BRIEF REPORT on the Gaps in the Knowledge about the Health Effects of the RF-EMF Exposures

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Note: This is not a comprehensive review of the gaps in the knowledge but it is presentation of few selected issues, considered to be of importance based on the to date executed research

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INTRODUCTION

When evaluating health risks of agents, the general notion is that, in an ideal situation, the three lines of evidence, coming from the epidemiological/human volunteer studies, from the animal studies and from the mechanistic laboratory in vitro studies, should point in the same direction. However, this is often not the case. The reasons for it might be diverse, but two of them are of most significance:

- difficulty to compare and validate different research studies, caused by the incomparable biological models and research methods,
- insufficient research in certain areas.

The insufficiency of the scientific evidence in certain areas of research, the so called gaps in the knowledge, makes it difficult to define the biological effects their consequences – the health effects.

In research on the biological and health effects of the EMF (ELF-EMF and RF-EMF) the to-date collected scientific evidence is often contradictory, with studies pointing in different, often opposite directions. In large part, responsibility for this situation lies on research funders and scientists themselves.

Research in the bioelectromagnetics arena, a relatively small arena of research in general, has been haphazard and lacking clear direction over the several decades. Research funding was provided but without clear direction of what is needed for the decision making on health effects and health hazard. Funding organizations, whether private or taxpayers, and decision making organizations did not provide clear directions for research but rather believed that, over the time, collected science will generated data-base for decision making.

This applies to the attempts of the WHO EMF Program that from time to time published list of research needs. Without the "supervision" of what will be happening in practice in labs, publication of the list of research needs alone had not much impact. Still scientists were doing whatever they wanted, in line with the academic scientific freedom, and often had "better" suggestions for needed research topics.

Lots of money were used for small studies that produced outcomes completely irrelevant for human health risk evaluation. Studies, like these executed by the US National Toxicology Program, are rarity. But just such studies were and still are needed. Studies where effects are examined using stringent rules and designed to produce results directly applicable in human health risk estimates. Instead of this there were, and are, performed studies producing bits and pieces of knowledge that are often impossible to reliably evaluate due to e.g. too small sample studied. Even the large consortia, funded by the European Union, have the same problem. These consortia were not sufficiently "supervised" in the research planning phase and scientists often drifted "off the topic" into areas that are not immediately useful for decision makers.

Dream of gathering, through this haphazard research, of a sufficiently large and validated database remained as a dream. Bioelectromagnetics is a too small and too diverse (frequency wise) scientific community to rapidly collect enough research to generate self-correcting scientific database. Database where is enough information that the errors in research are corrected by science itself. This did not happen. We have database consisting of bits and pieces… For example, the number of to date executed experimental studies on the frequencies used in wireless communication is just 1133 studies dispersed over a broad variety of experimental models and experimental procedures, frequently very small studies, insufficient to claim what is "claimed" by the authors in conclusions of their studies.

Research studies that I co-authored and research consortia that I co-participated in (e.g. EU Reflex Project) are also part-culprit in this "phenomenon" of the haphazardness of research.

Numerous bioelectromagnetics studies on a diverse variety of EMF exposures were published, lots of money was used but not so much of reliably validated science, useful for human health risk estimate, was generated.

This lack of sufficient knowledge poses, continuously, a serious problem to all users and providers of the wireless communication technology - how to reliably decide whether radiation emitted by the wireless devices is dangerous or is it not dangerous? Of course, proponents and opponents of both stances can easily point out to research studies that support their claim. But, as a whole, the evidence is still insufficient to reliably claim 'danger' or 'no danger'.

As I mentioned in my blogs and lectures over many years, we need, and urgently, **targeted research projects** that will generate scientific information, directly pertinent to human health hazard, for the use by the decision makers, the industry and the users. Projects need to be clearly defined and, somehow by someone, forced to stick to the original plans because leaving it to scientist alone will produce, yet again, haphazard data of little usefulness.

