

Exhibit F: An Update on Physical and Biological Variables, Cancer and Safety Standards by Igor Belyaev, Dr.Sc., Cancer Research Institute Slovak Academy of Sciences, Slovak Republic

This review is divided into comments on two separate sections, one for extremely-low frequency (ELF) and the other for radiofrequency (RFR) studies. Comments are presented to address deficiencies in the Preliminary Opinion on EMF issued by the SCENIHR Committee. The comments are relevant to sections of the BioInitiative Working Group letter including brain tumors, oxidative damage, genomic instability, mitochondrial damage, carcinogenic classifications, biological plausibility and methodological deficiencies.

Comments on ELF Sections

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).

Similar to effects of MW, the ELF effects depend on variety of parameters that should be taken into account and have not been considered by the SCENIHR report when comparing data from different studies.

Baldi et al analyzed the relationship between residential and occupational exposure to electromagnetic field and brain tumors in adults (Baldi, Coureau et al. 2010). A case-control study was carried out in southwestern France between May 1999 and April 2001. A total of 221 central nervous system tumors (105 gliomas, 67 meningiomas, 33 neurinomas and 16 others) and 442 individually age- and sex-matched controls selected from general population were included. Electromagnetic field exposure to ELF and radiofrequency separately was assessed in occupational settings through expert judgment based on complete job calendar, and at home by assessing the distance to power lines. Confounders such as education, use of home pesticide, residency in a rural area and occupational exposure to chemicals were taken into account. Separate analyses were performed for gliomas, meningiomas and acoustic neurinomas. A nonsignificant increase in risk was found for occupational exposure to electromagnetic fields [odds ratio (OR = 1.52, 0.92-2.51)]. This increase became significant for meningiomas, especially when considering ELF separately [OR = 3.02; 95 percent confidence interval (95% CI) = 1.10-8.25]. The risk of meningioma was also higher in subjects living in the vicinity of power lines (<100 m), even if not significant (OR = 2.99, 95% CI 0.86-10.40). These data suggest that occupational or residential exposure to ELF may play a role in the occurrence of meningioma. The insignificance of data obtained in group RF+ELF is well explained by majority of RF data showing no significant relationship of RF exposure with increased risks of meningioma (Carlberg, Soderqvist et al. 2013).

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). The ESC obtained from human foreskin were grafted into type-I three-dimensional collagen sponge scaffolds, and then were exposed with EMF (frequency 50 Hz, intensity 5 mT) for 14 days, 30 min daily. The effects of EMF on growth and proliferation of ESC were analyzed with staining of hematoxylin and eosin (H&E) and 4',6-diamidino-2-phenylindole (DAPI) under microscope or scanning electron microscope. The data of DAPI staining for 2 d, 7 d, 10 d and 14 d were collected respectively to investigate the cells proliferation. EMF promoted ESC proliferation compared with controls.

Belyaev analyzed the effect of ELF-MF on chromatin conformation in *E. coli* GE499 cells using anomalous viscosity time dependence technique (AVTD) (Belyaev 2011). Possible genotoxic effects of the specific combination of static and ELF-MF, which has been proven to affect chromatin conformation, were investigated by a clonogenic assay, by assessing cell-growth kinetics, and by analysis of the SOS-response by means of inducible *recA-lacZ* fusion-gene products and the beta-galactosidase assay. The genotoxic agent nalidixic acid (NAL) was used as a positive control and in combination with ELF-MF. Nalidixic acid decreased AVTD and induced a cytotoxic effect. In contrast to NAL, ELF-MF fields increased AVTD, stimulated cell growth, and increased cloning efficiency. In line with many previous studies, these effects depended on the frequency within the range of 7-11Hz. While NAL induced an SOS-response, exposure to ELF-MF did not induce the *recA-lacZ* fusion-gene product. Exposure to ELF-MF did not modify the genotoxic effects of NAL either. All together, the data show that ELF-MF, under specific conditions of exposure, acted as a non-toxic but cell-growth stimulating agent.

Cid et al verified hypothesis that ELF MF effect on cancer progression could be mediated by MF-induced effects on the cellular response to melatonin (MEL), a potentially oncostatic neurohormone (Cid, Ubada et al. 2012). HepG2 cells were exposed to intermittent 50 Hz, 10 microT MF, in the presence or absence of MEL at physiological (10 nM) or pharmacological doses (1 microM). The results indicated that the MF exerts significant cytoproliferative and dedifferentiating effects that can be prevented by 10 nM MEL. Conversely, MEL exerts cytostatic and differentiating effects on HepG2 that are abolished by simultaneous exposure to MF.

Dependence of ELF effects on number of physical and biological parameters

The SCENIHR report did not take into account dependence of ELF effects on number of physical and biological parameters when comparing the data from different studies. This is in significant contrast with generally accepted methodology which requires considering a number of such parameters which include cell type, frequency, intensity (Belyaev, Alipov et al. 1999; Belyaev and Alipov 2001; Shcheglov, Alipov et al. 2002) and which are similarly important for the MW effects (IARC 2013). Due to this fundamental flaw, incorrect comparisons of studies, which used completely different parameters were performed in the SCENIHR report. For example, negative study by (Buldak et al., 2012) was opposed to positive study (Luukkonen et al. 2011) on Page 164-165. Significant and decisive differences between these studies include exposure time (24 h in (Luukkonen et al. 2011) versus 16 min in (Buldak et al., 2012)), cell type (human neuroblastoma SHSY5Y cells (Luukkonen et al. 2011) versus AT478 murine carcinoma cells (Buldak et al., 2012)). Recent study by the same

authors confirmed and further extended evidence that prolonged exposure to ELF of human neuroblastoma SHSY5Y cells induce reactive oxygen species (ROS) and genomic instability (Luukkonen, Liimatainen et al. 2014).

Fijałkowski et al. analyzed effects of the rotating magnetic field (RMF, $f = 1-50$ Hz, RMF magnetic induction $B = 22-34$ mT, ptime of exposure $t = 60$ min, temperature of incubation 37 °C) on the growth rate, cell metabolic activity and ability to form biofilms by *E. coli* and *S. aureus* (Fijałkowski, Nawrotek et al. 2013). RMP exposure increased the growth dynamics, cell metabolic activities and percentage of biofilm-forming bacteria in both *S. aureus* and *E. coli* cultures. In line with many other studies, it was found that the RMF effects depended on frequencies and magnetic induction.

Sarimov et al have reported that magnetic field (MF) at 50 Hz within the peak amplitude range of 5-20 microT affected chromatin conformation in human lymphocytes from two healthy donors. These MF effects differed significantly between studied donors, and depended on magnetic flux density and initial condensation of chromatin. While the initial state of chromatin was rather stable in one donor during one calendar year of measurements, the initial condensation varied significantly in cells from another donor. Both this variation and the MF effect depended on temperature during exposure. Despite these variations, the general rule was that MF condensed the relaxed chromatin and relaxed the condensed chromatin. Thus, in this study individual effects of 50 Hz MF exposure at peak amplitudes within the range of 5-20 microT were observed in human lymphocytes in dependence on the initial state of chromatin and temperature.

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).

