2.9	±2.3	±2.1	±1.4
Bone marrow	1.4	1.0	±3.4	±3.2	±4.2	±3.2	±3.2	±2.4
Skin	3.4	2.2	±2.8	±2.3	±2.7	±2.0	±1.9	±1.2
Spleen	4.6	1.5	±3.2	±3.0	±3.5	±2.3	±2.4	±1.1

*Organ-averaged SAR were determined, applying the methodology of Kuster et al. (2006).

of the mobile phones may have been exposed to values of comparable magnitude.

Positive control mice

Six of the sentinel mice (three males and three females) received a single intraperitoneal (i.p.) injection of mitomycin C in aqueous solution (MMC, 1.0 mg/kg body weight, Sigma, Taufkirchen, Germany) at the end of the two-year bioassay and were used as positive control animals for evaluation of MN induction in peripheral blood. MMC is a chemotherapeutic drug that has been shown to induce MN in mice (Vijayalaxmi et al. 1997). The positive control animals were sacrificed 48 h after MMC injection and peripheral blood smears were prepared.

Peripheral blood smears

All mice alive at the end of the two-year RF-exposure period were included in this study. They were identical to the animals used for the carcinogenicity study by Tillmann et al. (2007). For the number of included animals, which differed from the original number of 50 animals due to mortality during the two-year exposure period, see Table I. Because of the large number of animals, necropsies were completed between day 3 and day 19 after the last RF- or sham-exposure. Each day, between one and seven mice from every treatment group were sacrificed. The mice were anesthetized with an overdose of carbon dioxide. For evaluation of MN induction peripheral blood was collected from the *Vena cava caudalis* and transferred into lithium-heparin-containing tubes (Sarstedt, Nümbrecht, Germany) to prevent clotting. Small drops of blood were then placed on clean microscope slides (Super-Frost®, Menzel, Braunschweig, Germany), and each drop was pulled behind a cover glass held at a 45° angle to prepare a thin smear over an area of 2–3 cm^2. One set of smears (at least two slides) was air-dried and another set (also at least two slides) was fixed in absolute methanol (Roth, Karlsruhe, Germany). Prior to analysis, slides were coded by combining exposure group and animal numbers.

Staining of smears and MN evaluation

Since RF and sham exposures were conducted over a period of two years, both acute and chronic effects were assessed using two different staining procedures to evaluate MN. One complete set of peripheral blood smear slides was air-dried and stained with May-Grünwald and Giemsa (both Merck, Darmstadt, Germany) (Schmid 1975) at the Fraunhofer ITEM. A light microscope (Photomicroscope III, Zeiss, Göttingen, Germany) was used to examine 2000 consecutive NCE to record the incidence of MN in each mouse. Another complete set of smears/slides was fixed in absolute methanol, air-dried, and mailed to UTHSCSA. Upon receipt, slides were stained with acridine orange (Sigma, St Louis, MO, USA; 0.01 mg/ml of 0.2 M phosphate buffer, pH 7.4) as described previously (Vijayalaxmi et al. 1997). A fluorescence microscope (Carl Zeiss Inc., Thornwood, NY, USA) fitted with appropriate filters for the acridine orange stain was used to examine 2000 consecutive PCE to record the frequency of MN in each mouse. In addition, 10,000 consecutive erythrocytes per animal were examined to evaluate the proportion of PCE (% PCE) in peripheral blood and thus effects of RF exposure on blood formation. All evaluations were performed in a blinded manner. Data were decoded after completion of the whole PERFORM-A1 carcinogenicity study (see also *Methods*: *Study design and guidelines*).

Statistical analysis

SAS software (2006), Version 9.1 for Windows was used for statistical analyses. The analysis of variance (ANOVA) test for repeated measures was used to assess significant differences in the incidence of MN between RF-exposed, sham-exposed, cage control, and positive control mice, and to compare between different RF frequencies (902 and 1747 MHz), maximal whole body SAR (0, 0.4, 1.3, and 4.0 W/kg), gender (male versus female mice), and all their interactions. The residuals were analyzed for homogeneity of variance and normality of distributions. Statistical significance was taken at a level of $p < 0.05$ for each effect. The Mann-Whitney rank sum test was also used for statistical analyses.

Results

Survivors

In the present investigation, the incidence of MN in peripheral blood smears of B6C3F1 mice exposed for two years to RF (902 or 1747 MHz, 2 hours/day, 5 days/week) was analyzed as an add-on to the PERFORM-A1 mouse carcinogenicity study. As only the animals surviving the whole two-year treatment period could be included, the final number of animals was smaller than the original 50 animals per group. The average number of animals analyzed per treatment group amounted to 39 (range: 35–44 animals; see Table I). Mortality was higher in female than in male animals, but was obviously not influenced by RF treatment in both sexes.

Polychromatic erythrocytes in peripheral blood

As judged by PCE counts in peripheral blood, there was no toxic effect of RF exposure on blood formation. There were no differences in the proportion of PCE between cage controls/sham-exposed and RF-exposed animals, nor between male and female animals. The mean amount of PCE in peripheral blood of the animals (approximately 3%) was within the normal range for B6C3F1 control mice (for an example, see Witt et al. 2000). In contrast, positive control mice injected with 1 mg/kg body weight MMC demonstrated a clear reduction in the percentage of PCE to 2.0 ± 1.4% for male and 2.1 ± 1.5% for female mice, as compared to 3.2 ± 0.4% and 3.2 ± 0.6% PCE, respectively, in cage control animals (Table III).

Micronuclei in polychromatic erythrocytes of the peripheral blood

Analysis of MN in peripheral blood PCE of mice is an appropriate measure of treatment-induced clastogenic activity and mitotic damage. An increase in MN in peripheral blood PCE indicates an acute clastogenic and/or aneugenic event. By combining the mice from all necropsy times for each treatment group, there was no evidence of an RF-induced increase in the mean frequencies of micronucleated PCE, as compared to the sham-exposed and cage control animals, irrespective of the frequency or exposure level of RF treatment or the sex of the animal. As expected, however, 48 h after injection of the positive control MMC the incidence of micronucleated PCE was significantly enhanced to 26.7 ± 6.1 MN/2000 PCE (males) and 35.3 ± 2.1 MN/2000 PCE (females), compared to 4.6 ± 1.2 MN/2000 PCE (males) and 4.4 ± 1.4 MN/2000 PCE (females) for the cage control animals. The mean incidences of MN/2000 PCE are presented in Table III. Due to the short life-span of PCE and their rapid maturation to NCE, analysis of MN in peripheral blood PCE can only indicate acute genotoxic effects within 72 h after treatment. Thus, combining the animals from all necropsy times (3–19 days after the last RF exposure) may mask early genotoxic effects. We therefore compared MN frequencies in animals sacrificed three days, 10–11 days, and 17–18 days after the last RF exposure (see Figures 2A and B). Nevertheless, there was no significant increase in MN frequency due to RF exposure at all necropsy times (early, intermediate, and late).

Micronuclei in normochromatic erythrocytes of the peripheral blood

Other than in rats and humans, micronucleated NCE are not selectively removed by the spleen from the peripheral blood of mice. As NCE exhibit a long life-span of greater than 30 days (Chaubey et al. 1993), increased frequencies of micronucleated NCE are therefore maintained in peripheral blood of mice at steady-state level for prolonged times. Thus, scoring of micronucleated NCE in peripheral blood of mice reflects average damage during at least the 30-day period preceding sacrifice. Due to the long life-span of NCE/micronucleated NCE in peripheral blood of mice, animals from all necropsy times per treatment were combined in the present

Table III. Polychromatic erythrocytes (PCE) and incidence of micronucleated normochromatic erythrocytes (NCE) and PCE in peripheral blood of mice chronically exposed to radiofrequency for 2 hours/day on 5 days/week over a period of two years.

