16 April 2014

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Re: ***Preliminary Opinion on Potential Health Effects of Exposure to Electromagnetic Fields (EMF)***

Gentlemen,

The BioInitiative Working Group has reviewed the *Preliminary Opinion on Potential Health Effects of Exposure to Electromagnetic Fields (EMF*) dated November 29, 2013. We submit the following comments and suggested revisions. Thank you for providing this opportunity for comment. We hope these suggested revisions will be incorporated in the Final Opinion.

OVERALL COMMENTS

1. This Preliminary Opinion is an inadequate basis for updating the 2009 EU opinion on '*Health Effects of Electromagnetic Fields (EMF)*' and should be sent back for major revisions. The conclusions drawn from the data presented are unreliable for judging possible health risks.

2. The Committee has not answered the question it was appointed to investigate. There is no conclusion in the Executive Summary on whether the Committee determined that possible health effects of EMF are established for childhood leukemia and exist for genotoxicity, for neurological effects, for brain tumors, male fertility, fetal and neonatal effects or other key areas of research. The title of the Opinion is 'Preliminary Opinion on **Possible Effects** of Electromagnetic Fields (EMF) on Human Health" (emphasis added). The Committee has given an answer to a different question, limiting its conclusions to whether certainty or causal effect is established. This was also the central failing of the SCENIHR 2009 Opinion on EMF. This Opinion is better titled "Preliminary Opinion on Scientific Certainty of Health Harm from Electromagnetic Fields (EMF).

3. The Opinion should be revised to clearly state whether the evidence supports a finding of **possible risk** for each type of evidence considered (each section). This report is not useful for the purpose intended due to the ambiguous basis for judging the sufficiency of the scientific evidence, which will eventually form a basis for concluding whether changes in the ICNIRP standards are warranted. The lack of a clear statement about the basis for judging what constitutes sufficient evidence of "Possible Effects", and the embedded up-shifting language to instead require a demonstration of 'conclusive or unequivocal evidence' (Exhibit A).

4. Sections on brain tumors are flawed. The report consistently ignores or dismisses published scientific studies that report positive findings at exposure levels below ICNIRP standards (Exhibit B-Hardell). The SCENIHR conclusion that evidence for glioma is weaker now than in 2009 is unjustified, and can only be reached by excluding key scientific studies that reach the opposite conclusion. *There is a consistent pattern of increased risk for glioma (a malignant brain tumor) and acoustic neuroma with use of mobile and cordless phones* according to studies from Orebro University, Sweden released in 2012 and 2013.

5. Further, the Opinion misreads evidence of effects of some studies it does present when drawing conclusions (Exhibit C: Misreading Evidence - De Iuliis). In one example, statistically significant damage to sperm DNA and sperm motility and vitality was reported at cell phone radiation exposure of only 1 W/kg. The preliminary Opinion on page 77 wrongly characterizes the evidence to show that only very high SARs cause this effect. It says *"(T)he authors claimed that their results clearly demonstrated that RF exposure can damage sperm function via mechanisms involving the leakage of electrons from the mitochondria and the induction of oxidative stress but* ***the employed SAR values are very high and not relevant to cell phone users."*** (emphasis added). Finally, the entire body of new evidence for risks to fertility and reproduction is dismissed in the Executive Summary with "*The previous SCENIHR opinion concluded that there were no adverse effects on reproduction and development from RF fields at exposure levels below existing limits. The inclusion of more recent human and animal data does not change that assessment"* and in Section 3.13.4 "(*T)herefore, it is concluded that there is strong overall weight of evidence against an effect of low level RF fields on reproduction or development."* These conclusions are possible only by omitting key data, ignoring the conclusions of the authors, and dismantling the significance of the De Iuliis et al results by misreporting it. Critical evidence is misquoted, and then relied on by SCENIHR to dismiss the essential point.

6. Evidence for neurological effects (Exhibit D) should be incorporated into the analysis and conclusions of the Final Opinion. The involvement of oxidative stress on neurological/behavioral effects of ELF EMF and RFR were dismissed as "*not firmly identified*" in the Executive Summary. Exhibit D documents a significant number of overlooked studies of extremely-low frequency radiation that are reported to cause nervous system effects in 90% of the 105 studies available from 2007 to 2014. New neurological RFR studies report effects in 68% of studies on radiofrequency radiation (or 144 of 211 studies) in 2014. This has increased from 63% in 2012 (93 of 150 studies) in 2012. These studies should be included in the Final Opinion. They will likely change the Preliminary Opinion that now avoids making a judgment about whether neurological effects are sufficiently established as a cause of possible health effects.

7. Genetic effects (damage to DNA) from radiofrequency radiation are reported in 65% (or 74 of 114 studies); and 83% (or 49 of 59 studies) of extremely-low frequency studies (Exhibit E). These studies span the 2006/2007 to 2014 time period and many are overlooked. They should be included in the Final Opinion. They will likely change the conclusion of the Preliminary Opinion that skirt the issue of whether genotoxicity is sufficiently established as a cause of possible health effects (Sections 3.5.2.5, 3.7.2.5, and 3.11.3).

8. Evidence for Impacts of Physical and Biological Variables on Study Results (Exhibit F)
The main flaw of the preliminary Opinion is in neglecting the mechanistic data on non-thermal (NT) effects of microwaves (MW). As reported in multiple studies in Exhibit F , these effects depend on a variety of biological and physical parameters including polarization, frequency and environmental EMF. *In vitro* and *in vivo* negative studies have covered a negligible minority of

real cell phone signals, so the studies cannot provide evidence that the vast majority of other real cell phone signals are safe. Thus, the results of negative studies profiled in the Opinion cannot be extrapolated to the issue of the safety or lack of safety of cell phones in use today. Well-conducted positive studies cannot be negated by poorly conducted negative studies. The claim of "inconsistency" in *in vitro* and *in vivo* data and "conflicting results" has at least one simple explanation. The studies were performed under different conditions. Thus, results cannot be directly compared. The SCENIHR report on inconsistency and conflicting results may rather reflect the level of superficial analysis of these studies. Another fundamental flaw is in neglecting many studies showing dependence of the NT MW effects on exposure duration or dose (defined in radiation physics as multiplication of SAR on exposure duration), see for review (Belyaev 2010 in Exhibit F). In addition to laboratory studies, when brain cancer risk was epidemiologically examined as a function of dose received in different time windows before diagnosis, increasing trend was observed with increasing RF dose (for exposures 7 years or more in the past) (Cardis, Armstrong et al. 2011). This study provided straightforward evidence for one of the most important Bradford Hill criteria which is dependence on dose.

Good epidemiological evidence for brain tumors from many other studies has been excluded (see Section 1 and Exhibits B and F). The SCENIHR preliminary Opinion is heavily biased in favor of the Danish subscriber cohort study of mobile phone subscribers. This study has major flaws that have been substantially documented since it's publication. It is not informative even according to the requirement of SCENIHR which says *"(T)he minimum requirement for exposure assessment for an epidemiological study to be informative is to include reasonably accurate individual exposure characterization over a relevant period of time capturing all major sources of exposure for the pertinent part of the body*" (page 10).

None of the sections adequately address the literature on mitochondrial function and ELF-EMF and RFR. The studies in Table 7 are largely negative studies, and do not begin to address the central questions. This section needs to be revised to more comprehensively document existing literature as shown in Exhibit G.

Mitochondria are commonly discussed in terms of the biochemical pathways and cascades of events by which they metabolize glucose and generate energy. But in parallel with this level of function there also appears to be a dimension of electromagnetic radiation that is part of the activity of these organelles. For example, electromagnetic radiation can be propagated through the mitochondrial reticulum, which along with the mitochondria has a higher refractive index than the surrounding cell and can serve to propagate electromagnetic radiation within the network (Exhibit G). These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by ELF-EMF and RFR (i.e. a possible health effect that should be documented in the Final Opinion).

<u>Electrophysiology:</u> None of the sections adequately address the literature on changes in electrophysiology with exposure to ELF-EMF and RFR. This is a major area of importance and many papers are available for review. This section needs to be revised to more comprehensively document existing literature, especially in the context of blood-brain barrier changes and the propensity for seizures with disrupted electrophysiology (Exhibit G).

Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma which can trigger a vicious circle of tissue damage from albumin and greater irritability, as discussed above. Evidence suggests that if the blood-brain barrier (BBB) is already disrupted, there will be greater sensitivity to EMF/RFR exposure than if the BBB were intact suggesting that such exposures can

further exacerbate vicious circles already underway. The combination of pathophysiological and electrophysiological vulnerabilities has been explored in relation to the impact of EMF/RFR on people with epilepsy. EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling. In a rat model the combination of picrotoxin and microwave exposure at mobile phone-like intensities led to a progressive increase in neuronal activation and glial reactivity, with regional variability in the fall-off of these responses three days after picrotoxin treatment, suggesting a potential for interaction between a hyperexcitable brain and EMF/RFR exposure.

All of these comments and criticisms argue most strongly for a conclusion in the SCENIHR Final Opinion on EMF that health effects are possible, and in some cases such effects are established.

EXHIBITS AND SPECIFIC FINDINGS AND CONCLUSIONS of The BioInitiative Working Group

Here the BioInitiative Working Group provides specific comments keyed to sections of the preliminary Opinion.

1. Evidence for Brain Tumors

The report consistently ignores or dismisses published scientific studies that report positive findings at exposure levels below ICNIRP standards (Exhibit A-Hardell). The SCENIHR conclusion that evidence for glioma is weaker now than in 2009 is unjustified, and can only be reached by excluding key scientific studies that reach the opposite conclusion. *There is a consistent pattern of increased risk for glioma (a malignant brain tumor) and acoustic neuroma with use of mobile and cordless phones* according to studies from Orebro University, Sweden released in 2012 and 2013.