Duan et al. exposed mice to ELF-EMF at 50 Hz, 8 mT, 28 days (Duan, Wang et al. 2013). A water maze test indicated that ELF-EMF exposure deteriorated significantly learning and memory abilities as compared with the control group. Administration of lotus seedpod procyanidins (LSPCs) had remarkably improved learning and memory abilities in exposed animals compared with the ELF-EMF group. ELF-EMF exposure significantly increased malondialdehyde (MDA), reactive oxygen species (ROS), nitric oxide (NO) and nitric oxide synthase (NOS), while the activities of glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) were decreased significantly. Along with improved learning and memory abilities in exposed animals, LSPCs administration effectively prevented oxidative damage caused by the ELF-EMF, most likely through the ability of LSPCs to scavenge oxygen free radicals and to stimulate antioxidant enzyme activity. The majority of experimental studies (9 out of 10 animal studies) show oxidative stress induced by ELF in brain (Consales, Merla et al. 2012).

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 μ T-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 $\geq 0.3 \mu\text{T}$, 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). Despite physical differences in and incompleteness of these mechanisms all of them relate ELF effects with ion cyclotron resonance frequencies and their harmoniques/subharmoniques (Belyaev and Alipov 2001; Sarimov, Markova et al. 2005). Poniedzialek et al. analyzed ELF effects on reactive oxygen species (ROS) production in human neutrophils in peripheral blood in vitro (Poniedzialek, Rzymiski et al. 2013). Two fluorescent dyes were used: 2'7'-dichlorofluorescein-diacetate and dihydrorhodamine. Phorbol 12-myristate 13-acetate (PMA), known as strong stimulator of the respiratory burst, was also used. Three different levels of magnetic induction have been analyzed: 10, 40 and 60 μT . The experiments demonstrated that only EMF tuned to the calcium ion cyclotron resonance frequency was able to affect ROS production in neutrophils. Statistical analysis showed that this effect depended on magnetic induction value of applied EMF.

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, Karabarounis et al. 2013; Shams Lahijani, Tehrani et al. 2013; Villarini, Ambrosini et al. 2013).

Mariucci et al exposed CD1 mice to ELF MF (50 Hz-1 mT) for 1 or 7 days (15 h/day) and sacrificed either at the end of exposure or after 24 h (Mariucci, Villarini et al. 2010). Mouse brains were dissected into cerebral cortex-striatum, hippocampus and cerebellum to evaluate primary DNA damage and hsp70 gene expression. An increase in primary DNA damage was detected in all cerebral areas of the exposed mice sacrificed at the end of exposure. This damage, evaluated by the comet assay, appeared to be repaired in mice sacrificed 24 h after a 7-day exposure. The results indicate that in vivo ELF-MF exposure induces transient brain DNA damage did not induce hsp70. Importantly, these results were further replicated by the same research group (Villarini, Ambrosini et al. 2013).

Ulku et al. investigated a set of elements in costa of rats chronically exposed to ELF-MF, 100 and 500 μT , 2 h/day during 10 months (Ulku, Akdag et al. 2011). The levels of elements were measured by using atomic absorption spectrophotometry (AAS) and ultraviolet (UV) spectrophotometry. Ca levels decreased in the ELF-500 exposure group in comparison to sham group ($p < 0.05$). Statistically significant decrease was found in Mg levels in the ELF-500 exposure group in comparison to sham and ELF-100 exposure groups ($p < 0.05$). Zn levels were found to be lower in the ELF-500 exposure group than those in the sham and ELF-100 exposure groups ($p < 0.05$). No significant differences were determined between groups in terms of the levels of P, Cu and Fe. Thus, long-term ELF-MF exposure could change the levels of some important elements such as Ca, Zn and Mg in rat bones.

Balassa et al. analyzed effects of a long-term ELF-MF (0.5 and 3 mT, 50 Hz) exposure on synaptic functions in the developing brain (Balassa, Varro et al. 2013). Rats were chronically exposed to MF during two critical periods of brain development, i.e. in utero during the second gestation week or as newborns for 7 days starting 3 days after birth, respectively. Excitability and plasticity of neocortical and hippocampal areas were tested on brain slices by analyzing extracellular evoked field potentials. The basic excitability of hippocampal slices (measured as amplitude of population spikes) was increased by both types of treatment (fetal 0.5 mT, newborn 3 mT). Neocortical slices seemed to be responsive mostly to the newborn treatment, the amplitude of excitatory postsynaptic potentials was increased. Fetal ELF-MF exposure significantly inhibited the paired-pulse depression (PPD) and there was a significant decrease in the efficacy of LTP (long-term potentiation induction) in neocortex, but not in hippocampus. On the other hand, neonatal treatment had no significant effect on plasticity phenomena. Results demonstrated that ELF-MF has significant effects on basic neuronal functions and synaptic plasticity in brain slice preparations originating from rats exposed either in fetal or in newborn period.

Gang et al. exposed planarian to either 140 or 400 nT peak amplitude-modulated 7 Hz magnetic fields for 6 min once per hour, 8 h per night for 5 days (Gang, Parker et al. 2013). The planarian exposed to either intensity magnetic field exhibited faster regeneration of photoreceptors and auricles compared to sham field and reference groups. The magnetic field exposure accommodated 50% of the variance during the faster growth days. Authors concluded that naturally-patterned, intermittently-presented weaker electromagnetic fields may produce enhanced regeneration rates in flat worms similar to those observed for 60 Hz, higher intensity fields.

Severini et al. exposed cohorts of *Xenopus laevis laevis* (Daudin) tadpoles during their immature period (approximately 60 days) to a 50 Hz magnetic field of $63.9 \leq B \leq 76.4$ microT rms (root mean square, average values) magnetic flux density (Severini, Bosco et al. 2010). Mean developmental rate of ELF-exposed cohorts was reduced with respect to controls (0.43 vs. 0.48 stages/day, $p < 0.001$) starting from early larval stages. Exposure increased the mean metamorphosis period of tadpoles by 2.4 days compared with the controls ($p < 0.001$). Maturation rates of exposed and control tadpoles changed during maturation period. Important mortality, alformations or teratogenic effects were not observed in exposed matured tadpoles. Authors concluded that a long-term exposure of *X. laevis* tadpoles to a relatively weak 50 Hz magnetic field causes a sub-lethal effect that slows down their larval developmental rate and delays their metamorphosis.

Panagopoulos et al studied the effect of 50-Hz alternating magnetic field on *Drosophila melanogaster* reproduction (Panagopoulos, Karabarbounis et al. 2013). Newly eclosed insects were separated into identical groups of ten males and ten females and exposed to three different intensities of the ELF magnetic field (1, 11, and 21 G) continuously during the first 5 days of their adult lives. The magnetic field decreased reproduction by up to 4.3%. The effect increased with increasing field intensities. The decline in reproductive capacity was found to be due to severe DNA damage (DNA fragmentation) and consequent cell death induction in the reproductive cells as determined by the TUNEL assay applied during early and mid-oogenesis (from germarium to stage 10) where physiological apoptosis does not occur. The increase in DNA damage was more significant than the corresponding decrease in reproductive capacity (up to ~7.5%). The TUNEL-positive signal denoting DNA fragmentation was observed exclusively at the two most sensitive developmental stages of

oogenesis: the early and mid-oogenesis checkpoints (i.e. region 2a/2b of the germarium and stages 7-8 just before the onset of vitellogenesis). The TUNEL-positive signal was observed in all three types of egg chamber cells, mainly in the nurse and follicle cells and also in the oocyte.