WHY THE RESEARCH SHOULD CONTINUE

The non-thermal effects = effects at low level exposures

- When discussing the possibility of biological and health effects of the radiation emitted by the wireless communication devices it is necessary to re-evaluate the meaning of the terms 'thermal' and 'non-thermal' effects. As the terms are currently used the interpretation of the data may, and does, lead to confusion.
- Exposures to the radiation emitted by the wireless communication devices is always adding energy to the biological system. This will cause temperature changes, no matter how miniscule and, potentially, biologically irrelevant for regulation of physiological processes. The better term is 'effects at low level exposures' = exposures at radiation levels permitted, or below, the current safety limits.
- Epidemiological case-control studies and studies examining sleep EEG provide compelling, though indirect evidence in humans, for the existence of the low level exposure effects (non-thermal effects). Epidemiological studies show the effects – increase in risk of developing glioma - for persons using regular cell phones that are in compliance with current safety limits. Such low level exposures should not cause any thermal effects. Thus, logically, any effects seen to be induced by the use of regular cell phone must be low level exposure effects (non-thermal effects). Similar indirect evidence is provided by the studies examining sleep EEG and using exposure levels similar to those of regular cell phones. Sleep EEG effects occur at the levels of exposure that, according to the current safety limits, should not cause any significant biological effect due to temperature elevation. Thus, again, logically, any effects seen to be induced by the exposures at the radiation levels similar to those emitted by regular cell phone must be low level exposure effects (non-thermal effects).
- Evidence coming out of epidemiological studies and sleep EEG studies is the most compelling, though indirect, of the existence of biological and health effects induced at low level exposures (non-

thermal effects).The evidence from epidemiological studies and from sleep EEG studies was reliably replicated.

- There is also large body of evidence provided by in vitro laboratory studies showing existence of low level exposure effects (non-thermal effects). There are replication problems caused by use of diverse biological models and exposure conditions, making direct comparison of results difficult and making it difficult to explain why some experiments replicate whereas others do not. However, this data is not directly applicable to human health risk evaluation.

MAJOR GAPS IN THE KNOWLEDGE

- Gene and protein expression changes in human volunteers
- Individual sensitivity
- Epidemiological studies lacking real radiation exposure data underestimate risks
- Effects on DNA
- Blood-Brain Barrier
- Skin - biological/health effects of 5G technology
- Development of standardized testing methods

<u>Gene and protein expression changes in human volunteers in response to wireless exposures</u>

- There is lack of scientific studies examining biochemical changes in human volunteers in response to radiation emitted by wireless communication devices. Only very few such studies, using human volunteers and examining a broadly understood biochemical responses, were conducted to date:
  - ✓ Brain glucose metabolism
    - 2011, Kwon MS, Vorobyev V, Kännälä S, Laine M, Rinne JO, Toivonen T, Johansson J, Teras M, Lindholm H, Alanko T, Hamalainen H. GSM mobile phone radiation suppresses brain glucose metabolism. J Cereb Blood Flow Metab 31 (12): 2293-2301
    - 2011, Volkow ND, Tomasi D, Wang GJ, Vaska P, Fowler JS, Telang F, Alexoff D, Logan J, Wong C. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. JAMA 305 (8): 808-813
  - ✓ Proteome expression changes
    - 2008, Karinen A, Heinävaara S, Nylund R, Leszczynski D. Mobile phone radiation might alter protein expression in human skin. BMC Genomics 9: 77
  - ✓ Micronuclei in buccal smears
    - 2010, Hintzsche H, Stopper H. Micronucleus frequency in buccal mucosa cells of mobile phone users. Toxicol Lett 193 (1): 124-130
    - 2008, Yadav AS, Sharma MK. Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations. Mutat Res Genet Toxicol Environ Mutagen 650 (2): 175-180
- This very short list of studies executed in human volunteers clearly indicates that we do not know at all whether low level exposures of humans to radiation emitted by wireless communication devices affects physiology of cells/tissues/organs in living human body.
- This complete lack of the knowledge whether radiation emitted by wireless communication devices elicits any biochemical responses in human body, debating the existence of health effects, or lack of them, is completely missing scientific basis.
- If radiation emitted by wireless communication devices affects, in any way, human physiology then it should be possible to demonstrate changes in gene and protein expression. Sufficient studies in this area have not been done yet. It is surprising, to the point of astonishment, that biochemical research on human volunteers was not executed as this information could either confirm or dismiss the claims of potential health effects.
- Screening biochemical responses of human body is becoming more important in the context of currently ongoing human trial of using cell phone radiation-like exposures to clinically treat patients with Alzheimer's disease. It is important to find out what the potential side effects of such therapy might be, y screening genes and proteins responding to exposures.
- **Execution of gene and protein expression studies is urgently needed and it will provide proof of whether radiation emitted by wireless communication devices has potential to significantly affect**