		Males			Females		
Frequency	Exposure level	MN/NCE	MN/PCE	% PCE	MN/NCE	MN/PCE	% PCE
Cage control	—	4.4 ± 2.3	4.6 ± 1.2	3.2 ± 0.4	2.3 ± 1.7	4.4 ± 1.4	3.2 ± 0.6
902 MHz	Sham	4.4 ± 2.0	4.5 ± 1.6	3.0 ± 0.6	2.8 ± 1.7	4.8 ± 1.8	2.9 ± 0.8
	Low	4.5 ± 2.3	4.4 ± 1.6	3.2 ± 0.6	1.9 ± 1.2	4.6 ± 2.2	3.2 ± 0.5
	Medium	3.3 ± 1.8	4.5 ± 1.8	2.9 ± 0.8	1.9 ± 1.3	4.7 ± 1.8	3.1 ± 0.7
	High	4.2 ± 2.0	4.5 ± 2.0	3.1 ± 0.5	2.7 ± 1.4	4.6 ± 1.8	2.9 ± 0.6
1747 MHz	Sham	4.1 ± 2.0	4.3 ± 2.0	3.0 ± 0.6	1.7 ± 1.3	4.5 ± 1.8	3.1 ± 0.6
	Low	3.2 ± 1.9	4.3 ± 1.7	3.1 ± 0.7	1.9 ± 1.0	4.5 ± 1.8	2.9 ± 0.7
	Medium	3.7 ± 1.9	4.5 ± 1.9	2.9 ± 0.7	2.3 ± 1.5	4.2 ± 1.7	2.9 ± 0.6
	High	4.3 ± 2.3	4.1 ± 1.8	3.1 ± 0.8	2.6 ± 1.6	4.6 ± 1.8	3.0 ± 0.8
Mitomycin C	1.0 mg/kg b.w.	7.7 ± 2.5	26.7 ± 6.1	2.0 ± 1.4	8.0 ± 4.0	35.3 ± 2.1	2.1 ± 1.5

Data represent group means ± standard deviation (SD) of the survivors only; Underlined data: statistically significant increase, compared to the cage controls, $p \leq 0.05$, Mann-Whitney rank sum test. For number of animals see Table I. MN/NCE: micronucleated NCE, analysis of 2000 consecutive normochromatic erythrocytes per animal (Fraunhofer ITEM); MN/PCE: micronucleated PCE, analysis of 2000 consecutive polychromatic erythrocytes per animal (UTHSCSA); % PCE: fraction of PCE, analysis of 10,000 consecutive erythrocytes per animal (UTHSCSA).

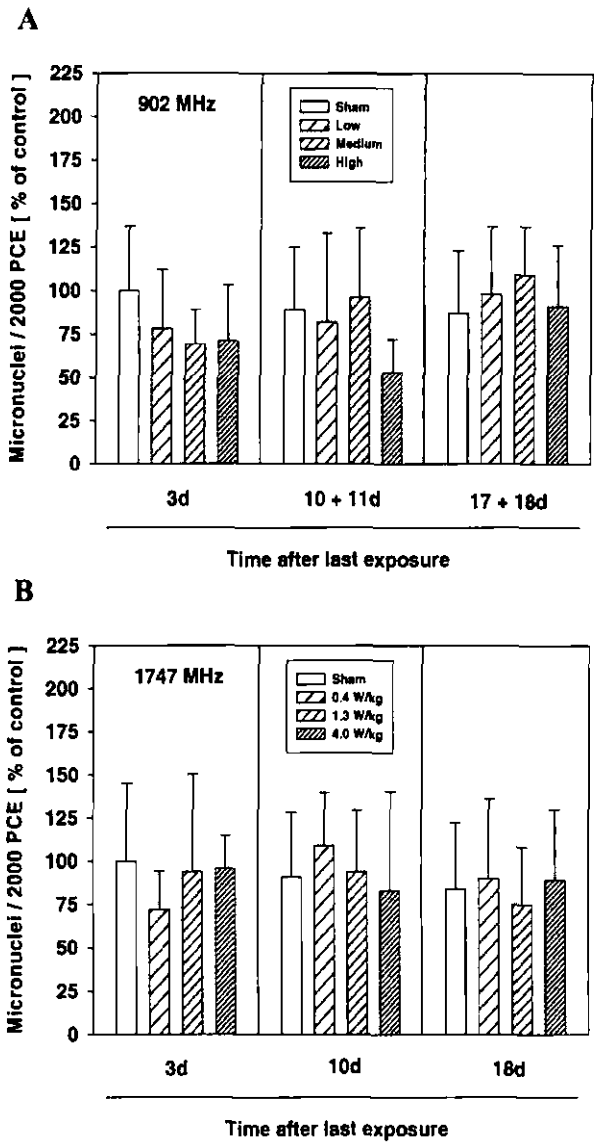

Figure 2. Influence of the time of sacrifice after the last RF exposure on micronucleus frequencies in peripheral blood PCE of RF-exposed B6C3F1 mice. Mice were sham-exposed or exposed to RF, peripheral blood smears were prepared, slides were stained with acridine orange, and PCE were analyzed as described in the *Methods* section. (A) 902 MHz: Each column represents mean ± SD of eight animals (males and females combined) per group and time point. For data analysis, animals necropsied three days, 10 and 11 days, or 17 and 18 days after the last RF exposure were combined to evaluate early, intermediate, and late effects. (B) 1747 MHz: Each column represents mean ± SD of 5–9 animals (males and females combined) per group and time point. For data analysis, animals necropsied three days, 10 days, or 18 days after the last RF exposure were combined to evaluate early, intermediate, and late effects.

investigation to analyze the chronic effect of RF exposure on DNA integrity. The mean incidences of MN/2000 NCE are presented in Table III. Analysis of NCE in the male animals demonstrated no significant differences between the RF-exposed and sham-exposed/cage control mice, and MN frequencies resembled those observed in PCE. Female mice, irrespective of the frequency (902 MHz and 1747 MHz) or exposure level used (low, medium, high), exhibited a consistently lower incidence of MN/2000 NCE as compared to the male animals. For example, the mean incidence of MN in the male cage controls amounted to 4.4 ± 2.3 MN/2000 NCE, whereas the mean frequency of micronucleated NCE in female cage controls was 2.3 ± 1.7 MN/2000 NCE. At 1747 MHz there seemed to be a slight exposure level-dependent increase in micronucleated NCE from 1.7 ± 1.3 MN/2000 NCE in sham-exposed female animals to 2.6 ± 1.6 MN/2000 NCE at the high exposure level. However, it did not reach statistical significance and the incidence measured in sham-exposed females was unusually low compared to the cage control animals. As expected, both male and female animals exhibited an increased MN incidence of 7.7 ± 2.5 and 8.0 ± 4.0 MN/2000 NCE 48 h after injection of the positive control MMC. These incidences were significantly lower than those observed for peripheral blood PCE. Overall, there were no significant differences in MN frequencies between RF-exposed and sham-exposed/cage control mice, both in peripheral blood PCE and NCE.

Discussion and conclusion

Induction of DNA damage in somatic cells can lead to the development of cancer and/or cell death. This is why in recent decades researchers have used several experimental techniques to investigate the extent of genetic damage in mammalian somatic cells exposed in vitro and/or in vivo to non-ionizing electromagnetic fields (Vijayalaxmi and Obe 2004, Verschaeve 2005, Vijayalaxmi and Obe 2005, Vijayalaxmi and Prihoda 2008).