Kang et al. analyzed specific electromagnetic field conditions (frequency and magnetic flux density) which significantly regulate osteogenic differentiation of adipose-derived stem cells (ASCs) (Kang, Hong et al. 2013). Before inducing osteogenic differentiation, ASC stemness was determined and uniform electromagnetic field was created using the solenoid coil. Then, authors selected positive (30/45 Hz, 1mT) and negative (7.5 Hz, 1mT) osteogenic differentiation conditions by quantifying alkaline phosphate (ALP) mRNA expression. Osteogenic marker (runx-2) expression was higher in the 30/45Hz condition and lower in the 7.5 Hz condition as compared with the nonexposed group. Both positive and negative regulation of ALP activity and mineralized nodule formation supported these responses. The data indicated that the ELF effects on osteogenic differentiation differ depending on the electromagnetic field conditions and thus provided evidence that ELF can control stem cell differentiation depending on frequency and intensity.

Iorio et al. investigated whether ELF-MF could affect myoblast migration (Iorio, Bennato et al. 2013). ELF-MF (1 mT; 50 Hz) resulted in a transient but significant increase of myoblast migration. This effect was associated with a marked increase of μ - and m-calpain activity followed by the concomitant variation in their subcellular localization. No significant changes in intracellular distribution and protein levels of calpastatin were detected. A significant decrease of myristoylated alanine-rich C-kinase substrate (MARCKS) expression and modifications of actin dynamics were reported. This study provided evidence for involvement of calpains in ELF-MF-mediated myoblast migration.

Page 129, line 26-27. This statement misleads the reader who is not expert in effects of weak EMF to judge results as nonreplicable. In fact, ELF effects similar to MW effects depend on cell type (Belyaev 2010) and this study just provides further support for this dependence. In addition, reference to (Focke, Schuermann et al. 2010) is missing in Reference list.

Page 130. Study of Girgert et al (Girgert, Hanf et al. 2010) is erroneously marked as Girgert et al 2009 and reference if not provided in the Reference list.

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Comments on RFR Sections

Main conclusions on health effects from RFR fields

1. The positive and negative studies were selected by unclear criteria, which (i) are different from those generally accepted and used by IARC and (ii) resulted in omission of majority of positive findings and almost all laboratory studies which were performed using conditions of EMF exposure similar as general public is exposed (see text below and reference list).
2. The report shows fundamental flaw in assessment of mechanisms for non-thermal EMF effects.
3. Analysis of data seem to be biased in favor of negative studies and negative interpretations.

Flawed assessment of negative studies

The main fundamental flaw of the report is neglecting the mechanistic data on non-thermal (NT) effects of microwaves (MW). As reported in multiple studies, these effects depend on variety of biological and physical parameters including polarization, frequency, modulation and environmental EMF (see (Belyaev 2010) and (IARC 2013)). The *in vitro* and *in vivo* studies included in the preliminary Opinion are largely negative studies only. Moreover, negative studies cannot be directly compared to positive studies if the exposure was performed under different conditions as it almost always done. Thus, obtained so far data of negative studies cannot be extrapolated to all real cell phone signals. The negative studies cannot neither dismiss positive studies, which were performed under other conditions, nor provide evidence for safety of majority of signals used for mobile communication. The reported "inconsistency" of *in vitro* and *in vivo* data (see for example page 120) and "conflicting results" (see for example page 121) has at least one simple explanation because the studies were performed under different conditions. Thus, results of most studies cannot be directly compared and conclusion by the SCENIHR report on inconsistency. Conflicting results instead reflect the level of superficial analysis. Another fundamental flaw deals with 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 (Belyaev 2010). 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 RFR 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 - dependence on dose.

Another important parameter is intermittence of exposure which involves interaction with adaptation mechanisms and accumulative effects of NT MW. Chavdoula et al. used a 6 min daily exposure of dipteran flies, *Drosophila melanogaster*, to GSM-900 MHz mobile phone electromagnetic radiation (EMR), to compare the effects between continuous and four different intermittent exposures of 6 min total duration on the insect's reproductive capacity as well as on the induction of apoptosis (Chavdoula, Panagopoulos et al. 2010). It was found that intermittent exposure, similar to continuous exposure, decreases the reproductive capacity and alters the actin-cytoskeleton network of the egg chambers, another known aspect of cell death, and that this effect is due to DNA fragmentation. Intermittent exposures with 10-min intervals between exposure sessions proved to be nearly equally effective as continuous exposure of the same total duration, however, longer intervals between the exposures seemed

to allow the organism the time required to recover and partly overcome the described effects of the GSM exposure.

The preliminary Opinion bases its conclusions mostly on SAR value, which is a main parameter for thermal MW effects but has much less value for NT MW to which general public is exposed to (Belyaev 2010; Panagopoulos, Johansson et al. 2013).

RFR epidemiologic evidence for carcinogenicity

The SCENIHR preliminary Opinion has conclusions on brain cancer that are heavily based on the Danish subscriber cohort study of mobile phone subscribers. However this study has not assessed exposure, has been heavily criticized and thus far is inconclusive. This study is not informative even according to the requirement of this SCENIHR reports : "*The 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).

The preliminary Opinion is internally inconsistent with this requirement as the authors have based their review largely on epidemiological studies, where individual exposure was not accurately assessed. These studies include those coauthored by Dr Schüz who is one of the authors for this SCENIHR report. For example, the UK Million women study (Benson et al 2013) included only two simple questions regarding usage of mobile phone which cannot estimate individual exposure in any reasonable degree. Following the general bias of this report in favor of negative finding, the authors forgot to state that this study found statistically significant increase of acoustic neuroma for long term users vs never users (10+ years: RR = 2.46, 95% CI = 1.07–5.64, $P = 0.03$), the risk increasing with duration of use (trend among users, $P = 0.03$).

Another example is the underestimation of importance of the positive findings of de Vocht et al (2013) on global link of mobile phone usage and brain cancer. "*The study is not informative for causal inference, as popular use of mobile phones can also reflect standard of living, which is also associated with, for example, availability of diagnostic services*". The SCENIHR's preliminary Opinion did not mention that this statement is relevant to most negative studies and especially to the Danish subscriber cohort study upon which this preliminary Opinion heavily relies. In contrast, the meta-analyses of studies which included only data on ipsilateral tumors in subjects using mobile phones for at least 10 years, show large and statistically significant increases in risk of ipsilateral brain gliomas and acoustic neuromas (Levis, Minicuci et al. 2011). The risk of head tumors was nearly doubled and was induced by long-term mobile phone use.

Consideration of the data on childhood cancers in relation to base stations is also biased in favor of weighting negative studies. While limitation of positive study by (Li et al. 2012) is provided, no limitations of negative study by (Elliott et al. 2010) is considered in contrast to about one-page description of such limitations provided by the authors (Elliott et al. 2010). In addition, the report did not provide the main positive result of the (Li et al. 2012) study which has shown increased (brain+leukemia) incidence related to base stations.

Brain cancer time trend analysis

The SCENIHR report provides biased consideration of available information. It should be noted that histology analysis and localization of tumors in respect to irradiation from mobile phone is of key importance for this analysis.