Had the preliminary Opinion not excluded key papers by Hardell et al, there would be more evidence about the higher risks to adults (and children) of glioma with cell phone use starting early in life. It is another compelling reason to include these Hardell et al studies that have been ignored. Inclusion of the Hardell et al studies provides valuable evidence of possible risks to children from cell phone use. Excluding these key papers has allowed the SCENIHR Committee to avoid making the necessary judgment that evidence already exists that children were reported in at least one study to have higher rates of glioma with mobile phone use than adults. It would lead to the conclusion that "brain tumors are a possible health effect of use of a mobile phone in children, and that risk appears to be far higher than for adults".

Because key studies are omitted, and because the standard for judging possible health effects has morphed into "unequivocal evidence" or "causal evidence", then the Preliminary Opinion wrongly concludes that no risks are established. These sections highlight the problems (yellow highlight).

Health effects from Radiofrequency (RF) fields, Page 4

Epidemiological studies on RF EMF exposure do not unequivocally indicate an increased risk of brain tumours, and do not indicate an increased risk for other cancers of the head and neck region, or other

malignant diseases including childhood cancer. Earlier studies raised open questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. Based on the most recent cohort and incidence time trend studies, it appears that the evidence for an increased risk of glioma became weaker while the possibility of an association of RF EMF exposure with acoustic neuroma remains open.

Health effects from RF fields, Page 12

Epidemiological studies on RF exposure do not unequivocally indicate an increased risk of brain tumours, and do not indicate an increased risk for other cancers of the head and neck region, or other malignant diseases including childhood cancer. Earlier studies raised open questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. Based on the most recent cohort and incidence time trend studies, it appears that the evidence for glioma became weaker while the possibility of an association with acoustic neuroma remains open.

Discussion of brain tumours and other tumours of the head and neck area, Pages 65-66

Overall, there is little evidence that moderate mobile phone use is associated with any cancer in the head and neck region. This is supported by large-scale epidemiological studies of three different designs. Only one case-control study shows risk increases at moderate usage levels, but the results are incompatible with observed time trends in incidence rates in reality checks and can therefore not be used for hazard assessment. Evidence is more controversial for heavy users of mobile phones; "heavy use" is a qualitative characterisation and difficult to quantify as the users with the highest life-long use are compared to those with lesser use (combining years of use and amount of daily use), with various definistons and cut-points. For instance, in Interphone, "heavy users"were approximately 10% of life-long heaviest regular users (or about 5% of all study subjects). It corresponds to, for example, half an hour of daily use over 10 years or more (in the communication of the outcome of the IARC Monograph (IARC 2013)), but this figure must not be interpreted as any suggestion of a safety limit. For the segment of the heaviest users, the largest case-control study in particular observed about 40% increased risks for glioma and for acoustic neuroma. It cannot be concluded from the available studies whether this reflects a causal association. Limitations of the case-control studies, including selection bias and reporting bias, raise concern that the observed association in small subgroups could be attributable to methodological shortcomings. Time trend analysis in incidence rates and the two cohort studies show no evidence of any risk, but would not detect small risk increases after longer latencies in heavy users only.

RF Epidemiological Studies: Conclusions on epidemiology of neoplastic diseases, Page 67

Epidemiological studies do not unequivocally indicate an increased risk of brain tumors, other cancers of the head and neck region, or other malignant diseases including childhood cancer.

Page 172.
Further studies of the effects of RF fields associated with mobile phone use and brain tumours in children are recommended as a high priority [R19]. These should include children of a younger age than those that have been studied to date, and be of sufficient duration to include assessments of cancer risk later in life.

Inclusion of the Hardell et al studies provides valuable evidence of possible risks to children from cell phone use. Excluding it has allowed the SCENIHR Committee to avoid making the necessary judgment that evidence already exists that children have higher rates of glioma with mobile phone use. It would lead to the conclusion that 'brain tumors are a possible health effect of use of a mobile phone in children, and that risk appears to be far higher than for adults'.

2. Misreading Evidence - Evidence for Effects on Fertility and Reproduction

The section must be rewritten based on the following peer-reviewed studies, and their conclusions, but particularly because of the mishandling of the De Iuliis et al (2009) study. This conclusion is also contradicted by a large number of new studies of RFR on sperm quality, motility and other male fertility parameters with very low-intensity cell phone radiation exposures; on pathological changes in the testes, and other serious health impacts that are reported by multiple laboratories around the world (see Exhibit B for references).

The De Iuliis study reports that very LOW SARs of 1.0 W/kg (which are well below today's safety limits) significantly reduced sperm quality parameters, and not just the higher SARs of 27 W/kg and higher which were also reported to decrease motility.

De Iuliis et al conclude that "(*H)igh quality spermatozoa selected in discontinuous Percoll gradients displayed a decline in both vitality and motility after exposure to RF-EMR in a dose-dependent manner. The control populations maintained an average vitality of 89%; however, significant reductions in vitality were observed at exposure levels as low as 1.0 W/kg (p,0.01) (Figure 2A). Similarly, the control populations maintained motilities at an average of 86% over the incubation period, however after exposure to RF-EMR at levels of 1.0 W/kg, motility was observed to significantly decrease to 68% (p,0.05) and decreased still further at higher SAR exposures (Figure 2B).*"

Further, "*The research described in this article suggests that one of the key environmental factors involved in the stimulation of sperm mitochondria to produce high levels of ROS, might be excess exposure to RF-EMR from sources such as mobile phones*."

DeIullis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa *in vitro*. PLos One 2009;4(7):e6446.

The SCENIHR preliminary Opinion mischaracterizes the fundamental exposure results the De Iullis et al, 2009 study and should be corrected. The preliminary Opinion on page 77 wrongly concludes that only very high SARs that are not relevant for cell phone users resulted in sperm damage. In fact, SAR levels as low as 1 W/kg can be common in men who keep a cell phone in their pants pocket, or use them near the genitals while sitting may experience such exposures.

Executive Summary, Page 13: Page 120: Conclusions on Reproduction and Developmental Effects: Page 172 – 173: and Page 177-179 Literature Identified but Not Cited.

It is quite stunning that the preliminary Opinion simply does not evaluate many key papers on RFR impacts to sperm and male fertility that it clearly knows to exist, because it lists them in Section 7 as "Literature Identified but Not Cited", and still has the temerity to conclude that the evidence for potential effects of RF fields on male fertility is weak. It would not be weak if these papers were properly included in the review (see Exhibit B: Reference List for Important Fertility and Reproduction Papers).

3.13.4. RF fields

"*The evidence suggesting that RF fields affect male fertility is weak and the existing ex vivo studies reporting positive effects have methodological problems. Cohort studies are recommended only if a study design is available that can overcome potential confounding and recall bias regarding phone use and the study has appropriate exposure assessment.*"

"*The previous SCENIHR opinion concluded that there were no adverse effects on reproduction and development from RF fields at non-thermal exposure levels. The inclusion of more recent human and animal data does not change this assessment. Therefore, it is concluded that there is strong overall weight of evidence against an effect of low level RF fields on reproduction or development."*

"De Iuliis et al, after 16 h exposure at 1800 MHz, SAR from 0.4 up to 27.5 W/kg also found an increase in ROS generation by the whole cell and mitochondria in a SAR-dependent manner, together with oxidative DNA damage (8-OHdG) and DNA fragmentation. Such effects translated to reduction in sperms motility and vitality. The authors claimed that their results clearly demonstrated that RF exposure can damage sperm function via mechanisms involving the leakage of electrons from the mitochondria and the induction of oxidative stress, but the employed SAR values are very high and not relevant to cell phone users."

This kind of reporting misquotes the statistics, and thus wrongly dismisses the significance of the De Iuliis et al results by not pointing out that a) these important adverse effects occur at as low an SAR as 1.0 W/kg which is half of the ICNIRP safety limit of 2 W/kg (the FCC/IEEE safety limit is 1.6 W/kg). The reporting also does not differentiate between very high SAR exposures of up to 27.5 W/kg and lower SARs where DNA damage is reported as well. De Iuliis et al point directly to a threat from cell phone use but the preliminary Opinion misquotes the authors, saying the levels where such effects were seen are 'not relevant to cell phone users.' It directly misrepresents both data and conclusions of this important paper.

Human sperm are are reported to be damaged by cell phone radiation at very low intensities in other studies, some reporting damage at exposure levels as low as 0.00034 – 0.07 μW/cm2 (Exhibit B). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage (Exhibit C and Chart)

Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (See Section 18 for references - Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Erogul et al, 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in Drosophila melanogaster. Gul et al (2009) reported rats exposed to stand-by level RFR (phones on but not transmitting calls) had a decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared (μW/cm2). See Exhibit C for references.

Though causal evidence of one or more mechanism(s) are not yet fully refined, it is generally accepted that oxidative stress and free radical action may be responsible for the recorded genotoxic effects of EMFs which may lead to impairments in fertility and reproduction. Free radical action and/or hydrolytic enzymes like DNAase induced by exposure to EMFs may

constitute the biochemical actions leading to adverse changes in hormones essential in males and female reproduction, DNA damage, which in turn causes damage to sperm motility, viability, and sperm morphology. Such exposures are now common in men who use and who wear wireless devices on their body, or use wireless-mode laptop computers. It may also account for damage to ovarian cells and female fertility, and miscarriage in women (ELF-EMF at 16 mG intermittent exposure). Section 18: Fertility and Reproduction, BioInitiative 2012 Report at www.bioinitiative.org

3. Evidence for Neurological and Behavioral Effects (Effects on the Nervous System)
Executive Summary, Page 14, Section 3.5.2.5

Evidence for neurological effects from a more comprehensive review of relevant papers should be incorporated into the analysis and conclusions of the Final Opinion (Exhibit D). The involvement of oxidative stress on neurological/behavioral effects of ELF EMF and RFR were dismissed as "*not firmly identified*" in the Executive Summary on page 14, but clearly the evidence supports a finding of 'possible health effect' if not 'probable effect'.