There are very few peer-reviewed scientific publications addressing the genotoxic potential of long-term (subacute to chronic) in vivo studies with whole-body exposure to RF in experimental animals such as mice and rats. The exposures not only varied in magnitude, but also with respect to the signal (carrier frequency and modulation), and detailed dosimetric evaluations were not always provided. Although needed, chronic in vivo studies are quite rare. For these reasons, the present investigation was added to the PERFORM-A1 mouse carcinogenicity study (Tillmann et al. 2007), thus offering the possibility to determine in a high number of animals the genotoxic potential of chronic exposure to different environmentally relevant RF signals, simulating exposure from GSM (902 MHz) and DCS (1747 MHz) handsets, and to directly correlate the results with the outcome of the carcinogenicity study. Irrespective of frequency or maximal

whole-body-averaged SAR (0.4, 1.3, or 4.0 W/kg body weight during phase I, 'GSM Basic') used, the results of the present study did not provide any evidence of RF-induced genotoxicity, which is in line with the lack of carcinogenic potential and RF-related death in the PERFORM-A1 main study and also with the absence of MN induction in a preceding short-term study (5-days and 6-weeks exposures) by Görlitz et al. (2005). Although higher slot-averaged whole-body SAR up to 33.2 W/kg were used in the study of Görlitz et al. (2005), incidence of MN in bone marrow PCE (5-days study), peripheral blood NCE (6-week study), keratinocytes, and spleen cells were not significantly different between sham- and RF-exposed mice.

In the present study, the occurrence of MN, as a sensitive measure for both clastogenic and aneugenic events, was evaluated in both peripheral blood PCE and NCE to detect acute as well as chronic DNA-damaging effects of RF exposure. Due to the PCE migration time from bone marrow to peripheral blood and subsequent maturation to NCE, an increase in micronucleated PCE in peripheral blood only indicates acute DNA damage taking place within a narrow time-frame of about 2–3 days before sampling or genomic instability of hematopoietic stem cells in the bone marrow. In contrast, an increase in micronucleated NCE covers genotoxic activities during more than three weeks preceding sampling and is therefore an appropriate measure for subchronic and chronic studies with repeated exposures (Chaubey et al. 1993, Witt et al. 2000). Nevertheless, in the present study, neither PCE nor NCE (irrespective of early or late sampling after the last exposure) demonstrated an RF-mediated increase in the incidence of MN, thus speaking against a genotoxic potential of chronic whole-body RF-exposure in B6C3F1 mice.

To ensure validity of the method, some sentinel animals were administered the known clastogen MMC. As expected, these positive control animals exhibited an increased frequency of MN in both peripheral blood PCE and NCE and a reduced PCE percentage. For NCE the MMC-induced increase in MN was significantly lower than that observed for peripheral blood PCE. However, sampling was performed 48 h after administration, and a time period of 48 h is too short to ensure complete maturation of micronucleated PCE to NCE. In Swiss mice, for example, the number of micronucleated NCE did not peak until 60 h after irradiation (Chaubey et al. 1993).

The spontaneous MN frequencies in peripheral blood NCE observed in the present study were within the range reported in other studies (Chaubey et al. 1993, Witt et al. 2000, Görlitz et al. 2005, Juutilainen et al. 2007) or even lower. Interestingly, cage control, sham-, and RF-exposed female animals all demonstrated lower MN incidences in peripheral blood NCE than male animals. This phenomenon, which is frequently observed for peripheral blood NCE (for example, see Witt et al. 2000 and Görlitz et al. 2005) and for bone marrow PCE, has often been interpreted as higher sensitivity and higher MN background levels in male animals (Mavournin et al. 1990). However, the reason(s) for this phenomenon is/are unclear, but may involve an enhanced rate of blood formation with inefficient enucleation or a lower DNA-repair capacity.

From the limited in vivo data concerning long-term whole-body exposure of mice to RF, there seems to be no clear evidence of genotoxic activity of repeated RF exposure. Nevertheless, there are a few subacute/subchronic in vivo studies with rats that indicate some genotoxic activity. For example, Trosic et al. (2002, 2004) and Trosic and Busljeta (2006) demonstrated a significant increase in MN in peripheral blood PCE of male Wistar rats after eight days and in bone marrow after 15 days of exposure to CW (continuous wave) RF of 2450 MHz (estimated whole-body SAR of 1.25 ± 0.36 W/kg, 2 h/day, 7 days/week for up to 30 days). The increase in both peripheral blood and bone marrow was small and not clearly exposure duration-related. These data are difficult to interpret, because (i) micronucleated PCE arise first in erythroid-lineage stem cells in the bone marrow and then emerge into the circulating peripheral blood, not the other way around, and (ii) in rats, the spleen scavenges abnormal micronucleated PCE and NCE and hence it should only be possible to demonstrate a clear increase in MN by using the very young PCE fraction at high numbers (Wakata et al. 1998). Demsia et al. (2004) reported an about 3-fold induction of MN in bone marrow PCE of male and female Wistar rats mainly head-exposed to 912 MHz with peak spatial SAR (10 g) of 0.42 W/kg (2 h/day on 30 consecutive days). MN induction was also observed in polymorphonuclear cells. The authors used rat bone marrow smears, stained with May-Grünwald and Giemsa (Schmid 1975), but did not devoid the slides of mast cell granules by, for example, cellulose columns. As mast cell granules stain identically to MN with the May-Grünwald-Giemsa stain (Romagna 1988), the significance of this positive finding has to be further evaluated. Another positive finding was reported by Ferreira et al. (2006) in newborn Wistar rats exposed in utero to CW 834 MHz in a metallic box resulting in a not well defined exposure situation. Due to an about 2-fold induction of micronucleated PCE in peripheral blood, the authors concluded that under the experimental conditions used, there might be a genotoxic effect of RF exposure in hematopoietic tissue during embryogenesis.

The first investigation on the genotoxic potential of chronic RF exposure in mice, also using MN induction as an endpoint, was reported by Vijayalaxmi et al. (1997). This study was appended to a primary investigation examining, in cancer-prone C3H/HeJ mice, the carcinogenic potential of chronic exposure to CW RF fields of 2450 MHz (average whole-body SAR of 1.0 W/kg; 20 h/day, 7 days/week over a period of 18 months). The final corrected results (Vijayalaxmi et al. 1998) indicated a small but statistically significant 0.5% increase in MN frequency in both bone marrow and peripheral blood PCE. As the MN incidences in both RF- and sham-exposed mice were still within the historical range for spontaneous MN in control mice (similar age) and the small increase in MN was not correlated with carcinogenicity in the same mice (Frei et al. 1998), a real genotoxic effect was considered to be unlikely by the authors.

There are some more chronic studies which used MN induction as an endpoint and indicate a lack of genotoxic potential of RF exposure. In a recent chronic study, evaluation of MN induction was added to two long-term mouse bioassays with female CBA/S (78 weeks of exposure) and transgenic/non-transgenic K2 mice (52 weeks of exposure), investigating whether RF exposure enhances the carcinogenic effect of ionizing or ultraviolet light (UV) irradiation (Juutilainen et al. 2007). Different frequencies (902.5 MHz, 902.4 MHz, and 849 MHz), signal modulations ('Nordic Mobile Telephone' network, CW, speech-modulated GSM Basic, and speech-modulated 'Digital Advanced Mobile Phone System' network) and whole-body-averaged SAR (1.5 W/kg, 0.35 W/kg, and 0.5 W/kg) were used. Nevertheless, MN incidence in both peripheral blood PCE and NCE was not altered by RF exposure, irrespective of RF frequency, modulation, SAR level, or mouse strain used, or application of preceding X-ray or parallel UV exposure. Besides evaluation of MN induction, Juutilainen et al. (2007) determined the percentage of PCE in peripheral blood, and, similar to our observations and the observations of Görlitz et al. (2005), found the PCE fraction to be not affected by RF exposure, thus indicating a lack of RF-mediated bone marrow toxicity. This was also in line with the 12-month interim examinations on hematology within the PERFORM-A1 study, demonstrating no RF-mediated changes (Tillmann et al. 2007).