At the time of IARC meeting in 2011 the following data were available and included into the IARC monograph (IARC 2013):

USA

According to data collected by the Surveillance, Epidemiology, and End Results (SEER) Program, age- and sex-specific trends and overall temporal trends in rates of incidence of brain cancer in the USA were flat or downward between 1992 and 2006, with the exception of women aged 20–29 years (Inskip *et al.*, 2010). In this age group, a statistically significant increasing trend was driven by the rising incidence in tumors of the frontal lobe. [It is the temporal lobe that is most heavily exposed to radiation when using a mobile phone at the ear (Cardis *et al.*, 2008).] Incidence of brain cancer in USA "could be consistent with the modest excess risks in the Interphone study" (Little, Rajaraman *et al.* 2012).

UK

Overall rates of incidence of cancer of the brain in males or females, or in any specific age group were not increased in England between 1998 and 2007 (de Vocht, Burstyn *et al.* 2011). For men and women, the incidence of tumors (primarily glioma) was increased ($p < 0.01$) in the temporal lobe that is most heavily exposed to radiation when using a mobile phone at the ear (Cardis, Deltour *et al.* 2008). The incidence increased also in frontal lobe for men ($p < 0.01$) and in the frontal lobe for women, although not statistically significant ($p = 0.07$). The incidence decreased in other parts of the brain. In a subsequent paper, the same authors reported separate time trends for cancers of the temporal lobe in the periods 1979–99 and 2000–08 (de Vocht, Burstyn *et al.* 2011). For men, a linear regression of age-adjusted rates showed an overall annual increase in 2000–2008 of 3.3% (95% CI, 1.1–5.4), whereas it was lower 2.0% (95% CI, 1.4–2.6) for 1979–1999. For women, a linear regression of age-adjusted rates showed an overall annual increase in 2000–2008 of 2.8% (95% CI, 0.9–4.8), whereas it was lower 1.4% (95% CI, 0.7–2.2) for 1979–1999. This change may be suggestive of increased rates for brain cancers of the temporal lobe in the recent years. [The linear regression used for this analysis was not an appropriate method and therefore the 95% confidence intervals reported may not be reliable.] p.190

After the IARC meeting in 2011 the following data were available

USA

Zada *et al.* studied incidence trends of primary malignant brain tumors in the Los Angeles area during 1992-2006 (Zada, Bond *et al.* 2012). Incidence data for histologically-confirmed brain tumors were obtained from the Los Angeles County Cancer Surveillance Program (LAC), the California Cancer Registry (CCR), and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program for 1992 to 2006. Annual percentage change (APC) was calculated for microscopically confirmed histological subtypes and anatomic sub sites. The overall incidence of primary malignant brain tumors decreased over the time period with the exception of glioblastoma multiforme (GBM) (astrocytoma grade IV). The annual age adjusted incidence rate of that tumor type increased statistically significant in the frontal lobe with APC +2.4 % to +3.0 % ($p < 0.001$) and temporal lobe APC +1.3 % to +2.3 % ($p < 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme increased also in cerebellum, APC +11.9 % ($p < 0.001$). In the parietal and occipital lobes or in overlapping lobes no statistically significant changes in incidence were seen. For lower grade astrocytoma decreases of annual age adjusted incidence rates were observed. The authors concluded that despite decreased incidences in other brain regions there was an increase in the incidence of glioblastoma multiforme in

frontal and temporal lobes and cerebellum. These parts of the brain are characterized by highest absorbed dose of radiation from mobile phones (Cardis, Deltour et al. 2008; Deltour, Wiart et al. 2011).

China

Ding et al. (Ding and Wang 2011) investigated time trends in the incidence of brain and nervous tumor in urban Shanghai, from 1983 to 2007, applying joinpoint regression models to analyze the annual incidence rates. From 1983 to 2007, the age-adjusted incidence rate of brain and nervous tumors increased gradually by 1.2% per year (95% confidence interval [CI] = 0.4% to 1.9%) among men and 2.8% per year (95% CI = 2.1 to 3.4) among women. While the authors concluded that this study did not support an association between cellular telephone use and increased risk of brain and nervous tumors, the conclusion was made on assumption about *latency periods shorter 5-10 years*. Authors themselves recognize that this conclusion is not valid for longer latency periods, which are indeed predictable for gliomas and acoustic neuromas. Thus, authors do not take into account that radiation induced glioma (RIG) studies would reasonably not show so soon, given significantly higher latency periods. Common conclusions reached across diverse cases on RIG is that mean latency time was in the order of many years (*range: 9–17 years*) (Prasad and Haas-Kogan 2009). Thus, while the incidence rate has been shown to be increased in urban Shanghai, the conclusion of the authors on lack of association with mobile phones is flawed.

Australia

A multicenter study was performed to determine the brain cancer incidence in Australia (the state of New South Wales (NSW) and the Australian Capital Territory (ACT)) with age-, sex-, and benign-versus-malignant histology-specific analyses (Dobes, Shadbolt et al. 2011). One hundred percent of tumors were histologically confirmed. Data were weighted for patient outflow and *data completeness*. Incidence rates were age standardized and trends analyzed using joinpoint analysis. An overall significant increase in primary malignant brain tumors was observed over the study period from 2000 to 2008 (APC, 3.9; 95%CI, 2.4–5.4). Overall increasing trend in malignant tumors was consistent for both males (APC, 2.3; 95% CI, 0.4–4.2) and females (APC, 2.3; 95% CI, 0.3–4.3). This increase appears to be largely due to an increase in malignant tumor incidence in the ≥ 65 -year age group. The same authors reported an analysis of incidence by tumor subtype (Dobes, Khurana et al. 2011). A significant increasing incidence in glioblastoma multiforme (GBM) was observed in the study period (annual percentage change [APC], 2.5; 95% confidence interval [CI], 0.4-4.6, n = 2275), particularly after 2006. In GBM patients in the ≥ 65 -year group, a significantly increasing incidence for men and women combined (APC, 3.0; 95% CI, 0.5-5.6) and men only (APC, 2.9; 95% CI, 0.1-5.8) was seen. Rising trends in incidence were also seen for meningioma in the total male population (APC, 5.3; 95% CI, 2.6-8.1, n = 515) and males aged 20-64 years (APC, 6.3; 95% CI, 3.8-8.8). Significantly decreasing incidence trends were observed for Schwannoma for the total study population (APC, -3.5; 95% CI, -7.2 to -0.2, n = 492), significant in women (APC, -5.3; 95% CI, -9.9 to -0.5) but not men.

Korea

Recent data from Korea has shown increase in brain cancer incidence (Jung, Won et al. 2013). Tumors of the brain and nervous system increased APC 1.0% per year for men and 0.5% per year for women during 1999 - 2010. The rate of increase was statistically significant for men ($p < 0.05\%$), while was not statistically significant for women. It should be noted that key parameters for the NT MW effects include sex and age (Belyaev 2010; IARC 2013). For both sexes, combined statistically significant rate of increase was 0.8% annually.

Nordic national cancer registers

In Denmark, the Danish cancer register has reported increase in brain cancer incidence of 40% in men, and by 29% in women during 2001-2010.