New neurological RFR studies to 2014 report effects in 68% of studies on radiofrequency radiation (or 144 of 211 studies) in 2014. This has increased from 63% in 2012 (93 of 150 studies) in 2012 (Exhibit D).

Studies of extremely-low frequency radiation are reported to cause nervous system effects in 90% of the 105 studies available in 2014.

These studies should be included in the Final Opinion. They will likely change the Preliminary Opinion that now avoids making a judgment about whether neurological effects are sufficiently established as a cause of possible health effects.

The Preliminary Opinion unnecessarily omits relevant studies on neurological effects (Exhibit D). Were they properly included, the Committee's conclusions would be different, i.e., a finding of possible health effect would have to be the clear conclusion.

There are studies on the interaction of cell phone radiation on EEG during sleep. Changes in sleep EEG have been reported by Hung et al. (2007), Regel et al. (2007), Lowden et al (2011), Schmid et al. (2012), Loughran et al. (2012), Mohammed et al. (2013), and Pelletier et al. (2012), whereas no significant effect was reported by Fritzer et al (2007), Mohler et al. (2010, 2012) and Nakatani-Enomoto et al. (2013). Loughran et al. (2012) provided an interesting conclusion in their paper: "(T)hese results confirm previous findings of mobile phone-like emissions affecting the EEG during non-REM sleep. Importantly, this low-level effect was also shown to be sensitive to individual variability. Furthermore, this indicates that "previous negative results are not strong evidence for a lack of an effect…"

Considering the effects of neurological/behavioral effects of radiofrequency radiation published since 2007, there are 30 human study papers of which 11 showed effects. The effects studied included behavioral arousal, memory effects to cognitive functions. There are 34 animal studies, of which 32 showed effects. Effects studies included motor hyperactivity to cognitive behaviors. A difference between the humans and animal studies is that most of the animal studies deal with chronic/repeated exposure, whereas the human studies are mostly acute (one time) exposure. Effects of chronic/repeated exposure studies should play more weight in considering the risk effect. It must be pointed out that neurophysiological and behavioral changes have been reported

in both animals and humans after acute (one time) exposure to RFR, and most of the EEG studies are acute exposure experiments.

Behavioral effects of ELF EMF have been further substantiated in research since 2007. These included: changes in locomotor activity (9 studies), learning and memory functions (10 studies), anxiety (5 studies); depression-like behavior (2 studies), perception (1 study), cognitive dysfunction (1 study), emotional state (1 study), sleep onset (1 study), and comb building in hornets (1 study. Since different behavioral effects have been observed in different exposure conditions, species of animals, and testing paradigms, they provide the strongest evidence that exposure to ELF EMF can affect the nervous system.

The involvement of oxidative stress on neurological/behavioral effects of ELF EMF was not carefully considered. Oxidative changes (free radicals) seens to play a critical role (Akdag et al., 2010, 2013; Akpinar et al., 2013; Cho et al., 2012; Chu et al., 2011; Ciejka et al., 2011; Deng et al., 2013; Coskun et al., 2009; Cui et al., 2012; Cui et al., 2012; Di Loreto et al., 2009; Duan et al., 2013; Falone et al., 2008; Manikonda et al., 2013; Martinez-Samano et al., 2012; Rauš Balind et al., 2014; Selaković et al., 2013; Tassel et al., 2012a, Turkozer et al., 2008). Other physiological factors, e.g., sex, age, stress, etc, that can affect the effects of ELF EMF should be considered. A paper by Falone et al. (2008) reported the brain of young rats showed an increase in anti-oxidative enzymes and defense against oxidative damage, whereas that of old rat showed a decrease. Janac et al. (2012) reported age-dependent effects of ELF EMF on locomotor activity in the Gerbils. Reyes-Guerrero et al. (2010) found that the fields affected olfactory bulb estrogen receptors in female but not in male rats. Sun et al. (2010) reported that, after in ovo (in the egg) exposure to ELF EMF, chicks showed memory deficit only when they were under stress.

Effects have been reported after exposure to low (environmental) levels of ELF EMF. For example, Ross et al (2008) showed 'perception' alternation in human subjects exposed to magnetic field at 10 nT (0.00001 mT); a study by Fournier et al (2012) on effect of brain development in the rat at 30 nT (0.00003 mT), and Stevens (2007) indicated changes in emotional states in humans exposed to 8-12 Hz magnetic field at 5 mT (0.005 mT).

Executive Summary, Page 14, Section 3.7.2.5.

A summary of the research literature on the neurological effects of ELF EMF published in 2007-2014 allows the SCENIHR Committee to survey the relevant literature more comprehensively. (In most studies, even only magnetic field was mentioned; there was no explicit statement that electric fields had been eliminated. In most ELF EMF exposure systems used in laboratory system, electric fields were also generated unless grounding was done. Thus, cells or animals were actually exposed to both magnetic and electric fields.)

- Neurotransmitters are chemicals that carry (transmit) signals from one nerve cell to another. Neurotransmitters are released from one nerve cell and react with molecules called receptors on another nerve cell. The reaction alters the activity of the second nerve cell. Activities in nerve cell could also change the properties of these receptors (mainly by changing the concentration or the affinity of the receptors to neurotransmitters). In the updated EMF literature, all the studies are on the effects of ELF EMF exposure on neurotransmitter receptors. Manikonda et al. (2007) reported effects of chronic ELF EMF exposure on NMDA receptors in the hippocampus of the rat. Salunke et al. (2013) reported that ELF EMF-induced anxiety in the rat involved NMDA receptors in the brain. There is a report on effects of magnetic field serotonin and dopamine receptors in the brain of the rat (Janac et al., 2009). Changes in subtypes of serotonin receptors 5HT(2A)

in the prefrontal cortex was reported. However, Masuda et al. (2011) reported that another type of serotonin receptor 5HT (1B) was not significantly affected after magnetic field exposure in an *in vitro* experiment. The researchers were trying to replicate two experiments carried out previously showing magnetic field exposure affected 5HT(1B) receptor. Some of the co-authors of the Musuda study were actually co-authors of one of these earlier studies. However, the 5HT(2A) receptors, particularly in the frontal cortex, are believed to be related to the psychiatric syndromes of depression in humans. Kitaoka et al. (2013) and Szemerszky et al. (2010) did report depression-like behavior in mice and rats, respectively, after chronic exposure to magnetic fields. There are two reports on dopamine receptors. Shin et al. (2007, 2011) reported an increase in D-1 dopamine receptors and activity in the striatum of the rat after magnetic field exposure. Dopamine in the striatum is involved in Parkinson's disease. Wang et al. (2008) reported that ELF magnetic fields potentiated morphine-induced decrease in D-2 dopamine receptors. The implication of these data is not readily clear. Both D-1 and D-2 dopamine receptors in the brain are involved in depression and drug addiction. There is one study on the cholinergic system. Ravera et al. (2010) reported changes in the enzyme acetylcholinesterase in cell membrane isolated from the cerebellum after magnetic field exposure. Interesting, these researchers also reported 'frequency window' effects in their experiment. Window effects, i.e., effects are observed at a certain range(s) of EMF frequency or intensity, were first reported by Ross Adey and Susan Bawin and Carl Blackman in the 1980s. A recently study by Fournier et al. (2012) reported an 'intensity window' effect of ELF magnetic field on neurodevelopment in the rat. The cholinergic systems in the brain play a major role in learning and memory functions.

• Behavioral effects of ELF EMF have been further substantiated in recent research. These included: changes in locomotor activity (Balassa et al., 2009; Dimitrijevic et al., 2014; Janac et al., 2012; Legros et al., 2012; Raus et al., 2012b; Shin et al., 2007, 2011; Todorovic et al., 2012), learning and memory functions (Che et al., 2007; Corbacio et al., 2011; Cui et al., 2012; Duan et al., 2013; Fournier et al., 2012; Fu et al., 2008; Harakawa et al., 2008; He et al., 2011; Liu et al., 2008b; Sun et al., 2010), anxiety (Balassa et al., 2009; He et al., 2011; Korpinar et al., 2012; Liu et al., 2008a; Salunke et al., 2013); depression-like behavior (Kitaoka et al., 2013; Szemerszky et al., 2011), perception (Ross et al., 2008), cognitive dysfunction (Davanipour et al., 2014), emotional state (Stevens, 2007), sleep onset (Hung et al., 2007), and comb building in hornets (Ishay et al., 2007). Since different behavioral effects have been observed in different exposure conditions, species of animals, and testing paradigms, they provide the strongest evidence that exposure to ELF EMF can affect the nervous system.

• In some of these observed neurological effects, oxidative changes (free radicals) again seemed to play a role (Akdag et al., 2010, 2013; Akpinar et al., 2013; Cho et al., 2012; Chu et al., 2011; Ciejka et al., 2011; Deng et al., 2013; Coskun et al., 2009; Cui et al., 2012; Cui et al., 2012; Di Loreto et al., 2009; Duan et al., 2013; Falone et al., 2008; Manikonda et al., 2013; Martinez-Samano et al., 2012; Rauš Balind et al., 2014; Selaković et al., 2013; Tassel et al., 2012a, Turkozer et al., 2008). Increase in free radicals causes cellular damages. Most of these effects are changes in enzymes involved in maintenance of oxidative balance in cells. A paper by Falone et al. (2008) reported an interesting finding. The researchers observed that, after magnetic field exposure, the brain of young rats showed an increase in anti-oxidative enzymes and defense against oxidative damage, whereas that of old rat showed a decrease. Thus, aging may make an individual more susceptible to the detrimental effects of ELF EMF. There are other factors that could affect an animal's response to ELF EMF. Janac et al. (2012) reported

age-dependent effects of ELF EMF on locomotor activity in the Gerbils. Reyes-Guerrero et al. (2010) found that the fields affected olfactory bulb estrogen receptors in female but not in male rats. Sun et al. (2010) reported that, after in ovo exposure to ELF EMF, chicks showed memory deficit only when they were under stress. Indeed, Lahijani et al. (2011) reported histological changes in the brain of chicks exposed to ELF EMF in ovo.