Two additional chronic in vivo studies published by Vijayalaxmi et al. (2003) and Verschaeve et al. (2006) also pointed to a lack of genotoxicity and co-genotoxicity of RF exposure. Appended to a carcinogenicity study, Vijayalaxmi et al. (2003) investigated MN induction in the bone marrow of male and female Fisher rats. In this study, pregnant Fisher rats (from the 19th day of gestation) and their nursing offspring (until weaning) were exposed to a far-field 1600 MHz iridium wireless communication signal followed by chronic head-only exposures of male and female offspring to a near-field 1600 MHz signal (2 h/day, 5 days/week, for two years). After two years, bone marrow was collected from all surviving rats and the incidence of MN/2000 PCE was evaluated. There were no significant differences between RF-exposed, sham-exposed, and cage control animals, but positive controls treated with MMC exhibited a significantly increased MN frequency. As observed also in the present study, there was good correlation between absence of genotoxicity and absence of carcinogenicity, as there was no significant increase in tumor development in the same rats (Anderson et al. 2004). Finally, Verschaeve et al. (2006) investigated the co-genotoxic effect of RF-exposure and a drinking water mutagen. Female Wistar rats exposed to 900 MHz (GSM Basic) for 2 hours/day on 5 days/week for two years (average whole-body SAR: 0.3 or 0.9 W/kg) in parallel received 3-chloro-4-(dichloromethyl)- 5-hydroxy-2(5H)-furanone. MN frequencies were evaluated after 3, 6, and 24 months of exposure in peripheral blood PCE, and in addition, DNA damage was assessed by the comet assay in white blood cells, liver, and brain. Interestingly, the data also did not provide any evidence of a genotoxic or co-genotoxic activity of RF exposure.

In conclusion, the present chronic study in B6C3F1 mice exposed to GSM (902 MHz) and DCS (1747 MHz) RF, including the most relevant extremely low frequency (ELF) amplitude modulation components of these signals, at three different maximal exposure levels (i.e., 0.4, 1.3, and 4.0 W/kg body weight during phase I, 'GSM Basic') did not demonstrate acute, delayed, or chronic genotoxicity of RF exposure in peripheral blood erythrocytes. Seeing that some subacute/subchronic in vivo studies have pointed to a tendency towards genotoxic activity of RF exposure, this discrepancy has to be further evaluated in terms of exposure technology and methodological aspects. However, bearing in mind all the chronic genotoxicity studies mentioned above, the overall data suggest that long-term chronic exposure to RF, especially to the frequencies used for wireless mobile communications, does not induce excess genotoxicty in mice and rats. This is in line with a lack in carcinogenic potential of RF found in the same studies.

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APPENDIX AB

Electromagnetic field exposures act via activation of voltage-gated calcium channels.

How this leads to diverse impacts on health including cardiac effects

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Problem 1:

How can electromagnetic fields (EMFs) impact our biology and medicine - for better or for worse?

A great puzzle:

These EMFs are composed of low energy photons, with energy per photon too low to influence the chemistry of the body!

How can they influence our biology through non-thermal effects?

Safety standards assume that they can't - that only thermal effects need to be considered: If no thermal effects there cannot be biological effects.

And yet, there are thousands of papers in the scientific literature reporting biological effects of exposures well within safety standards!

Problem 2:

For over 30 years, it has been known that *pulsed* electromagnetic fields are often much more biologically active then are non-pulsed fields.

That is inconsistent with the thermal/heating paradigm:
Pulsed fields either produce less heating or the same amount, depending on how the experiment is set up.

So we meet again the great puzzle:
How can such low frequency EMFs influence our biology - for better or for worse?
Energy per photon is too low to influence the chemistry of the body!
Can they influence our biology through non-thermal effects?
There is a substantial literature reporting that they do.

I recently solved this important puzzle:

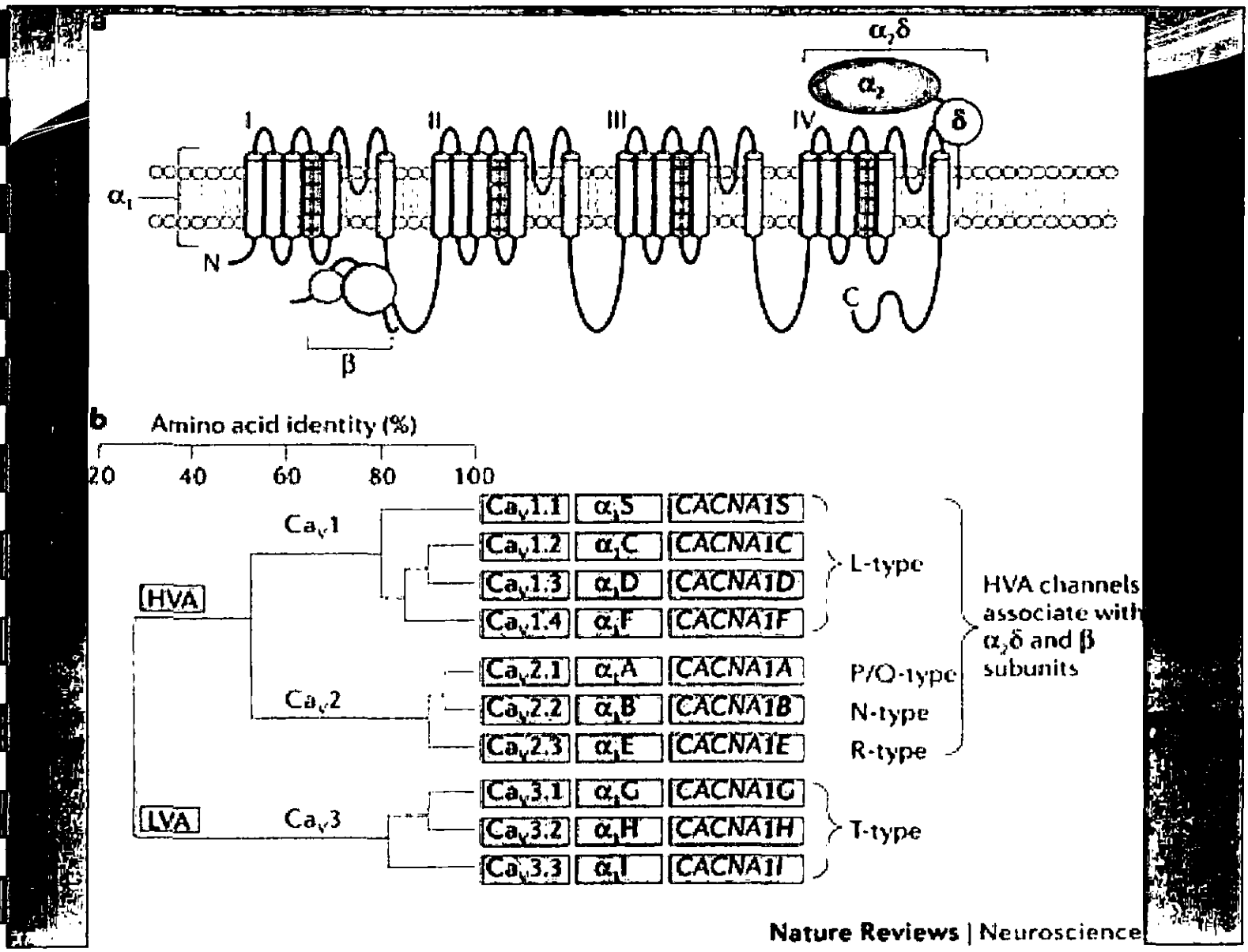
EMFs activate voltage-gate calcium channels.

And it is the downstream effects of the increased intracellular Ca^{2+} ([Ca2+]i) that leads to the biological effects of EMF exposure.

The most central evidence:

A whole series of studies have shown that in studies of exposures to microwave/ lower frequency EMFs, all of the effects produced can be blocked by calcium channel blockers - drugs that block voltage-gated calcium channels (VGCCs).

The VGCCs involved include the L-type VGCCs but also T-type, N-type and P/Q type VGCCs, because of effects of blockers specific for each of these channel types.