(<http://www.sst.dk/publ/Publ2011/DAF/Cancer/Cancerregisteret2010.pdf>)

Finland

In Finland, age-adjusted (world) brain cancer incidence rates per 100,000 person-years has not changed significantly since 1997

(<http://www.kreftregisteret.no/no/Registrene/Kreftstatistikk/>). Age-adjusted (world) incidence rates per 100 000 person-years by primary site and five-year period was in females 12,0 in 1992-96, 13,6 in 1997-01, 14,2 in 2002-06, 13,7 in 2007-11

(<http://stats.cancerregistry.fi/stats/eng/veng0006i0.html>)

Age-adjusted (world) incidence rates per 100,000 person-years by primary site and five-year period was in males 10,7 in 1992-96, 10,6 in 1997-01, 11,7 in 2002-06, 11,2 in 2007-11.

(<http://stats.cancerregistry.fi/stats/eng/veng0005i0.html>)

Norway

In Norway, age-adjusted (world) brain cancer incidence rates per 100 000 person-years has grown since 1997 (<http://www.kreftregisteret.no/no/Registrene/Kreftstatistikk/>). Age-adjusted (world) incidence rates per 100,000 person-years by primary site and five-year period was in females 10.6 in 1992-96, 13.3 in 1997-01, 17.3 in 2002-06, and 16.4 in 2007-11. Age-adjusted (world) incidence rates per 100,000 person-years by primary site and five-year period was in males 10.7 in 1992-96, 12.2 in 1997-01, 14.1 in 2002-06, and 14.2 in 2007-11.

Sweden

In Sweden, no statistically significant changes in brain cancer incidence per 100,000 person was shown in Cancer Register (Socialstyrelsens Cancerregister) during 1996 -2011.

(<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>). There is a scientifically reasonable suspicion that underreporting of brain cancers masks the brain cancer incidence in Sweden (Barlow, Westergren et al. 2009).

All Nordic countries. NORDCAN

Nordic cancer register (NORDCAN) shows increases in brain cancer incidence. NORDCAN project presents the incidence, mortality, prevalence and survival statistics from 41 major cancers in the Nordic countries (<http://www-dep.iarc.fr/NORDCAN/english/frame.asp>). In Denmark, a statistically significant increase in incidence rate per year for brain and central nervous system tumors (combined) was seen during 2001-2011 both in men, *annual percentage change (APC)*, 3.77, [95% CI 2.90; 4.64] and in women 3.68, [95% CI 2.29; 5.10]. While no statistically significant changes are observed in incidence rate per year for brain and central nervous system tumors during last 10 years in other Nordic countries (Finland, Iceland, Norway, and Sweden), a statistically significant increase is seen during last 10 years in men 1.02, 95%CI [0.40;1.65] and women, 1.05, 95%CI [0.35;1.74] in all Nordic countries combined.

Quality and completeness of cancer registers

The SCENIHR preliminary Opinion reaches an indefensible and highly controversial conclusion on brain cancer: "*That renders all studies reporting increased risks of such magnitude implausible. The reason for the increases are methodological artefacts*". First, the time trends for brain cancer incidence is positive according to at least some data shown

above. Second, it generally accepted that if two pieces of data do not fit each other both pieces should be scientifically analyzed. As a matter of fact, the utility of Cancer registries depends heavily on their quality including the *completeness* with which patients eligible for registration are ascertained (Bray and Parkin 2009; Parkin and Bray 2009). The *completeness* of cancer registry data – the extent to which all of the incident cancers occurring in the population are included in the registry database – is an extremely important attribute of a cancer registry (Parkin and Bray 2009). However, registries rarely report their completeness because it is difficult to measure (Bullard, Coleman et al. 2000).

Incompleteness was found in the Swedish Cancer Register (Barlow, Westergren et al. 2009). Underreporting of brain cancers including gliomas in Swedish Cancer Register was about 3.7% of the cases reported in 1998 (Barlow, Westergren et al. 2009).

It was estimated, that the Thames Cancer Registry (UK) attains 92.1% completeness 5 years after diagnosis for all cancers (Bullard, Coleman et al. 2000). Recent data have confirmed relatively low completeness of the Thames Cancer Registry with estimates ranging from around 78% (female melanoma) to 95% (female stomach cancer) (Robinson, Sankila et al. 2007). The Finnish data appeared to be more complete, with estimates ranging from around 96% completeness for prostate cancer to 100% for ovarian cancer (Robinson, Sankila et al. 2007).

The best characterized is the Cancer Register of Norway (CRN) (Larsen, Smastuen et al. 2009). A total of 93.8% of the cancer cases registered in the period 2001–2005 were morphologically verified. The proportion of DCO (death certificate only) cases 2001–2005 was only 0.9%, and only 2.2% were registered with primary site unknown (PSU). The overall completeness for the period 2001–2005, estimated by the capture/recapture method, was 98.8%. The lowest completeness was estimated for pancreas (95.7%), multiple myeloma (95.5%), leukemia (94.6%) and central nervous system (93.8%). Authors recognize that cancers of the central nervous system did not meet the highest standards. Nevertheless, recent registration data from Norway are among the most complete among the European Registries (Larsen, Smastuen et al. 2009).

Recent study has indicated the US cancer registries data may be incomplete as related to cancer mortality (German, Fink et al. 2011). Confirmation rate was estimated as 93.4 (95% CI, 92.6–94.2) (per 100 deaths) = the number of individuals who died sometime in 2002–2004 and had been diagnosed with brain cancer sometime in 1993–2004 for whom the cancer site listed in the population-based cancer registry matched the site (underlying cause) on their death certificate, divided by the total number of these decedents (both matched and unmatched). Detection rate was estimated 93.7 (95% CI, 90.5–96.9) = the number of individuals diagnosed with brain cancer (ICD-10, the International Statistical Classification of Diseases and Related Health Problems, 10th Revision) sometime in 1993–1995 who died sometime in 1993–2004 for whom the cancer site listed in the population-based cancer registry matched the site (underlying cause) on their death certificate, divided by the total number of these decedents (both matched and unmatched).

Similar incompleteness has been reported by Meguerditchian et al for the National Cancer Data Base (NCDB) (Meguerditchian, Stewart et al. 2010). Claims for patients with breast cancer surgery from one payer in Western New York (WNY) were matched with NCDB for participating hospitals for 2001-2003 using available identifiers (reporting hospital, gender, birth date, ZIP code). Four hundred seventy patients with health insurance provided by IHA with a breast procedure and a diagnosis code for breast cancer between January 1, 2001 and

January 1, 2003 at the participating institutions were identified by ICD-9 and CPT codes. These patients were matched to all breast cancers reported to the NCDB from the CoC-approved hospitals during the same period and in the same geographic area. The final match rate between the two datasets was 93.4% (430 patients). Forty cases identified by IHA remained unmatched to the registries.

The time trends for *incompleteness* of the Cancer Registers is not known. Finally, Cancer Register's data should be questioned if no consistence is observed between them and epidemiological data on mobile phone usage.