• The possible medical applications of ELF EMF should be given more attention. Several studies indicate that ELF EMF could enhance recovery of functions after nervous system damage and have protective effects against development of neurodegenerative diseases. Cuccurazzu et al. (2010) reported an ELF EMF-induced neurogenesis and repair of the nervous system after damage. Kumar et al. (2010) and Das et al. (2012) showed an enhanced restoration of functions after spinal injury in the rat. Kumar et al. (2013) further showed that ELF EMF exposure restored spinal cord injury-induced tonic pain and changes in neurotransmitter concentrations in the brain of the rat. Maestú et al. (2013) reported improvement in pain sensation in fibromyalgia patients after magnetic field stimulation. A possible beneficial effect on cerebral ischemia has been reported by Rauš Balind et al. (2014). Piacentini et al. (2008) reported a promotion of neural differentiation by ELF EMF. Kim et al. (2013) and Bai et al. (2013) reported stimulation by ELF EMF on neural differentiation of stem cells. Effects on stem cells and hippocampal neurogenesis also have been reported by Podda et al. (2013) and Leone et al. (2014). Protective effects of ELF EMF have been reported by Raus et al (2012a, b) after cerebral ischemia, Tassel et al. (2012a, b) on the development of Huntington's Disease, and Manjhi et al. (2013) on spinal cord injury induced osteoporosis. Furthermore, Cvetkovic et al. (2009) reported alteration of EEG by application of certain frequencies of magnetic fields. This may be useful in the treatment of certain neurological disorders such as sleep and psychiatric disorders. Static magnetic field has been shown by Wang et al. (2010) to act like an anti-Parkinson drug. Static magnetic field also has been shown to have anti-angiogenesis properties (Wang Z, Yang P, Xu H, Qian A, Hu L, Shang P. Inhibitory effects of a gradient static magnetic field on normal angiogenesis are reported in Bioelectromagnetics (6):446-453, 2009), which can be translated into an anticancer activity. Use of ELF EMF for cancer treatment has been extensively investigated. There is a study showing that pulsed electromagnetic fields turned on adenosine receptors in brain cancer cells that inhibit cancer growth (Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, Setti S, Cadossi R, Borea PA, Varani K. The anti-tumor effect of A_3 adenosine receptors is potentiated by pulsed electromagnetic fields in cultured neural cancer cells is reported in PLoS One 7(6):e39317, 2012). Interesting, this effect was not observed when normal brain cells were exposed to magnetic field. The waveform of the fields may play an important role in the effect produced. There are several studies on pulsed (instead of sinusoidal) magnetic fields (Aldinucci et al., 2009; Capone et al., 2009; Cook et al. 2009; Glover et al., 2009) and complex fields (Ross et al., 2008). It has been speculated that intermittent EMF or fields that have a transient nature could be more biologically potent than constant fields. The conditions and parameters of the fields that could produce either detrimental or beneficial effects need further investigation. Furthermore, it is still not clear whether acute (one time) exposure would elicit effects different from chronic/repeated exposure. In the 2007-2014 literature, there are many studies reporting effects of chronic/repeated exposure. The study by Liu et al. (2008a) indicates that duration of exposure could be an important factor.

• The majority of the studies used magnetic fields above 0.1 mT (1 gauss; the highest was 8 mT). The intensities are much higher than those in the public environment. Thus,

caution should be taken in extrapolating the high-intensity cell and animal studies to environmental human exposure situation. Exposure to magnetic fields of 0.4 mT (0.0004 mT) has been implication in an increased risk of childhood leukemia. And, the recent report by Li et al. (Li DK, Ferber JR, Odouli R, Quesenberry CP Jr. A Prospective Study of In-utero Exposure to Magnetic Fields and the Risk of Childhood Obesity. Sci Rep. 2:540, 2012) on an increased risk of obesity of humans exposed prenatally to magnetic field at 0.25 mT (0.00025 mT). There is also a report of a blood pressure lowering effect in humans with mild-to-moderate hypertension after exposure to magnetic fields at 1 μT (0.001mT) (Nishimura T, Tada H, Guo X, Murayama T, Teramukai S, Okano H, Yamada J, Mohri K, Fukushima M. A 1-μT extremely low-frequency electromagnetic field vs. sham control for mild-to-moderate hypertension: a double-blind, randomized study. Hypertens Res. 34(3):372-377, 2011.) Apparently, humans are sensitive to magnetic field at level less than 1 mT. There is a study by Ross et al (2008) showing 'perception' alteration in human subjects exposed to magnetic field at 10 nT (0.00001 mT), a study by Fournier et al (2012) on effect of brain development in the rat at 30 nT (0.00003 mT), and a study by Stevens (2007) indicating changes in emotional states in humans exposed to 8-12 Hz magnetic field at 5 mT (0.005 mT). These data do suggest magnetic fields at very low intensities could cause neurological effects in humans. In the 1990s, there were a series of more than 20 studies published by Reuven Sandyk showing that pulsed magnetic fields at pT (1 pT = 0.000000001 mT) levels could have therapeutic effects on Parkinson's disease and multiple sclerosis (see e.g., Sandyk R. Reversal of cognitive impairment in an elderly Parkinsonian patient by transcranial application of picotesla electromagnetic fields. Int J Neurosci. 91(1-2):57-68, 1997, or, search for 'Sandyk R' in the PubMed.) However, Sandyk's findings have never been independently confirmed.

- In summary, ELF EMF affects neurological functions and behavior in animals and humans. There is no definite data showing that these effects are detrimental to human health. However, since effects have been observed, it is advisable that one should limit one's exposure to EMF.

Exhibit D is a summary of the research literature on the neurological effects of ELF EMF published in 2007-2014.

4. Evidence for Genotoxicity (Genetic Damage to DNA)

There are many more publications on genotoxicity of ELF-EMF and RFR since 2007 than the SCENIHR Working Group considered.

Genetic effects (damage to DNA) from radiofrequency radiation are reported in 65% (or 74 of 114 studies) (Exhibit E).

For ELF-EMF, genetic effects are reported to occur in 83% (or 49 of 59 studies) of extremely-low frequency studies (Exhibit E).

These studies should be included in the Final Opinion. They will likely change the conclusion of the Preliminary Opinion that skirt the issue of whether genotoxicity is sufficiently established as a cause of possible health effects (Sections 3.5.2.5, and 3.11.3).

Effects of EMF on oxidative status, a change of which disturbs all physiological functions is poorly analyzed because many relevant peer-reviewed papers are missing from the assessment.

• The effects of both RF and ELF fields are very similar. This is surprising because the energies carried by these EMFs are billions of folds different. An explanation for similar genetic effects has been provided by a recent paper by Blank and Goodman (Blank M, Goodman R. DNA is a fractal antenna in electromagnetic fields. Int. J. Radiat. Biol. 87(4):409-415, 2011) in which they stated that '…the wide frequency range of interaction with EMF is the functional characteristic of a fractal antenna, and DNA appears to possess the two structural characteristics of fractal antennas, electronic conduction and self symmetry.' However, similarities in effects between ELF and RF fields have also been reported in studies of other physiological processes, e.g., neurochemical and behavioral effects (Cf. Lai, H., Carino, M.A., Horita, A. and Guy, A.W. Opioid receptor subtypes that mediate a microwave-induced decrease in central cholinergic activity in the rat. Bioelectromagnetics 13:237-246, 1992; Lai, H. and Carino, M.A.

Intracerebroventricular injections of mu and delta-opiate receptor antagonists block 60-Hz magnetic field-induced decreases in cholinergic activity in the frontal cortex and hippocampus of the rat. Bioelectromagnetics 19:433-437, 1998; Lai, H., Carino, M.A. and Ushijima, I. Acute exposure to a 60 Hz magnetic field affects rats' performance in the water maze. Bioelectromagnetics 19:117-122, 1998; Wang, B.M. and Lai, H. Acute exposure to pulsed 2450-MHz microwaves affects water maze learning in the rat. Bioelectromagnetics 21:52-56, 2000.) Thus, there is a basic interaction mechanism of biological tissues with electromagnetic fields that is independent of frequency.
Many studies have implicated the involvement of free radical processes in the genetic effects of EMF: ELF-EMF (Butdak et al., 2012; Jouni et al., 2012; Luukkonen et al., 2014; Tiwari et al.,2014); RFR (Agarwal et al., 2009; Atasoy et al., 2012; Burlaka et al., 2013; Campisi et al., 2010; De Iuliis et al., 2009; Esmekaya et al., 2011; Ferreira et al., 2006; Gajski and Garaj-Vrhovac, 2009; Garaj-Vrhovac et al., 2011; Guler et al., 2010, 2012; Kesari and Behari, 2009; Kesari et al., 2010; Khalil et al., 2012; Kumar et al., 2010; Liu et al., 2013a,b; Luukkonan et al., 2009; Tomruk et al., 2010; Tkalec et al., 2013; Wu et al., 2008; Xu et al., 2010; Yao et al., 2003). Increase in free radical activity and changes in enzymes involved in cellular oxidative processes are the most consistent effects observed in cells and animals after EMF exposure. However, they are reports indicating that EMF could induce genetic effects without the involvement of free radicals (ELF- Alcaraz et al., 2013; RFR- Ferreira et al., 2006; Furtado-Filho et al., 2013) and increase in free radical after EMF exposure did not lead to genetic effects (Frahm et al., 2006). There are at least a couple of hundred published papers on the effects of EMF exposure on cellular oxidative processes. Many biological effects of EMF can be explained by intracellular changes in oxidative status, including the genetic effects reported in this review.