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The conclusion that such EMFs act biologically by activating VGCCs, is further supported by hundreds of studies showing that low intensity microwave EMF exposures are followed by changes in calcium fluxes and/or by changes in calcium signaling.

There are also hundreds of studies showing that low-intensity microwave EMFs can produce oxidative stress responses and oxidative stress, as we will see later, is produced by downstream effects of VGCC activation.

Furthermore this conclusion is also supported by biophysical modeling studies of Panagopoulos et al, showing that EMFs can act through their interactions with the charged amino acid residues which regulate channel opening and closing, to open voltage-gated ion channels. Thus, EMF VGCC activation is biophysically plausible and was predicted from biophysical modeling!
(BBRC 2000 Jun 16;272(3):634-40; BBRC 2002 Oct 18;298(1):95-102.

The finding that EMF exposure acts via activation of VGCCs, provides for the first time, an answer to the puzzle of how exposure to EMFs composed of low energy photons can affect our biology and medicine. Because increased intracellular Ca2+ [Ca2+]i produced by VGCC activation can act, in turn, to stimulate NO synthesis, such NO increases may also have an important role.

Pilla recently showed that such low-intensity pulsed microwave frequency EMF exposures produce almost instantaneous increases in both [Ca2+]i and also of NO synthesis (all occurring in less than 5 seconds):
Pilla AA. Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems. Biochem Biophys Res Commun 2012;426:330-3.

This provides strong support for the inference that EMFs activate VGCCs directly.

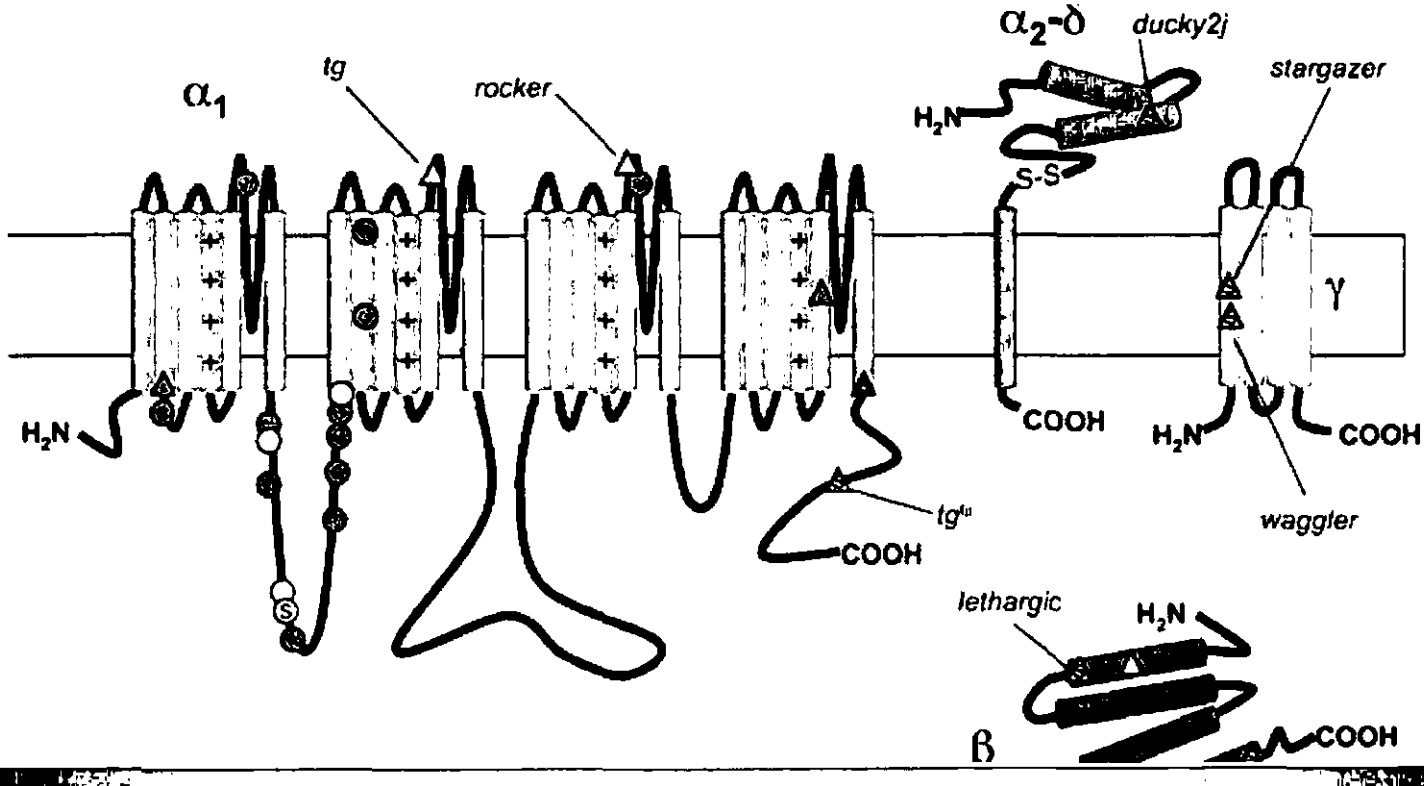
The VGCCs have been shown to have a universal or near universal role in converting electrical effects into chemical changes in the cell. For example WA Catterall (Cold Spring Harb Perspective Biol 2011;3 a003947) states that "Thus, voltage-gated Ca^{2+} channels are the key signal transducers of electrical excitability, converting the electrical signal of the action potential in the cell surface membrane to an intracellular Ca^{2+} transient." Tsien and Barrett (Ch.3 in Zamponi, Voltage-Gated Calcium Channels, 2005) stated that "But the critical and specific role of Ca^{2+} channels in signal transduction is unique: in every instance, the conversion of an electrical signal to a chemical message requires the activation of Ca^{2+} channels."

Thus, the central and specific role of VGCCs in transducing effects of EMFs into chemical signaling changes should, perhaps, not have been surprising.

However, the advocates of the current safety standards, claim to this day, that there are no biophysically viable mechanisms for these weak field EMFs to produce non-thermal effects in our bodies. This claim is argued as follows (see Sheppard AR et al, Health Phys 2008;95:365-396):

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.