human physiology and, by using genome-wide and proteome-wide approaches, such research will provide a list of genes and proteins responding to exposures.

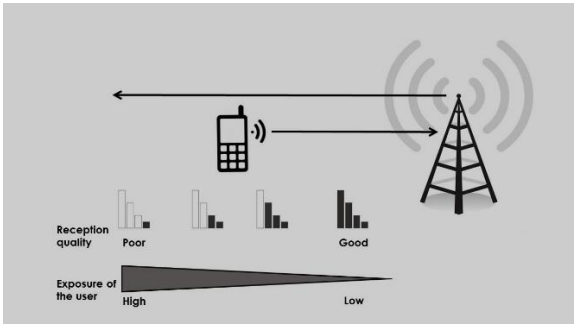
- **The information, on responding genes and proteins, will allow predictions of what physiological functions of the human body might be, potentially, affected and will provide starting point for developing evidence-based hypotheses for further studies.**

Individual sensitivity to radiation emitted by wireless communication devices

- It is commonly known that different people respond in different way to the same chemical or physical factors because of the differences caused by different genetic makeup of each individual and because of differences in epi-genetic factors each individual experiences throughout the life. This phenomenon is known as individual sensitivity. People differ in their sensitivity to radiation too. Therefore, it is plausible to consider that some people might be more sensitive than others to electromagnetic fields, including radiation emitted by the wireless communication devices.
- In the vast majority of studies executed to date persons were acutely exposed to predominantly cell phone radiation and, during or shortly after the exposure were asked to describe their feelings, including question of whether they were able to recognize when the radiation was on and when it was off. Such set up of experiments is relatively crude and biased by the potential stress of the study subject, especially when the study subject suspects that exposure is causing harm. Furthermore, such studies do not provide answers concerning chronic exposures.
- It is very likely that individual sensitivity to radiation emitted by wireless communication devices affects some part of population. The question is what the cut-off level of radiation is when the vast majority is not affected. Also, it is important to determine in what the small minority might be affected.
- Answers to these questions will not be provided by the studies asking how people feel in response to low level acute exposures. To resolve this question are necessary, the above mentioned, studies examining biochemistry of human body in response to radiation exposure. Using proteomics and transcriptomics will be possible to determine whether some people are more sensitive (individual sensitivity) and in what way.
- **There is a need for extensive human proteomics and transcriptomics and other 'omics' studies using samples taken from people exposed for different periods of time to different levels of radiation emitted by wireless communication devices. This approach will allow to find out what is the size of human sub-population that is more sensitive than the general population and to what levels and periods of exposure.**

Epidemiological studies lacking real radiation exposure data underestimate risks

- Epidemiological studies are commonly considered as the most important evidence for evaluation human health risk.
- Three replicates of case-control studies (Interphone, Hardell, CERENAT) indicate that avid use of cell phone (ca. 30min/day for 10 years) increases risk of developing glioma by 40-170%.
- The cohort studies (Danish Cohort, Million Women study) did not find increased risk of developing glioma.
- All epidemiology studies have completely unreliable exposure data
    - Length of calls or length of phone subscription with service provider or saying whether you ever or never used cell phone, does not inform about the real exposure of the cell phone user.
    - Using the above "exposure data", persons with very different radiation exposures are placed in the same exposed group for statistical evaluation.
    - This leads to underestimation of the cancer risk in all epidemiology studies
    - The problem will continue because the ongoing cohort study COSMOS collects exposure data as length of calls