• An important observation of the studies is that EMF can interact with other entities and synergistically cause genetic effects. These entities include: ELF-EMF- cisplastin (Buldak et al., 2012; El-Bialy et al., 2013), bleomycin (Cho et al., 2007), gadolinium (Cho et al., 2014); hydrogen peroxide and methyl methane sulfonate (Koyama et al., 2008), menadione (Luukkonan et al., 2011, 2014; Markkanen et al., 2008), ionizing radiation (Mairs et al., 2007; Journi et al., 2012 Yoon et al., 2014); RFR- chemical mutagens (Baohong et al., 2005), clastogens (Kim et al., 2008), x-rays (Manti et al., 2008), ultraviolet ray (Baohong et al., 2007), aphidicolin (Tiwari et al., 2008), picrotoxin (López-Martín et al., 2009), doxorubicin (Zhijian et al., 2010), and incoherent

electromagnetic noise (Wu et al., 2008; Yao et al., 2008). Most of the compounds that interact with EMF are mutagens. This is important because in real life situations, a person is usually exposed to many different environmental factors simultaneously. Synergism of these factors with EMF should be considered more seriously.

• Several long term/repeated exposure papers are included in this update: ELF-EMF (Borhani et al., 2011; Cuccurazzu et al., 2010; Erdal et al., 2007; Fedrowitz and Loscher, 2012; Mariucci et al., 2010; Panagopoulous et al., 2013; Udroiu et al., 2006), and RFR (Asasoy et al., 2012; Atli Serkeroglu et al., 2013; Burlaka et al., 2013; Chavdoula et al., 2010; Deshmukh et al., 2013; Ferreira et al., 2006; Garaj-Vrhovac et al., 2011; Guler et al., 2010, 2012; Kesari and Behari, 2009; Kesari et al., 2010; Lakshmi et al., 2010; Paulraj and Behari, 2006; Tomruk et al., 2010; Yan et al., 2008). These data are important in the understanding of the biological effects of EMF exposure in real life situation, since human environmental EMF exposure is both chronic and intermittent. Within these long-term exposure studies, there are several that investigated the effect of EMF exposure on developing animals (ELF-EMF: Borhani et al., 2011; Cuccurazzu et al., 2010; Panagopoulous et al., 2013; Udroiu et al., 2006, RFR: Burlaka et al., 2013; Ferreira et al., 2006; Guler et al., 2010, 2012; Serkeroglu et al., 2013; Tomruk et al., 2010; Zalata et al., In press). Data of effects of EMF exposure on growth and development of young animals are urgently needed. There are several studies indicating that RFR may affect reproduction, particularly with effects on sperm physiology and DNA (Agarwal et al., 2009; Atasoy et al., 2012; Avendano et al., 2012; Chavdoula et al., 2010; de Iuliis et al., 2009; Liu et al., 2013b; Panagopoulous et al., 2007). Similar effects of ELF-EMF on sperm have also been reported, e.g., Hong R, Zhang Y, Liu Y, Weng EQ. Effects of extremely low frequency electromagnetic fields on DNA of testicular cells and sperm chromatin structure in mice. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 23(6):414-417, 2005; Iorio R, Scrimaglio R, Rantucci E, Delle Monache S, Di Gaetano A, Finetti N, Francavilla F, Santucci R, Tettamanti E, Colonna R. A preliminary study of oscillating electromagnetic field effects on human spermatozoon motility. Bioelectromagnetics. 28(1):72-75, 2007; Iorio R, Delle Monache S, Bennato F, Di Bartolomeo C, Scrimaglio R, Cinque B, Colonna RC. Involvement of mitochondrial activity in mediating ELF-EMF stimulatory effect on human sperm motility. Bioelectromagnetics. 32(1):15-27, 2011.

• Another area that needs more research is the biological effects of low-intensity exposure. This is particularly true for ELF-EMF, since intensities of ELF-EMF in the environment are in microtesla (mT) levels. There are many studies on biological effects of low-intensity RFR (see Table 1 in Levitt, B.B. and Lai, H. Biological effects from exposure to electromagnetic radiation emitted by cell tower base stations and other antenna arrays. Environ. Rev. 18:369-395, 2010.) However, most cell and animal studies in ELF-EMF used fields in the millitesla (mT) level. Exceptions are the study of Sarimov et al. (2011) listed below in the reference section and the study of de Bruyn and de Jager (2010) (**de Bruyn L** and **de Jager L**. Effect of long-term exposure to a randomly varied 50 Hz power frequency **magnetic field** on the fertility of the mouse. **Electromag. Biol. Med.** 29(1-2):52-61, 2010).

• Two other important findings of these recent studies are that the effects of EMF are shown to be waveform specific and cell-type specific. Regarding waveform specificity, Campisi et al. (2010) reported increases in free radical activity and DNA fragmentation in brain cells after acute exposure to a 50-Hz amplitude-modulated 900-MHz RFR, whereas

a continuous-wave 9000-MHz field produced no effect. Franzellitti et al. (2010) showed increased DNA strand breaks in trophoblasts after exposure to a 217-Hz modulated 1.8 GHz-RFR, but a continuous-wave field of the same carrier frequency was without effect. Tkalec et al (2013) reported that AM-modulated (1 KHz sinusoidal) 900-MHz RFR is more potent than non-modulated field in causing DNA damage in coelomocytes of exposed earthworms. Luukkonen et al. (2009) reported a continuous-wave 872-MHz RFR increased chemically-induced DNA strand breaks and free radicals in human neuroblastoma cells, whereas a GSM-modulated 872-MHz field had no significant effect. Zhang et al. (2008) found that gene expression in rat neurons is more sensitive to intermittent than continuous exposure to a 1.8 GHz-RFR. López-Martín et al. (2009) found that GSM and unmodulated RFR caused different effects on c-Fos gene expression in the rat brain. Regarding cell-type specificity, Nylund and Leszczynski (2006) and Remondini et al. (2006) reported different patterns of gene expression in different types of cells after exposure to RFR. Zhao et al. (2007) found than neurons are more sensitive to a 1.9 GHz cell phone radiation than astrocytes. Schwarz et al. (2008) reported DNA strand breaks and micronucleus formation in human fibroblasts, but not in lymphocytes, after exposure to a 1950-MHz UMTS field. Furthermore, Xu et al (2013) found DNA damages in some cell types and not in others after exposure to 1800-MHz RFR. Valbonesi et at. (2014) reported that HSP70 expression and MAPK signaling pathways in PC12 cells were affected by GSM-217 Hz signal and not by CW or GSM-talk signals. In ELF-EM research, Giorgi et al. (2011) found that DNA transposition in E. coli was *decreased* after exposure to a sinusoidal magnetic field and *increased* after exposure to a pulsed magnetic field. Kim et al. (2012) described DNA strand breaks in human fibroblasts after exposure to ELF magnetic field. They found that the pattern of changes depended on the eddy current and Lorentz force in the field. Nahab et al. (2007) reported that a square-continuous ELF magnetic field was more effective than sinusoidal-continuous or pulsed field in inducing sister chromatid exchange in human lymphocytes. These findings underscore the complexity of interaction of EMF with biological tissues and may partially explain why effects were observed in some studies and not others. It is essential to understand why and how certain wave-characteristics of an EMF are more effective than other characteristics in causing biological effects, and why certain types of cells are more susceptible to the effect of EMF? That there are different biological effects elicited by different EMF wave characteristics is critical proof for the existence of nonthermal effects.

• Many biological/health effects have been reported in cells and animals after exposure to EMFs in both the ELF and RF ranges. (Sixty-five percent of the RFR papers and 82% of the ELF-EMF papers in the publication list below reported effects.) It is highly dishonest for a scientist to summarily deny the existence of biological effects of EMF. A biological effect of EMF can be detrimental to health, but can also be turned into a beneficial means for the treatment of human diseases. Denying any effects hampers the development of electromagnetic treatments for diseases. Examples of possible clinical uses of EMF are: Alzheimer's disease (Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, Wang L, Zhang G, Sava V, Tan J, Cao C. Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimers Dis. 19(1):191-210, 2010); Parkinson's disease (Wang Z, Che PL, Du J, Ha B, Yarema KJ. Static magnetic field exposure reproduces cellular effects of the Parkinson's disease drug candidate ZM241385. PLoS One. 5(11):e13883, 2010); bone regeneration (Lee HM, Kwon UH, Kim H, Kim HJ, Kim B, Park JO, Moon ES, Moon SH. Pulsed electromagnetic field stimulates cellular proliferation in human intervertebral disc cells. Yonsei Med. J. 51(6):954-959, 2010);

cancer treatment (Costa FP, de Oliveira AC, Meirelles R, Machado MC, Zanesco T, Surjan R, Chammas MC, de Souza Rocha M, Morgan D, Cantor A, Zimmerman J, Brezovich I, Kuster N, Barbault A, Pasche B. Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. Br. J. Cancer. 105(5):640-648, 2011), and tissue regeneration (Gaetani R, Ledda M, Barile L, Chimenti I, De Carlo F, Forte E, Ionta V, Giuliani L, D'Emilia E, Frati G, Miraldi F, Pozzi D, Messina E, Grimaldi S, Giacomello A, Lisi A. Differentiation of human adult cardiac stem cells exposed to extremely low-frequency electromagnetic fields. Cardiovasc. Res. 82(3):411-420, 2009).