Let's look at the known properties of the VGCCs to see whether this argument holds up.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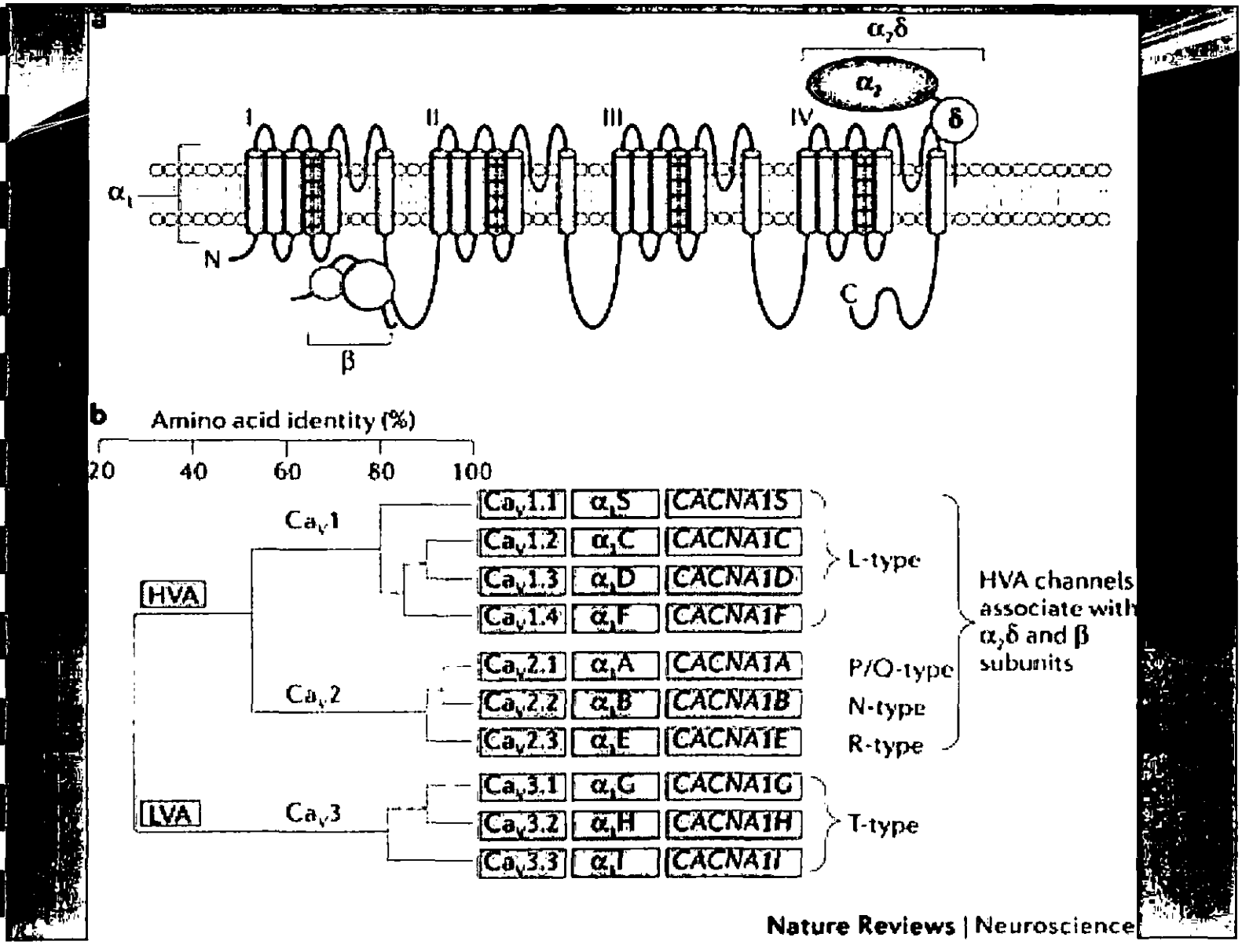

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In summary, a central role of VGCC activation in responses to low level EMFs is shown by:

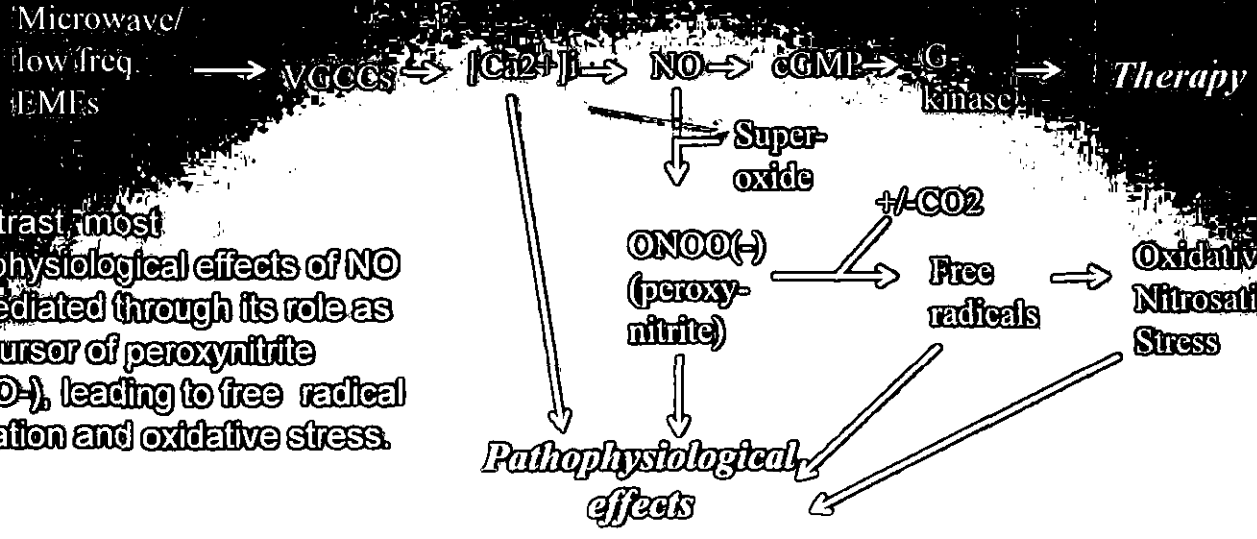
1. In 26 different studies, effects of low intensity microwave/lower frequency EMFs were blocked by calcium channel blockers.
2. In each of these studies, all such effects were blocked or greatly lowered, suggesting a widespread, perhaps universal role of VGCCs in producing such effects.
3. Hundreds of studies show changes in Ca^{2+} fluxes and/or Ca^{2+} signaling following microwave EMF exposure, consistent with effects of VGCC activation.
4. Pilla showed that pulsed field microwave exposure produces an almost instantaneous (<5 sec.) increase in Ca^{2+}/calmodulin-dependent nitric oxide (NO) synthesis, consistent with a direct VGCC activation response.
5. Panagopoulos et al, in studies published in 2000 and 2002, predicted based on detailed biophysical modeling, that VGCCs could be directly activated by low intensity EMFs.
6. The properties of the voltage sensor of the VGCCs predicts that the VGCCs are exquisitely sensitive to low intensity EMFs. It is clear that VGCC activation is an exception to the claim that there cannot be a biophysically viable mechanism for low intensity EMF effects.
7. VGCC activation has a universal or near universal role in converting electrical signals to chemical signals in the body.
8. Low level EMFs activate VGCC-like channels in plants.

There can be no question that VGCCs are the major, perhaps the only targets of low intensity EMFs in the body.

How then does VGCC activation act to produce biological changes in the body?

Most physiological responses to [Ca2+]i and NO act as follows:

NO increases levels of cGMP, leading in turn to stimulation of the cGMP-dependent protein kinase (protein kinase G).



In contrast, most pathophysiological effects of NO are mediated through its role as a precursor of peroxynitrite (ONOO-), leading to free radical generation and oxidative stress.

Arthur A. Pilla published a model of therapeutic effects of EMFs and reviewed the evidence supporting it, a model that was very similar but not identical to mine that you just saw on the preceding slide. He states in the title, abstract and first sentence of his paper that these are all non-thermal effects.

Nonthermal electromagnetic fields: from first messenger to therapeutic applications.
Pilla AA.
Electromagn Biol Med. 2013 Jun;32(2):123-36.

I proposed a similar mechanism to the Pilla mechanism for this in two papers.

Some Relevant Papers for my talk:

Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. Pall ML. J Cell Mol Med. 2013 Aug;17(8):958-65.
This paper was honored to be included on the "Global Medical Discovery" site as one of the most important medical papers of 2013.

- Pall ML. 2014 Electromagnetic field activation of voltage-gated calcium channels: role in therapeutic effects. Electromagn Biol Med. 2014 Apr 8.
- Pall ML. 2014 Microwave electromagnetic fields act by activating voltage-gated calcium channels: Why the current international safety standards do not predict biological hazard. Recent Res Devel Mol Cell Biol, 7(2014): 0-00 ISBN: 978-81-308-0000-0.
- Pall ML. 2013 The NO/ONOO- cycle as the central cause of heart failure. Int J Mol Sci. 2013 Nov 13;14(11):22274-330.

Health Impacts by Microwave Radiation

There are multiple studies showing that each of these responses have been reported to be produced by microwave radiation exposures

There may be arguments about how strong the evidence is, but there is no question that there is substantial evidence.

None of these can be explained by heating -- they can all be explained by VGCC activation and downstream effects!