Conclusion on brain cancer time trend data and mobile phones

Cancer incidence data are derived from cancer registries and quality of these data dependent on quality and completeness of cancer registers. Completeness and quality of most cancer registries are not comprehensively characterized and vary between cancer registers. At least some cancer registries including better described Nordic Cancer Register show increased time trends in brain cancer incidence, especially in those parts of brain which are mostly exposed to radiation from mobile phones. Taking into account the IARC statement regarding the role of incidence data in phone risk assessment, the incidence data do not contradict to the increased cancer risk seen in epidemiological studies at latencies more than 10-25 years (Carlberg, Soderqvist et al. 2013; Hardell and Carlberg 2013; Hardell, Carlberg et al. 2013; Hardell, Carlberg et al. 2013). The IARC Working Group further noted that these descriptive analyses would be null if an excess in cancer risk from mobile-phone use became manifest only decades after phone use began, or if an increase affected only a small proportion of the cases by location.

On page 68 the SCENIHR report states: "it appears the evidence for glioma became weaker". This conclusion is in evident contradiction with available data. Recent publications including those omitted in the SCENHIR report and mentioned in these comments make this evidence much stronger than during the last IARC meeting in 2011 and demands IARC classification "carcinogen, group 1" for EMF exposures from mobile phones.

In vivo studies

Similar to other parts of this report, the conclusions from *In vivo* studies, p 68- , are fundamentally flawed because they are not based on mechanistic studies and consideration of important physical and biological parameters (IARC 2013).

As a matter of fact, only negligible amount of real signals (frequency, modulation, polarizaton) were tested in mentioned *in vivo* studies. Thus, the statement, p 68, "*Overall, it was concluded that RFR fields such as those emitted by mobile phones were not carcinogenic in laboratory rodents*" may be relevant only to these limited number of tested signals. Similarly the statement: "*Overall, because a considerable number of well-performed studies using a wide variety of animal models have been mostly negative in outcome, the animal studies are considered to provide strong evidence for the absence of an effect*" deals with only minority of real signals and cannot be used as an argument against overwhelming evidence for increased cancer risks following from epidemiological studies, which involved all possible signals. What is even more important, most positive studies involved exposure to the more realistic exposure that includes combined signals from real mobile phones. These are the most relevant for health risk assessment, but were omitted in the SCENIHR report (see below).

It is fundamentally flawed to question results of epidemiological studies obtained with exposure to all signals from mobile phones by *in vivo* or *in vitro* negative studies obtained with negligible number of mobile phone-like signals.

Genotoxic RFR effects, p. 70

These studies were omitted from review in the preliminary Opinion and should be incorporated. Positive studies on RFR/mobile phone genotoxicity include but are not limited to (Guler, Tomruk et al. 2010; Cam and Seyhan 2012; Guler, Tomruk et al. 2012; Karaca, Durmaz et al. 2012; Sekeroglu, Akar et al. 2012; Atasoy, Gunal et al. 2013; Atli Şekeroğlu, Akar et al. 2013; Hanci, Odaci et al. 2013; Liu, Duan et al. 2013; Liu, Gao et al. 2013; Pesnya and Romanovsky 2013).

Considering Belyaev's group studies (Belyaev, Markova et al. 2009; Markova, Malmgren et al. 2010) the SCENIHR preliminary opinion stated, page 72, that effects at 905 MHz were inconsistent. It should be noted that this "inconsistency" was actually individual variability, which nature has recently been established to be dependant on individual state of chromatin at time of exposure (Sarimov, Alipov et al. 2011). One of the main results following from the Belyaev's group studies including those unmentioned neither in this nor in previous SCENIHR report (Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005) is strong dependence of effects from mobile phones on carrier frequency/frequency channel. Effects at 905 MHz/GSM channel 74 on DNA repair foci were consistently lower compared to effects at 915 MHz/GSM channel 124 regardless cell type, human lymphocytes, fibroblasts or stem cells. In addition, the data indicated stronger effects of exposure to RF from UMTS mobile phone at frequency at 1947.4 MHz, middle channel. Importantly, human stem cells (not "stem cells" as spelled in the SCENIHR preliminary opinion on page 72, line 16) were most sensitive to MW exposure providing a mechanistic link to carcinogenesis. This is because stem cells are the generally accepted cellular target for origination of different types of tumors and leukemia. These data provided evidence that different frequency channels of different types of mobile communications should be separately tested for health effects and that primary human stem cells are an key cellular focus for *in vitro* EMF studies dealing with carcinogenesis.

Mechanisms for non-thermal MW effects below ICNIRP safety levels

It is generally accepted now that MW induce effects under non-thermal intensities which are generally called non-thermal effects. The SCENIHR preliminary opinion states that: "*(I)n view of the lack of verification of any proposed non-thermal interaction mechanism, established knowledge does not suggest effects accumulating with time*".

First, this statement is in contradiction with generally accepted Bradford Hill criteria: "*Plausibility: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.*" . . . no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other "absurd" associations, that "*it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected*". And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.' the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As

Sherlock Holmes advised Dr Watson, '*when you have eliminated the impossible, whatever remains, however improbable, must be the truth.*' "(Hill 1965).

Second, there are a number of studies showing accumulation of effects with time (Belyaev 2010).

Third, the majority of scientists consider NT MW effects within the frame of mechanisms using quantum mechanics and physics of nonlinear systems in biological non-equilibrium systems, which are relevant for mechanisms of NT MW in biological systems (Belyaev 2010). It is generally accepted that more than one physical theory may describe the same phenomena (compare for example Debye model of phonons in a box and Einstein model of quantum harmonic oscillators for solids). Thus, the demand of a generally accepted mechanism is not scientifically justified and represents methodological flaw. Most representative so far international IARC expert panel has concluded: "*Although it has been argued that RF radiation cannot induce physiological effects at exposure intensities that do not cause an increase in tissue temperature, it is likely that not all mechanisms of interaction between weak RF-EMF (with the various signal modulations used in wireless communications) and biological structures have been discovered or fully characterized*", see page 104 (IARC 2013). Thus, the IARC Working Group does not reject physical mechanisms for mobile phone exposure and recognizes that either new mechanisms may come or already known mechanisms may be better characterized to explain the non-thermal effects.

Among other mechanisms, radical pairs mechanism is widely accepted. In many recent reports unmentioned by the SCENIHR preliminary opinion it has been shown that ROS may be involved in radical pair reactions, thus, radical pairs may be considered one of the mechanisms of transduction able to initiate cell oxidative stress (Georgiou 2010; Apollonio, Liberti et al. 2013; Bodera, Stankiewicz et al. 2013; Burlaka, Tsybulin et al. 2013). Furthermore, many of the changes observed in RF-exposed cells were prevented by (pre)treatment with antioxidants (IARC 2013). In addition, recent review has summarized studies on EMFs exposure and oxidative stress in brain (Consales, Merla et al. 2012). While the data from different studies should be compared with care in view of variation in physical and biological parameters, most part of collected data have shown effects of ELF and RF EMF on oxidative stress in brain (Consales, Merla et al. 2012). IARC monograph states: "*even small effects on radical concentration could potentially affect multiple biological functions*", page 103 (IARC 2013).