- It must be pointed out that, consistent with previous research, not very much of the cellular and animal genetic research data directly indicate that EMF (both RF and ELF EMF) is a carcinogen. However, the data show that EMF can possibly alter genetic functions and thus it is advisable that one should limit one's exposure to EMF.

The genotoxicity assessment flaws lead to dismissal of the fertility implications of oxidative damage on sperm. Both genotoxicity (DNA damage to genes) in general and the consequence that genotoxicity from mechanisms related to free-radicals (oxidative damage to DNA) to sperm from cell phone radiation (RFR) mean that two promising lines of scientific evidence in SCENIHR's Opinion are compromised.

5. Evidence for Fetal and Neonatal Effects

Effects on the developing fetus from in-utero exposure to cell phone radiation have been observed in both human and animal studies since 2006. Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy). Sources include exposure to whole-body RFR from base stations and WI-FI, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant mother, and greater susceptibility to leukemia and asthma in the child where there have been maternal exposures to ELF-EMF. Divan et al (2008) found that children born to mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al, 2008). Aldad et al (2012) showed that cell phone radiation significantly altered fetal brain development and produced ADHD-like behavior in the offspring of pregnant mice. Exposed mice had a dose-dependent impaired glutamatergic synaptic transmission onto Layer V pyramidal neurons of the prefrontal cortex. The authors conclude the behavioral changes were the result of altered neuronal developmental programming in utero. Offspring mice were hyperactive and had impaired memory function and behavior problems, much like the human children in Divan et al (2008). Fetal (in-utero) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school.

See Herbert and Sage, Section 19: Fetal and Neonatal Effects of EMF and Section 20: Findings in Autism (ASC) Consistent with Electromagnetic Fields (EMF) and Radiofrequency Radiation (RFR) Exposure in the BioInitiative 2012 Report at www.bioinitiative.org for references and as published in Pathophysiology, Volume 20, Issue 3.

[Herbert M, Sage C (2013) Autism and EMF/RFR? Plausibility of a Pathophysiological Link-Part I. Pathophysiology Volume 20, Issue 3, 191-209, June 2013]

Fragopoulou et al (2012) reports that brain astrocyte development followed by proteomic studies is adversely affected by DECT (cordless phone radiation) and mobile phone radiation (Fragopoulou and Margaritis, Section 5: EMF Transcriptomics and Proteomics Research 2007-2012, BioInitiative 2012 Report at www.bioinitiative.org)

Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted. A precautionary approach may provide the frame for decision-making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

(Bellieni and Pinto, 2012 – Section 19, Fetal and Neonatal Effects, BioInitiative 2012 Report at www.bioinitiative.org)

6. Evidence for Heat Shock Protein Effects

3.5.1.4 Conclusions on neoplastic diseases from RF Exposure and 3.7.1.4 Conclusions on neoplastic diseases from ELF Exposure

SCENIHR emphasizes epidemiology studies of health effects such as cancers that generally affect a relatively small percentage of those exposed and take many years to develop. It does not include studies of the natural protective mechanisms in virtually all cells that protect against the immediate changes that lead to the long term health effects. Living cells synthesize stress proteins when exposed to potentially harmful stimuli that include electromagnetic fields (EMF) across a wide range of non-ionizing frequencies. Stress protein synthesis and oxidative damage to DNA stimulated by EMF are considered likely to lead to cancer and other diseases. Like the DNA damage, these effects occur at exposures well below levels that are now considered safe. Stress proteins can also be protective when induced prior to surgery, as in reducing oxidative damage following heart bypass surgery. Given the goals of SCENIHR, analysis of cell biology studies is essential. An EMF safety standard, based on the far more sensitive natural biological response, would not only be more realistic than the thermal criterion, but more protective as well.

7. Evidence for Impacts of Physical and Biological Variables on Study Results

The main flaw of the preliminary Opinion is in neglecting the mechanistic data on non-thermal (NT) effects of microwaves (MW). As reported in multiple studies in Exhibit F , these effects depend on variety of biological and physical parameters including polarization, frequency and environmental EMF. *In vitro* and *in vivo* negative studies have covered a negligible minority of real cell phone signals, so the studies cannot provide evidence that the vast majority of other real cell phone signals are safe. Thus, the results of negative studies profiled in the Opinion cannot be extrapolated to the issue of the safety or lack of safety of cell phones in use today. Well conducted positive studies cannot be negated by poorly conducted negative studies. The claimed of "inconsistency" in *in vitro* and *in vivo* data and "conflicting results" has at least one simple explanation. The studies were performed under different conditions. Thus, results cannot be directly compared. The SCENIHR report on inconsistency and conflicting results may rather reflect the level of superficial analysis of these studies. Another fundamental flaw is in

neglecting many studies showing dependence of the NT MW effects on exposure duration or dose (defined in radiation physics as multiplication of SAR on exposure duration), see for review (Belyaev 2010 in Exhibit F). In addition to laboratory studies, when brain cancer risk was epidemiologically examined as a function of dose received in different time windows before diagnosis, increasing trend was observed with increasing RF dose (for exposures 7 years or more in the past) (Cardis, Armstrong et al. 2011). This study provided straightforward evidence for one of most important Bradford Hill criteria which is dependence on dose.

Good epidemiological evidence for brain tumors from many other studies has been excluded (see Section 1 and Exhibits B and F). The SCENIHR preliminary Opinion is heavily biased in favor of the Danish subscriber cohort study of mobile phone subscribers. This study has major flaws that have been substantially documented since it's publication. It is not informative even according to the requirement of SCENIHR which says *"(T)he minimum requirement for exposure assessment for an epidemiological study to be informative is to include reasonably accurate individual exposure characterization over a relevant period of time capturing all major sources of exposure for the pertinent part of the body*" (page 10).

ELF Carcinogenicity: Page 131 of the SCENIHR provides misleading and flawed conclusions on ELF and neoplastic diseases. As a matter of fact, the increased risk of childhood leukemia with daily average exposure above 0.3 to 0.4 μT is as strong as never before. All available studies from Europe, America and Asia consistently show such correlation. It has been further supported by recent meta-analysis by Zhao et al. (Zhao, Liu et al. 2014). The statement of lack of mechanisms for ELF effects is wrong. Recent studies provided more evidence for such mechanisms even if they have not been comprehensively studied, see below. Considerations of ELF carcinogenicity in the SCENIHR report did not use standard methods such as the Bradford Hill criteria which do not require complete knowledge of mechanisms in case when epidemiological evidence is overwhelming as in case of childhood leukemia (Zhao, Liu et al. 2014).

ELF affects cell proliferation: In line with many previous studies, new studies unmentioned in the SCENIHR report provide further evidence that ELF can affect cell proliferation under specific conditions of exposure (Segatore, Setacci et al. 2012; Bae, Do et al. 2013; Jadidi, Safari et al. 2013). Bai et al. investigated ELF effects on proliferation of epidermal stem cells (ESC) (Bai, Zhang et al. 2012). See additional comments in Exhibit F.

ELF induced ROS and genomic instability: Induction ROS and is generally considered as a candidate mechanism for carcinogenicity for EMF (IARC 2013). Several recent studies unmentioned in the SCENIHR report provided further evidence for this mechanism in case of ELF exposure (Duan, Wang et al. 2013; Khaki, Khaki et al. 2013)**.** See additional comments in Exhibit F.

Mechanisms for effects of weak ELF: While all mechanisms of ELF effects are not known with certainty, new important data emerged about these mechanisms which were neglected by the SCENIHR report. For ELF fields, these mechanisms involve magnetoreception of fields in the μT-range which is observed in many studied animals including lizards (Nishimura, Okano et al. 2010). It should be stressed that the lack of precise knowledge for this mechanism (radical pairs and magnetite are mainly considered) does not preclude general acceptance of these phenomena. In analogy, and in accordance to the Bradford Hill criteria, lack of precise knowledge on mechanism for leukemogenesis of weak ELF ≥0.3 μT, which was consistently shown in children

in multiple studies (Zhao, Liu et al. 2014) should not preclude classification of μT-range ELF as an IARC carcinogen group 1. The SCENIHR report completely neglects variety of mechanisms based on ELF effects on ions (Halgamuge and Abeyrathne 2011; Foletti, Grimaldi et al. 2013). See additional comments in Exhibit F.

ELF section omits significant number of ELF positive studies: Except for aforementioned studies, ELF section of the SCENIHR report omits significant number of other ELF positive studies. These include but not limited to (Mariucci, Villarini et al. 2010; Nishimura, Okano et al. 2010; Ravera, Bianco et al. 2010; Severini, Bosco et al. 2010; Ulku, Akdag et al. 2011; Bai, Zhang et al. 2012; Ince, Akdag et al. 2012; Martirosyan 2012; Portelli, Madapatha et al. 2012; Balassa, Varro et al. 2013; Gang, Parker et al. 2013; Iorio, Bennato et al. 2013; Kang, Hong et al. 2013; Khaki, Khaki et al. 2013; Li, Zhang et al. 2013; Martirosyan, Baghdasaryan et al. 2013; Panagopoulos, Karabarbounis et al. 2013; Shams Lahijani, Tehrani et al. 2013; Villarini, Ambrosini et al. 2013) See additional comments in Exhibit F.

8. Literature Identified but Not Cited (pages 217-219).

Entire bodies of relevant evidence are ignored, or key papers are not quoted (but they appear in the reference list as "literature identified but not cited"). This is not explained, and functionally disables scientific review of highly relevant emerging scientific studies. An explanation is needed. Further, revisions should be made to include many or most of them in the Final Opinion to include these and other relevant papers. These papers are included as 'literature identified but not cited' – as examples of the problem.