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	[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	These were reported in occupational exposures [21]; 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 cell; excessive VGCC activity and [Ca2+]i levels produces these electrical changes in the heart	[3]

Most physiological responses to [Ca2+]i and NO act as follows:

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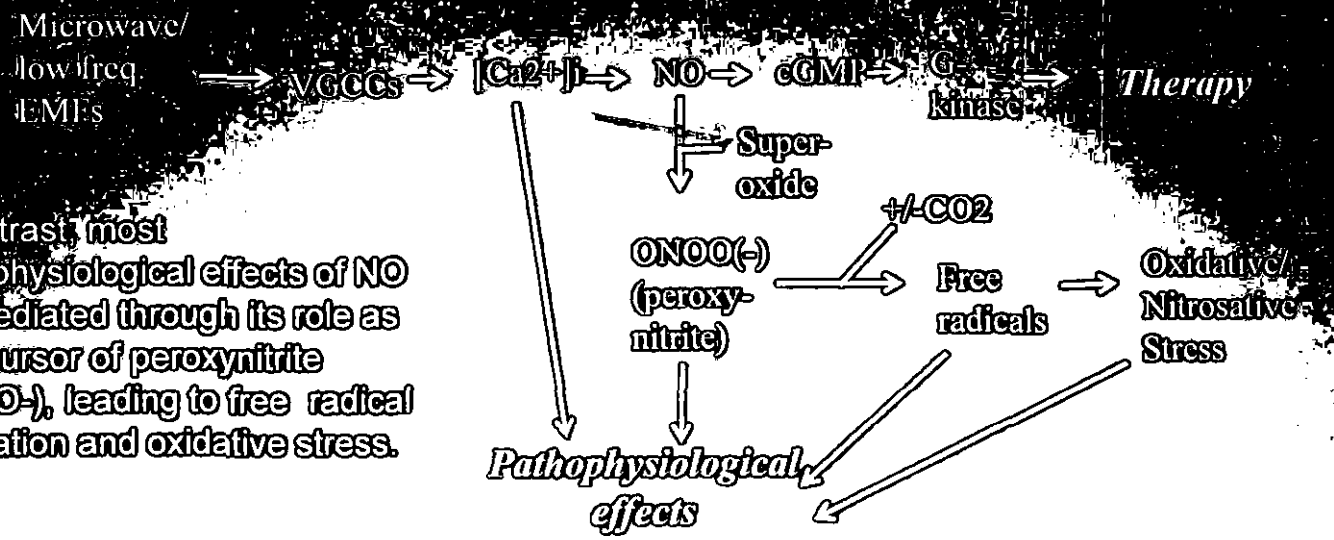

In contrast, most pathophysiological effects of NO are mediated through its role as a precursor of peroxynitrite (ONOO-), leading to free radical generation and oxidative stress.

So let's go on the cardiovascular effects of microwave EMFs.

L-type and T-type VGCCs are known to have very high levels in the pacemaker cells of the sino-atrial node:
(Bohn et al, FEBS Lett 2000;48:73-76; Mangoni et al, Prog Biophys Mol Biol 90:38-63).

Both L-type and T-type VGCCs are known to control the heart beat. Consequently, microwave EMFs may be expected to have direct effects on these pacemaker cells.

There are studies, in two cases going back to the 1960s, showing that isolated animal hearts exposed to microwave EMFs (again, well within current safety standards) developed tachycardia and arrhythmia.

These are probably direct effects of the fields on the cardiac pacemaker cells. Levitina NA 1966 Investigation of the nonthermal effect of microwaves on the cardiac rhythm of frogs. Byull Eksp Biol Med 62(12):64-66. Frey AH, Seifert E 1968 Pulse modulated UHF energy illumination of the heart associated with change in heart rate. Life Sci 7:505-512.

Pulsed microwave EMF exposures showed effects on frog hearts and on heart muscle cells that influenced Ca^{2+} fluxes – suggests now a possible VGCC effect on the heart.

Schwartz et al, Bioelectromagnetics 1990;11:349-58; Wolke et al., Bioelectromagnetics 1996; 17:144-53.

Let's consider a second set of studies, studying excessive VGCC activity in humans.
There are rare mutations in the gene for the main type of L-type VGCC in the heart and in the brain – rare mutations that cause Timothy syndrome.

Babies born with this mutation, rapidly develop tachycardia and arrhythmia and also autism and typically die at age 2 to 6 of sudden cardiac death.

The mutation in Timothy syndrome causes the channel to be very slow in closing, such that much greater Ca^{2+} flows into the cell – so great excess of VGCC activity.

And that then causes arrhythmia and sudden cardiac death.

The mutation in Timothy syndrome causes the channel to be very slow in closing, such that much greater Ca^{2+} flows into the cell – so great excess of VGCC activity.

Transferring the Timothy syndrome mutation to the mouse, produces similar cardiac changes and autism type changes.

Excessive activity of another VGCC can also cause cardiac arrhythmia in humans.

Conclusion: Excessive VGCC activity can cause arrhythmia and sudden cardiac death.

Citations: Splawski I et al., Proc Natl Acad Sci U S A. 2005;102:8089-96; Barrett CF, Tsien RW. Proc Natl Acad Sci U S A. 2008;105:2157-62; Groen JL, et al., Hum Mol Genet. 2015 ;24:987-93.

There are a number of detailed studies showing that genetic polymorphisms in the genes encoding the VGCCs can have roles in

1. arrhythmias including both
   - tachycardia and
   - bradycardia (what is called Brugada syndrome)
2. sudden cardiac death

Citations: Jagu et al, Front Physiol 2013;4:article 254; Splawski et al Cell 2004;119:19-31; Burashnikov E, et al. Heart Rhythm 2010;7:1872-82.

Are tachycardia and bradycardia opposites?

Clearly they are in two ways – they produce opposite effects of the heartbeat

and they are produced, in turn, by high VGCC activity (tachycardia)

and by low VGCC activity (bradycardia)

But there are two ways in which they are not opposite:

Animal studies have shown that high level EMF exposures or repeated or prolonged exposures, can,over time, lead to bradycardia and arrhythmias. (see Zhang et al, PLOS One 2014; 9(7),e101532 and citations therein)

And there are mutations causing familial tachycardia-bradycardia syndrome, where the two are linked.

Why is this connection between tachycardia and bradycardia important?

In part, because there have been many events where apparently healthy athletes have died of sudden cardiac death and some others where it has been possible to save them, and because of the perception that these have increased rapidly in recent years, this raises the issue of whether these are caused by EMF exposure. Drezner et al, (Heart Rhythm 2008 5:794-9)showed an apparent increase over a 7 year period (2000-2006), with a correlation coefficient with year of 0.844.

Most such events are associated structurally normal hearts and with bradycardia/arrhythmias, but not tachycardia. (Harmon et al, Circ Arrhythm Electrophys 2014; 7:198-204; Chung et al, J Electrocardiol 2013: Oct 1; Sangwatanaroj Clin Cardiol 2001;24:776-81).

So can excessive VGCC activity lead to bradycardia/arrhythmia?