One of the main arguments against NT MW effects, so called kT-paradox, has further been challenged by consideration of biological processes far from thermodynamic equilibrium (Cifra, Fields et al. 2011). Subculture structures such as molecular motors operate, in general, under conditions far from thermodynamic equilibrium and, therefore, the formalism of non-equilibrium thermodynamics, which was generally used in critics of mechanisms for NT MW effects, for coupled mechano-chemical processes is not applicable (Chowdhury 2013). Therefore, one has to use the more sophisticated toolbox of stochastic processes and nonequilibrium statistical mechanics for theoretical treatment of molecular motors. Theoretical studies by Srobar in development of fundamental theory by H. Fröhlich have not been considered neither in this nor in previous SCENIHR Opinion on EMF (Srobar 2009; Srobar 2009).

Effects of RFR exposure on oxidative stress, p 177

This chapter provides a biased record of very minor part of oxidative stress studies without definition how these studies have been chosen for analysis. Recent positive studies on

RF/mobile phone oxidative stress and genotoxicity have not been included (Haghani, Shabani et al. 2013) (Tomruk, Guler et al. 2010; Esmekaya, Ozer et al. 2011; Kumar, Behari et al. 2012) (Lu, Huang et al. 2012) (Tkalec, Stambuk et al. 2013) (Deshmukh, Banerjee et al. 2013) (Shahin, Singh et al. 2013) (Eser, Songur et al. 2013) (Burlaka, Tsybulin et al. 2013) (Esmekaya, Aytekin et al. 2011) (Avci, Akar et al. 2012) (Ceyhan, Akkaya et al. 2012) (Sokolovic, Djordjevic et al. 2013) (Oksay, Naziroglu et al. 2012) (Sisodia, Rifat et al. 2013) (Liu, Duan et al. 2013) (Jelodar, Akbari et al. 2013) (Liu, Gao et al. 2013) (Ghanbari, Mortazavi et al. 2013) (Guler, Tomruk et al. 2010; Guler, Tomruk et al. 2012) (Imge, Kilicoglu et al. 2010) (Jelodar, Akbari et al. 2013) (Liu, Duan et al. 2013) (Naziroglu, Cig et al. 2012) (Ni, Yu et al. 2013) (Ozgun, Gler et al. 2010) (Park, Seo et al. 2013)

Replication studies

The most representative so far international IARC panel have included in the RF monograph, pages 101-102: "*The reproducibility of reported effects may be influenced by exposure characteristics (including SAR or power density, duration of exposure, carrier frequency, type of modulation, polarization, continuous versus intermittent exposures, pulsed-field variables, and background electromagnetic environment), biological parameters (including cell type, growth phase, cell density, sex, and age) and environmental conditions (including culture medium, aeration, and antioxidant levels)*" (IARC 2013). IARC admits also that some of the discrepancies between EMF replication studies could be due to differences in species, page 416 (IARC 2013). And at the page 104: "*Biological systems are complex and factors such as metabolic activity, growth phase, cell density, and antioxidant level might alter the potential effects of RF radiation*". Physical factors that affect interpretation of study results are considered in the IARC monograph in more detail on pages 385-387 (IARC 2013).

The SCENIHR preliminary Opinion requires "*replication studies in a strict sense*" for positive findings (page 101). Furthermore, those studies which consistently showed positive findings were criticized for deviations in protocols (p 101, lines 41-49). No such criticism was applied to studies which failed to "replicate" original positive finding (for example page 102, lines 39-49) even if the key parameters of experiments were or might be different between original studies and "replications". At many occasions, the SCENIHR preliminary Opinion states that replication of positive findings is essential before weight is given to positive results. However, the SCENIHR preliminary Opinion has never applied the same criteria to negative studies even if statistical power was not evaluated in most of them and thus the value of possibly missed effects is not known. As a matter of fact, not one of the negative studies has been replicated "*in a strict sense*" and not one of positive studies has been "unreplicated"/dismissed in "*in a strict sense*". Application of double standards for assessment of positive and negative studies is methodologically flawed and makes the SCENIHR preliminary Opinion internally inconsistent.

The SCENIHR report missed successful replications of positive studies (Grigoriev, Grigoriev et al. 2010; Havas and Marrongelle 2013).

In addition to aforementioned omitted studies reporting positive effects, this preliminary Opinion omitted many other recent positive studies which include but not limited to:

(Fragopoulou, Samara et al. 2012) (Karaca, Durmaz et al. 2012) (Dasdag, Akdag et al. 2012) (Celikozlu, Ozyurt et al. 2012) (Sharma, Sisodia et al. 2013) (Lv, Chen et al. 2014) (Jin, Zong et al. 2012) (Trivino Pardo, Grimaldi et al. 2012) (Aboul Ezz, Khadrawy et al. 2013) (Kesari, Kumar et al. 2011) (Redmayne, Smith et al. 2013) (Deshmukh, Banerjee et al. 2013; Deshmukh, Megha et al. 2013) (Aboul Ezz, Khadrawy et al. 2013) (Cam and Seyhan 2012)

(Cervellati, Valacchi et al. 2013) (Finnie, Cai et al. 2010) (Jorge-Mora, Misa-Agustino et al. 2011) (Kwon, Vorobyev et al. 2011) (Panagopoulos, Chavdoula et al. 2010; Panagopoulos and Margaritis 2010; Panagopoulos and Margaritis 2010) (Shckorbatov, Pasiuga et al. 2010) (Suhhova, Bachmann et al. 2013) (Vishnu, Nithyaja et al. 2011) (Sun, Shen et al. 2013) (Tomruk, Guler et al. 2010) (Wu, Wang et al. 2012) (Xu, Chen et al. 2013)

Negative studies were preferentially included into the report even if the same group published both positive and negative studies analyzing different endpoints. An example is the group of Lopez-Martin, which has published negative study on apoptosis in adult male Sprague-Dawley rats exposed for 1 hour to 900 MHz. This negative study was included to the SCENIHR report on page 157. However, the same group has published study revealing that similar exposure at 900 MHz and intensities lower than those from mobile phones induces c-fos proto-oncogene and glial fibrillary acid protein (GFAP) marker in brain of exposed male Sprague-Dawley rats (Carballo-Quintas, Martinez-Silva et al. 2011). This positive study has not been included in the SCENIHR report.

Omission of positive studies showing detrimental effects of RFR exposure and their possible mechanisms especially negatively affects conclusions of the SCENIHR report. An example is data from by Deshmukh et al., which show effects of RFR on cognitive function, DNA damage and oxidative stress in rats exposed under the same conditions (Deshmukh, Banerjee et al. 2013; Deshmukh, Megha et al. 2013).

Exclusion of positive studies questions the conclusions of the SCENIHR report on RFR health effects because some of them describe critical effects which were not considered by the SCENIHR report. Example is study by Aboul Ezz (Aboul Ezz, Khadrawy et al. 2013) which investigated the effect of RFR (frequency 1800 MHz, specific absorption rate 0.843 W/kg, power density 0.02 mW/cm², modulated at 217 Hz) on the concentrations of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in the hippocampus, hypothalamus, midbrain and medulla oblongata of adult rats. Adult rats were exposed daily to EMR and sacrificed after 1, 2 and 4 months of daily RFR exposure and 1 month after 4 months of daily RFR exposure. RFR exposure induced significant changes in DA, NE and 5-HT in all studied areas of adult rat brain. The authors concluded that exposure of adult rats to RFR may cause disturbances in monoamine neurotransmitters and this may underlie many of the adverse effects reported after RFR including memory, learning, and stress. In a recent German study, 24 out of 60 participants were exposed to MW from a base station (cell tower) at a power density of < 60 $\mu\text{W}/\text{m}^2$, 20 participants to 60 - 100 $\mu\text{W}/\text{m}^2$, and 16 participants to more than 100 $\mu\text{W}/\text{m}^2$ (Buchner and Eger 2011). The values of the stress hormones adrenaline and noradrenalin increased significantly during the first 6 months after exposure to the GSM base station; the values of the precursor substance dopamine substantially decreased in this time period. The subject's initial endocrine state was not restored even after 1.5 years. Due to the non-regulable chronic difficulties of the stress balance, the phenylethylamine levels dropped until the end of the investigation period. These effects show a dose response relationship.