Blood-Brain Barrier Evidence

Nittby H, Brun A, Strömblad S, Moghadam MK, Sun W, Malmgren L, Eberhardt J, Persson BR, Salford LG (2011). Nonthermal GSM RF and ELF EMFELF MF effects upon rat BBB permeability. Environmentalist, 31(2), 140-8

Heat Shock Protein (Stress Protein) Evidence

Calabrò E, Condello S, Currò M, Ferlazzo N, Caccamo D, Magazù S, Ientile R. Modulation of heat shock protein response in SH-SY5Y by mobile phone microwaves. World J Biol Chem. 3 (2):34-40, 2012. (3.5)

Perez FP, Zhou X, Morisaki J, Jurivich D. Electromagnetic field therapy delays cellular senescence and death by enhancement of the heat shock response. Exp Gerontol. 2008 Apr;43(4):307-16. Epub 2008 Jan 29. (3.5 & 3.10)

Two other highly relevant papers on stress proteins that were ignored and should be incorporated. They are:

Blank M, Goodman R (2009) Electromagnetic Fields Stress Living Cells. Pathophysiology 16:71-78.

Blank M (2012) Evidence for Stress Response (Stress Proteins). In BioInitiative Report (2012) A Scientific Perspective on Health Risk of Electromagnetic Fields. Section 7, pp. 1-39. Published Online December 31, 2012 http://www.bioinitiative.org/report/index.htm

9. Mitochondrial Function and Disruptions in Electrophysiology

None of the sections adequately address the literature on mitochondrial function and ELF-EMF and RFR. The studies in Table 7 are largely negative studies, and do not begin to address the central questions. This section needs to be revised to more comprehensively document existing literature as shown in Exhibit G.

Mitochondria are broadly vulnerable, in part because the integrity of their membranes is vital to their optimal functioning – including channels and electrical gradients, and their membranes can be damaged by free radicals which can be generated in myriad ways including ELF-EMF and RFR exposure at environmental levels. Moreover, just about every step in their metabolic pathways can be targeted by environmental agents, including toxicants and drugs, as well as mutations.

Mitochondria are commonly discussed in terms of the biochemical pathways and cascades of events by which they metabolize glucose and generate energy. But in parallel with this level of function there also appears to be a dimension of electromagnetic radiation that is part of the activity of these organelles. For example, electromagnetic radiation can be propagated through the mitochondrial reticulum, which along with the mitochondria has a higher refractive index than the surrounding cell and can serve to propagate electromagnetic radiation within the network (Exhibit G). These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by ELF-EMF and RFR (i.e. a possible health effect that should be documented in the Final Opinion).

Other types of mitochondrial damage have been reported in at least some of the studies that have examined the impacts of EMF/RFR upon mitochondria. These include reduced or absent mitochondrial crista, mitochondrial DNA damage, swelling and crystallization, alterations and decreases in various lipids suggesting an increase in their use in cellular energetics, damage to mitochondrial DNA, and altered mobility and lipid peroxidation after exposures. Also noted has been enhancement of brain mitochondrial function in Alzheimer's transgenic mice and normal mice. The existence of positive as well as negative effects gives an indication of the high context dependence of exposure impacts, including physical factors such as frequency, duration, and tissue characteristics (Exhibit G).

Secondary mitochondrial dysfunction (i.e. environmentally triggered rather than rooted directly in genetic mutations) could result from EMF/RFR to damage channels, membranes and mitochondria themselves as well as from toxicant exposures and immune challenges. In a meta-analysis of studies of children with mitochondrial disorder and autism, the spectrum of severity varied, and 79% of the cases were identified by laboratory findings without associated genetic abnormalities.

Electrophysiology: None of the sections adequately address the literature on changes in electrophysiology with exposure to ELF-EMF and RFR. This is a major area of importance and many papers are available for review. This section needs to be revised to more comprehensively document existing literature, especially in the context of blood-brain barrier changes and the propensity for seizures with disrupted electrophysiology (Exhibit G).

Nervous system electrophysiology when disrupted by ELF-EMF and RFR can produce alterations in molecular, cellular and systems physiological function. It occurs in the brain as well as in the body, and impacts the transduction into the electrical signaling activities of the brain and nervous

system. If the cells responsible for generating synapses and oscillatory signaling are laboring under cellular and oxidative stress, lipid peroxidation, impaired calcium and other signaling system abnormalities, then mitochondrial metabolism will fall short, all the more so because of the challenges from the immune system which in turn can be triggered to a major extent by environment. How well will synaptic signals be generated? How well will immune-activated and thereby distracted glial cells be able to modulate synaptic and network activity? Microglial activation can impact excitatory neurotransmission mediated by astrocytes. Cortical innate immune response increases local neuronal excitability and can lead to seizures. Inflammation can play an important role in epilepsy.

Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma which can trigger a vicious circle of tissue damage from albumin and greater irritability, as discussed above. Evidence suggests that if the blood-brain barrier (BBB) is already disrupted, there will be greater sensitivity to EMF/RFR exposure than if the BBB were intact suggesting that such exposures can further exacerbate vicious circles already underway. The combination of pathophysiological and electrophysiological vulnerabilities has been explored in relation to the impact of EMF/RFR on people with epilepsy. EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling. In a rat model the combination of picrotoxin and microwave exposure at mobile phone-like intensities led to a progressive increase in neuronal activation and glial reactivity, with regional variability in the fall-off of these responses three days after picrotoxin treatment, suggesting a potential for interaction between a hyperexcitable brain and EMF/RFR exposure.

One critical issue here is nonlinearity and context and parameter sensitivity of impact. In one study, rat brain slices exposed to EMF/RFR showed reduced synaptic activity and diminution of amplitude of evoked potentials, while whole body exposure to rats led to synaptic facilitation and increased seizure susceptibility in the subsequent analysis of neocortical slices. Another study unexpectedly identified enhanced rat pup post-seizure mortality after perinatal exposure to a specific frequency and intensity of exposure, and concluded that apparently innocuous exposures during early development might lead to vulnerability to stimuli presented later in development.

10. ELF Studies Support a Finding of “Probable’ or ‘Known’ Carcinogen

Overall, the ELF MF epidemiological evidence points consistently to an increased risk for childhood leukemia. In such circumstances, considering that no other interpretation (chance, bias, or confounding) could be substantiated in the past decade, the association became more credible and even in the absence of a mechanistic interpretation ELF MF should be upgraded to a 2A or even a group 1 carcinogen.

Many epidemiological studies of ELF MF and childhood leukemia were of high quality and there are no shortcomings that may prevent a causal interpretation. The WHO IARC panel was of the opinion that the studies allowed a causal interpretation; otherwise no classification into group 2B would have been possible. Only bias and confounding could not be ruled out with sufficient scientific certainty. This assessment was also supported by the lack of consistent support by *in vitro* and animal evidence.

3.7. Health effects from ELF fields (Page 123)

3.7.1. Neoplastic diseases

3.7.1.1. Epidemiological studies

Page 123, lines 24-31:

In summarizing the previous SCENIHR statement that endorsed the IARC classification of ELF magnetic fields as possibly carcinogenic to humans "due to consistently observed increased childhood leukemia risk in epidemiological studies" SCENIHR claimed that shortcomings in these studies prevented a causal interpretation.

In fact, the IARC panel was of the opinion that the studies allowed a causal interpretation; otherwise no classification into group 2B would have been possible. Only bias and confounding could not be ruled out with sufficient scientific certainty. This assessment was also supported by the lack of consistent support by *in vitro* and animal evidence.

Many epidemiological studies of ELF MF and childhood leukemia were of high quality and there are no shortcomings that may prevent a causal interpretation. Of course, the retrospective nature of most studies and the inevitable misclassification if measurements are done years after the assumed initiation of the disease introduce problems of interpretation. Considering the potential sources of bias IARC noted that although selection bias could have led to higher risk estimates, not the whole effect can be attributed to bias. This is corroborated by the fact that studies that relied on distance from power lines or wire-codes only and did not contact participants found the same effects. Misclassification bias, on the other hand, if non-differential would lead to reduced risk estimates. The same is true for the most likely scenarios of differential misclassification.

Overall, the epidemiological evidence points consistently to an increased risk. In such circumstances, considering that no other interpretation (chance, bias, or confounding) could be substantiated in the past decade, the association became more credible and even in the absence of a mechanistic interpretation ELF MF should be upgraded to a 2A or even a group 1 carcinogen.

In a recent study of distance from power lines and childhood cancer in Britain covering the period from 1962 through 2008 (Bunch et al. 2014) elevated childhood leukemia risks were reported for distances below 200 or 600 m from high-voltage power lines (400/275 kV) from the 1960s to the 1980s but no significant increases in more recent years. Authors interpreted this result as more likely due to changing population characteristics among those living near power lines than to physical factors. Indeed, the reported data speak for a change in population distribution around power lines. This study raises important questions about the importance of stability of residences for epidemiological studies of localized exposures, but overall speaks in favor of a relationship between ELF MF and childhood leukemia.

Page124-125:

SCENIHR mentioned in their previous report (2009) two studies that addressed the issue of survival from childhood leukemia and exposure to ELF MF. These studies reported poorer survival at increased levels of exposure (above 0.2/0.3 μT). In 2012 Schüz et al. reported results of a pooled study including data from 6 countries. This pooled analysis reported somewhat increased hazard ratios at moderately increased average exposure levels up to 0.3 μT but no increased hazard ratios above 0.3 μT. This study has been mentioned in the new SCENIHR report but without further discussion of its implications. Although the study included more than 3000 cases the small number of children at elevated exposure levels and the lack of follow-up data on post diagnostic exposure for most of the cases prohibit far reaching conclusions.