Most physiological responses to [Ca2+]i and NO act as follows:

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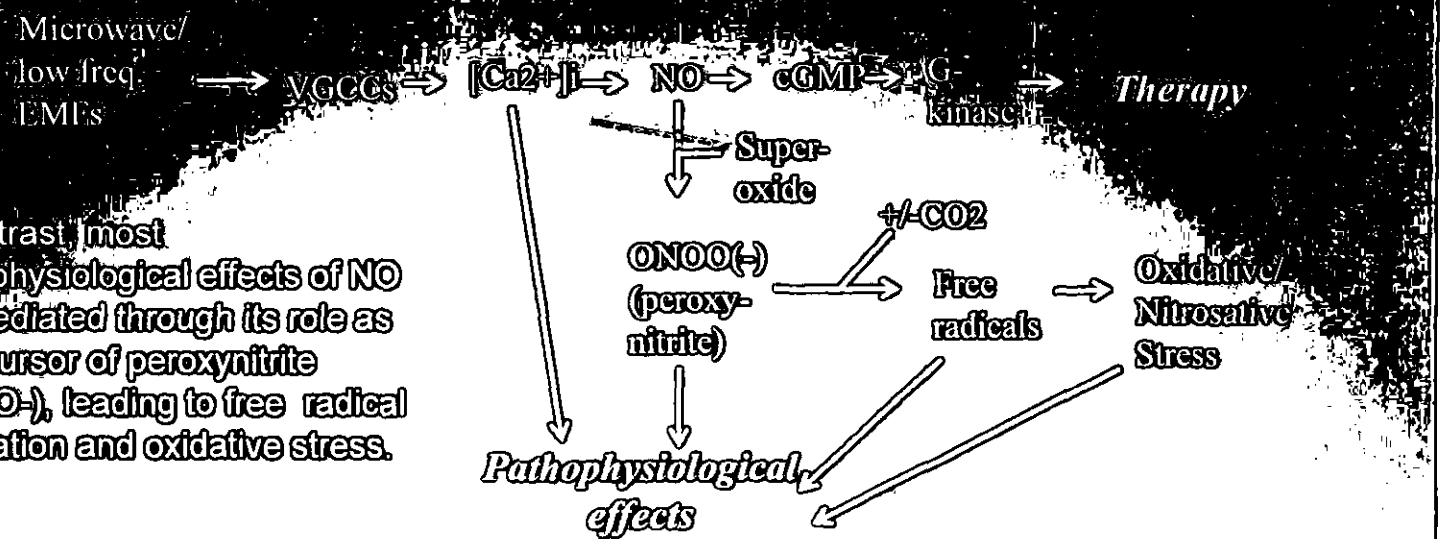

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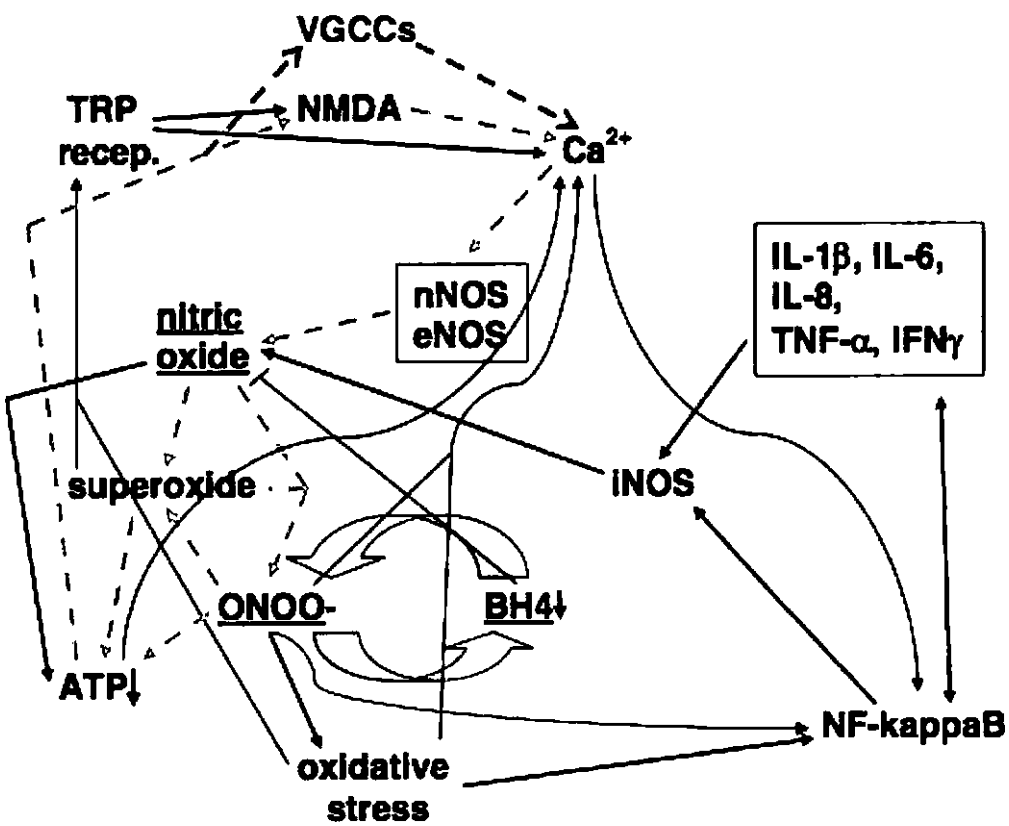
VGCCs
TRP
recep.
NMDA
Ca2+
nNOS
eNOS
IL-1β, IL-6,
IL-8,
TNF-α, IFNγ
nitric
oxide
superoxide
iNOS
ONOO-
BH4
ATP
NF-kappaB
oxidative
stress

Study	Effects Reported
Schwan 1977	Cardiology changes
Dwyer 1978	Bradycardia, hypotension
Sadicikova (USSR)	Bradycardia, hypo & hypertension, cardiac pain, systolic murmur
Kalyada (USSR)	"cardiovascular changes"
Sadichikova (USSR)	Changes in cardiovascular system
Pressman 1970	QRS interval in ECG increased (bradycardia)
Domanski (USSR)	Bradycardia, hypotension, ECG changes
Lerner (1980)	Bradycardia
Stuchley (1978)	Bradycardia (measured in 2 ways), hyper & hypotension, cardiac pain, systolic murmur.

1981
U.S. NASA
(National
Aeronautics &
Space
Administration)
Review

Jauchem JR (1997)) Int Arch Environ Health reviewed some of the Soviet studies on occupational exposures.

These found that extremely low exposures frequency (ELF) exposures among high voltage switchyard workers apparently produced increased arrhythmias and tachycardia. (Note: ELF exposures also work via VGCC activation)

Occupational microwave/radiofrequency exposures produced hypotension and bradycardia or tachycardia.

More recently, there have been a number of studies of apparent effects on people living near cell phone "base stations", with most of these being European studies.

- Seven of these studies found various cardiovascular effects, with some reporting bradycardia, arrhythmias and other ECG changes. There is also one study of "smart meter" exposures that also showed cardiovascular effects.

Perhaps the best overview of this area is the "Guideline of the Austrian Medical Association for the Diagnosis and Treatment of EMF-Related Health Problems and Illnesses(http://freiburger-appell-2012.info/media/EMF%20Guideline%20OAK-AG%20%202012%2003%2003.pdf)

The first things that they list as measures of previous EMF exposures are the following cardiovascular measurements:

Blood pressure and heart rate including:

24-hour blood pressure monitoring
24-hour ECG
24-hour heart rate variability

So here again, we are looking at very similar effects on the heart and heart rate control.

Conclusions:

There are a large number of observations that support our overall hypothesis that EMFs may act directly on the pacemaker cells to produce changes in control of the heart, leading to tachycardia, bradycardia, arrhythmia and sudden cardiac death:

1. EMFs are known to act via VGCC activation to produce excessive [Ca2+]i,calcium signaling, NO, peroxynitrite and oxidative stress.
2. VGCCs are expressed at high levels in the pacemaker cells of the sino-atrial node and have essential roles in controlling the heart beat.
3. High VGCC activity can lead to tachycardia, arrhythmias and sudden cardiac death (SCD) as in Timothy syndrome.
4. Bradycardia can also be associated with arrhythmias and SCD.
5. Genetic polymorphisms in the VGCC genes can produce increased susceptibility to each of the changes listed in 3 and 4.
6. Low intensity microwave EMFs can influence the above listed changes in isolated animal hearts and in epidemiological studies, in humans exposed to such fields.
7. High level, prolonged or repeated microwave EMF exposures may produce bradycardia, arrhythmia and SCD through downstream effects of VGCC activation leading to NO/ONOO(-) cycle initiation in the pacemaker cells of the sino-atrial node.
8. SCD and sudden cardiac arrest in young, apparently healthy athletes and other individuals are associated with bradycardia and arrhythmia.