Provocation studies, p. 108

In view of complex dependence of NT MEW effects on physiological state of the object, individual sensitivity, physical parameters of exposure, duration and time after exposure the provocation studies should not be considered as informative regarding exposure to all real mobile communication systems including cellphones because only minor part of these parameters (frequency, modulation, duration of exposure et cetera) have been analyzed.

Conclusions on symptoms. p. 115

Similar to other conclusions on RFR health effects, conclusions on symptoms on page 115 do not take into account dependence of RFR effects on physical parameters such as frequency and modulation. In contrast to this flawed approach by the SCENIHR report, in recent study Redmayne et al. evaluated associations between New Zealand early-adolescents' subjective well-being and self-reported use of, or exposure to different types of wireless phones and internet technology (Redmayne, Smith et al. 2013). In this cross-sectional survey, participants completed questionnaires in class about their cellphone and cordless phone use, their self-reported well-being, and possible confounding information such as whether they had had influenza recently or had a television in the bedroom. Parental questionnaires provided data on whether they had WiFi at home and cordless phone ownership and model. Data were analysed with Ordinal Logistic Regression adjusting for common confounders. Odds ratios (OR) and 95% confidence intervals were calculated. The number and duration of cellphone and cordless phone calls were associated with increased risk of headaches (>6 cellphone calls over 10 minutes weekly, adjusted OR 2.4, CI 1.2-4.8; >15 minutes cordless use daily adjusted OR 1.74, CI 1.1-2.9). Using a wired cellphone headset was associated with tinnitus (adjusted OR 1.8, CI 1.0-3.3), while wireless headsets were associated with headache (adjusted OR 2.2, CI 1.1-4.5), feeling down/depressed (adjusted OR 2.0, CI 1.1-3.8), and waking in the night (adjusted OR 2.4, CI 1.2-4.8). Several cordless phone frequencies bands were related to tinnitus, feeling down/depressed and sleepiness at school, while the last of these was also related to modulation. The only significant negative regression was less likely Waking nightly for those with Wi-Fi at home (adjusted OR 0.7, CI 0.4-0.99). Being woken at night by a cellphone was strongly related to tiredness at school (OR 3.49, CI 1.97-6.2). There were more statistically significant associations (36%) than could be expected by chance (5%). Several were dose-dependent relationships. The obtained data were in line with previous findings of others and suggested limiting use of cellphones and cordless phones to less than 15 minutes daily, and employing a speaker-phone device for longer daily use.

Methodological flaw in assessment

In contrast to generally accepted methodology used by IARC, this SCENIHR report subjectively divides studies into informative and non-informative (page 83-84). As a result the same studies SCENIHR report assess differently as compared to IARC : "*For in vivo studies our assessment of evidence is weaker than IARC, based on the same studies as used in the IARC evaluation*". While the SCENIHR report requires statistical power for negative studies (page 17), the majority of negative studies which the preliminary Opinion relies upon did not analyze statistical power and were not able to determine at what level of sensitivity the RFR effects might be missed. It is not stated in the SCENIHR preliminary Opinion how many experts evaluated each study and whether experts were allowed to evaluate own studies. The SCENIHR report inconsistently uses criteria for replication studies and verification of results. Strict following to generally accepted key biological and physical parameters the conditions is demanded at some occasions of the SCENIHR report. On the other hand, the effects of gender and biological efficiency of low SAR values is used to question validity of results (lines 3-4, page 103). Effects of low SARs and gender were described in many papers (Belyaev 2010; IARC 2013) and thus cannot be used as argument against NT MW effects.

Exclusion of studies with exposure to real mobile phones, which are most relevant for assessment of health effects from mobile telephony p. 117

On Page 117 the SCENIHR report states that studies with exposure to real mobile phones "*are of no use for health risk assessment, as the exposures would have been highly complex and very variable, especially if the animals were unrestrained and free to move in their*

cages". This is fundamentally flawed statement which results in excluding mostly important for health risk assessment studies and thus masking health risks from mobile communication. As a matter of fact, the studies with real mobile phones, given the EMF field was measured from the phone, represent most valuable type of studies for assessment of risks from mobile telephony. The reasons were recently analyzed in review by Belyaev that has not been included in the SCENIHR report (Belyaev 2010). In brief, real signals contain multiple (hundreds and even thousands, in dependence on type of mobile communication) components, such as carrier frequencies or frequency bands, different types of modulations. It is generally accepted that all these parameters are important for effects of MW (IARC 2013). Exposure to mobile phone may reproduce the majority of real signals during the same exposure session and thus provide the best possibility to assess detrimental effects from mobile telephony. Another type of exposure, to which the SCENIHR report has chosen to rely upon, is exposure to one fixed frequency and fixed modulation which reproduces one from thousands possible signals. While one RFR frequency/frequency band/modulation can induce detrimental effect, another one can be inactive (Belyaev 2010). In addition, mobile phones emit not only MW but also ELF fields, which have also been shown to produce detrimental effects (www.bioinitiative.org) and to interfere with MW effects (Belyaev 2010; Sun, Shen et al. 2013). Importantly, most of aforementioned studies with mobile phones as source of EMF exposure and omitted by the SCENIHR report show detrimental effects and most importantly indicate mechanism of these effects based on induction of ROS. Data obtained with selected frequency/frequency band/modulation provides possibility to assess only this specific signal and may be important for consideration of biophysical mechanisms for NT MW effects. However, these studies are evidently less important for health risk assessment by the reasons provided above.

Recommendations

The main issue of further research is to promote studies on biophysical mechanisms that will provide a mechanistic basis for risk assessment. Such parameters as frequency, modulation, polarization should be given priority for mechanistic studies so that physical and biological variables that influence study outcome can be taken into account. For risks assessment in laboratory studies, the complexity and interplay of variables from real systems of mobile communication should also be taken into account. In other words, to assess health risks from any type of mobile communication, all specific frequency channels and all specific modulations should be investigated in combinations as at real exposures. Recent studies indicated that financial interests may affect the outcome of EMF laboratory studies (Huss, Egger et al. 2007; Huss, Egger et al. 2008). Also recent review reports that the negative results produced by studies funded by the cell-phone companies are affected by many biases and flaws, giving rise to a systematic underestimate of the risk (Levis, Minicuci et al. 2011). On the contrary, studies producing positive results - without errors and financial conditioning - indicate a cause/effect relationship supported by biological plausibility (Levis, Minicuci et al. 2011). In view of these facts, it is recommended to take into account the source of funding in evaluation of the results.

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