Page 126-131:

SCENIHR provides a brief overview of *in vitro* and *in vivo* animal studies of ELF MF exposure and endpoints relevant for the issue of potential mechanisms of a relationship between ELF-MF and neoplastic diseases. While the presentation encompasses all publications of relevance since the last report it again lacks a discussion of the difficulties of such studies and the very small likelihood to detect an effect of exposure due to the lack of a profound biophysical mechanism as a starting point.

In conclusion, the preliminary opinion of SCENIHR concerning ELF MF covers the relevant literature and no essential omission has been detected. However, it is recommended to not separate the findings from previous reports but to assess the evidence as a whole. Furthermore, it appears that SCENIHR does not sufficiently challenge the validity especially of studies that did not find an effect of exposure.

Contributed by Prof. Michael Kundi, PhD med habil Institute of Environmental Health, Medical University of Vienna, Vienna, Austria

11. RFR Studies Support a Finding of 'Probable' or 'Known' Human Carcinogen

A recent publication by Hardell and Carlberg reports that "(*F)urther research has thus strengthened the evidence in support of an increased risk of malignant brain tumours and acoustic neuroma associated with use of mobile phones. Based on the latest findings and using the so called Hill viewpoints from the 1960's exposure to RF-EMF from mobile phones may now be classified as a human cancer causing agent, Group 1, according to the definitions used by IARC*."

Hardell L, Carlberg M. Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones. *Rev Environ Health* 2013;38:97-106. doi: 10.1515/reveh-2013-0006**.**

There is credible scientific evidence that RF exposures cause changes in cell membrane function, metabolism and cellular signal communication, as well as activation of proto-oncogenes and triggering of the production of stress proteins at exposure levels thousands of times below current regulatory limits. There is also generation of reactive oxygen species, which cause single- and double-strand DNA damage, chromosomal aberrations and nerve cell death. A number of different effects on the central nervous system have also been documented, including activation of the endogenous opioid systems, changes in brain function including memory loss, slowed learning, motor dysfunction and performance impairment in children, and increased frequency of headaches, fatigue and sleep disorders. Melatonin secretion is reduced, resulting in altered circadian rhythms and disruption of several physiological functions. See Chapters 1, 5–12 of the 2007 BioInitiative Report [1], [2-6] and Chapters 1, 5-24 of the 2012 BioInitiative Report [7]. These effects can reasonably be presumed to result in adverse health effects and disease with chronic and uncontrolled exposures, and children may be particularly vulnerable [1,19] . The young are also largely unable to remove themselves from such environments. Second-hand non-ionizing radiation, like second-hand smoke may be considered a public health concern based on the evidence at hand.

Exposure to electromagnetic fields (both extremely low-frequency ELF-EMF from power frequency sources like power lines and appliances; and radiofrequency radiation or RFR) has

been linked to a variety of adverse health outcomes that may have significant public health consequences. The most serious health endpoints that have been reported to be associated with extremely low frequency (ELF) and/or radiofrequency radiation (RFR) include childhood and adult leukemia, childhood and adult brain tumors, and increased risk of the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS). In addition, there are reports of increased risk of breast cancer in both men and women, genotoxic effects (DNA damage, chromatin condensation, micronucleation, impaired repair of DNA damage in human stem cells), pathological leakage of the blood–brain barrier, altered immune function including increased allergic and inflammatory responses, miscarriage and some cardiovascular effects. Insomnia (sleep disruption) is reported in studies of people living in very low-intensity RF environments with WI-FI and cell tower-level exposures. Short-term effects on cognition, memory and learning, behavior, reaction time, attention and concentration, and altered brainwave activity (altered EEG) are also reported in the scientific literature. Biophysical mechanisms that may account for such effects can be found in various articles and reviews. [2-7]

The BioInitiative Working Group concluded in 2007 that existing public safety limits were inadequate to protect public health, and agreed that new, biologically-based public safety limits were needed more than five years ago. The 2007 BioInitiative Report was been prepared by more than a dozen world-recognized experts in science and public health policy; and outside reviewers also contributed valuable content and perspective.

From a public health standpoint, experts reasoned that it was not in the public interest to wait. In 2007, the evidence at hand coupled with the enormous populations placed at possible risk was argued as sufficient to warrant strong precautionary measures for RFR, and lowered safety limits for ELF-EMF. The ELF recommendations were biologically-based and reflected the ELF levels consistently associated with increased risk of childhood cancer, and further incorporated a safety factor that is proportionate to others used in similar circumstances. The public health cost of doing nothing was judged to be unacceptable in 2007.

12. Plausible Biological Mechanisms are Known

Oxidative stress through the action of free radical damage to DNA is a plausible biological mechanism for cancer and diseases that involve damage from ELF to the central nervous system.

Plausible biological mechanisms are already identified that can reasonably account for most biological effects reported for exposure to RF and ELF at low-intensity levels (oxidative stress and DNA damage from free radicals leading to genotoxicity; molecular mechanisms at very low energies are plausible links to disease, e.g., effect on electron transfer rates linked to oxidative damage, DNA activation linked to abnormal biosynthesis and mutation). It is also important to remember that traditional public health and epidemiological determinations do not require a proven mechanism before inferring a causal link between EMFs exposure and disease. Many times, proof of mechanism is not known before wise public health responses are implemented.

"Obviously, melatonin's ability to protect DNA from oxidative damage has implications for many types of cancer, including leukemia, considering that DNA damage due to free radicals is believed to be the initial oncostatic event in a majority of human cancers [Cerutti et al., 1994]. In addition to cancer, free radical damage to the central nervous system is a significant component of a variety of neurodegenerative diseases of the aged including Alzheimer's disease and Parkinsonism. In experimental animal models of both of these conditions, melatonin has proven highly effective in forestalling their onset, and reducing their severity." [9]

The De Iuliis et al study which is quoted by the SCENIHR committee with respect to both genotoxicity and oxidative stress, and to sperm motility damage discusses that oxidative damage is a plausible mechanism for these effects.

"Oxidative stress has been known for some time to limit the fertilizing potential of human spermatozoa through the induction of peroxidative damage to the sperm plasma membrane [13,20]. Oxidative stress is also known to be associated with DNA damage in human spermatozoa [21]. Furthermore, the source of the free radicals responsible for generating such stress appears to be the mitochondria [15]. However, the factors responsible for inducing the mitochondria to leak electrons and propagate the production of ROS have not been elucidated. The research described in this article suggests that one of the key environmental factors involved in the stimulation of sperm mitochondria to produce high levels of ROS, might be excess exposure to RF-EMR from sources such as mobile phones."

See also Exhibit C: Reference List for Important Fertility and Reproduction Papers

13. Consistent Failure to Identify the Potential for Health Effects (Opinion-wide)

The evaluative language quoted below indicates the disparity between what was asked of the authors (to identify Possible Effects of EMF) and what they eventually chose to use as a basis for their analysis process that no change in the ICNIRP standards is warranted at this time (see Exhibit A).

> SIXTEEN (16) instances of "no causal evidence" or "prevents a causal interpretation" or "is not causally linked" or "not informative for causal linkage".
>
> THREE (3) instances of "does not provide convincing evidence".
>
> THREE (3) instances of "not definitive".
>
> SEVEN (7) instances of "do not unequivocally indicate".

These criteria are inconsistent with a review that is titled "Possible Effects". Further, the approach in judging the emerging evidence is inconsistent with the charter of the Scientific Committee* to give advice needed for "*consumer safety, public health and the environment on new or emerging problems.*" Some statements acknowledge important new evidence of effect; yet then shift the burden of proof to a higher level requiring that adverse health effect, a known mechanism, a causal level of evidence be conclusively demonstrated, or physical evidence of harm be demonstrated. There is nothing in the report that says the authors were directed to provide proof of effect (or consistent indications, or consistent demonstration of effect; or consistent support for, or certainty of effects) at levels below ICNIRP limits. With the same flawed approach in drawing conclusions from emerging science as demonstrated by the SCENIHR, hardly any environmental or occupational condition would be qualified as an emerging or newly identified health risk*.

*Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention

to the new or emerging problems which may pose an actual or potential threat. They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the **Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)** and are made up of external experts.

Preparation of this review has been completed with generous donations of the time and resources of authors of the BioInitiative Working Group.

Qualifications of the BioInitiative 2012 Working Group

The 2012 BioInitiative Report was prepared by 29 authors from ten countries, ten holding medical degrees (MDs), 21 PhDs, and three MsC, MA or MPHs. Among the authors are three former Presidents of the Bioelectromagnetics Society and five full members of BEMS. One distinguished author is the Chair of the Russian National Committee on Non-Ionizing Radiation. Three were members of the 2011 IARC Working Group that established RFR as a Group 2B Possible Human Carcinogen (Hardell, Belyaev and Blackman). Another was until recently a Senior Advisor on Science, Policy, Emerging Issues, Integrated Environmental Assessment to the European Environmental Agency. Full titles and affiliations of authors is in Section 25 of the BioInitiative Report at www.bioinitiative.org. See specific conclusions and findings of the BioInitiative 2012 Report at www.bioinitiative.org. It is incorporated by reference in this comment.

In twenty-four technical chapters, the BioInitiative Working Group authors discuss the content and implications of about 1800 new studies since 2007. Overall, these new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9); carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on the fetus, neonate and offspring (Section 18 and 19); effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18); and findings in autism spectrum disorders consistent with EMF/RFR exposure effects. Global precautionary actions that have been taken in countries around the world, and recommended by medical and research experts are documented in Section 22. Use of the Precautionary Principal and it's relevance are presented in Section 23. Key scientific evidence and public health policy recommendations are in Section 24.

Respectfully submitted on behalf of the BioInitiative Working Group by:

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