- Length of call does not say "much" about radiation exposure as seen in the graph below – two persons speaking for the same length of time but speaking in different locations may have very different radiation exposures but in all to date executed epidemiology studies these persons will be analyzed in the same length exposed group.
- This kind of surrogate information about exposures, that has nearly nothing to do with real life radiation exposure, will cause underestimation of the health risk. We do not know how large is such underestimation

- **There is an urgent need to develop smart phone apps that will measure exposure of user to cell phone, cell tower and wi-fi radiation. Such apps are already available and should be tested for their accuracy and usefulness in epidemiological studies.**
- **Exposure information gathered by the smart phone apps can be continuously collected for every user and stored for use in epidemiological studies.**

Effects on DNA

Publication of the partial results of the US NTP study, examining GSM and CDMA exposures effects on rats and mice, fueled debate on genotoxicity of mobile phone radiation.

- NTP study observed DNA "damage" as determined by the comet assay. However, detection of the acute DNA damage by comet assay does not automatically mean that the GSM or CDMA radiation is genotoxic
- In all living cells DNA damage occurs spontaneously and is efficiently repaired.
- Before concluding that DNA damage observed in NTP study, or earlier in research of Henry Lai, experiments need to show what the fate of the damaged DNA is.
  - Is the DNA damaged by radiation exposures are radiation exposures impairing process of repair of DNA?
  - Is DNA damage repaired or does it persist in further generations of cells? Considering the efficiency of DNA repair mechanisms in cells, claims that mobile phone radiation is genotoxic, are not proven yet.
  - We do not know if mobile phone radiation exposure associated DNA damage leads to genotoxicity and mutagenicity or whether it is repaired.
  - What is the role, if any, of the oxidative response induced by the radiation exposure in generation of the DNA damage?
- **The research needs in respect to DNA are of importance because the findings will ether support or contradict the notion of carcinogenicity of the radiation emitted by the wireless communication devices and will provide evidence for or against genotoxicity of this radiation**
  - **Does DNA damage occur in human body exposed to radiation emitted by the wireless communication devices?**
  - **Is damage of DNA caused by radiation exposure or is radiation exposure impairing repair of spontaneously damaged DNA?**
  - **If DNA damage is detected - what is the fate of the damaged DNA, will it be repaired or not?**
  - **If DNA damage occurs, are inhibitors of oxidative stress able to prevent it?**

Blood-Brain Barrier (BBB)

- The possibility of induction of leakage of the blood-brain barrier by exposures to cell phone radiation may have two fold implications. It could impair the physiology of the brain and it could be used as a non-invasive method of drug delivery to the brain.

- There is a large number of studies that addressed the issue of RF-EMF exposures and BBB leakage.
- Several studies stand out, showing contradicting results:
  - ✓ Series of research studies from Salford & Persson research team showing leakage of the BBB
    - Nittby et al. Pathophysiology. 2009, 16:103-112; Nittby et al. Bioelectromagnetics. 2008, 29:219-232; Belyaev et al. Bioelectromagnetics. 2006, 27:295-306; Salford et al. Microsc Res Tech. 1994, 27:535-542
  - ✓ Research study form US Air Force lab showing lack of effect on BBB
    - McQuade et al. Radiation Res. 2009, 171:615-621
  - ✓ Recent research from China and from Turkey suggests leakage of BBB
    - Tang et al. Brain Res. 2015, 1601:92-101; Sirava & Seyhan. J. Chem. Neuroanatomy 2016, 75(Pt B):123-127
  - ✓ Possible mechanism for BBB leakage suggested by Chinese team that agrees with mechanism suggested by in vitro research from Finland – stress response in endothelium
    - Tang et al. Brain Res. 2015, 1601:92-101
      - Increased expression of mkp-1; De-phosphorylation of ERK; Activation of mkp1/ERK pathway
    - Leszczynski et al. Differentiation 70, 2002, 120-129
      - Phosphorylation of Hsp27; Phosphorylation of p38MAPK; Activation of the p38MAPK/Hsp27 pathway; Weakening of cell-cell contact; Cell shrinking; Non-apoptotic cell 'blebbing'; Generation of growth factors

Skin and 5G

- Lack of science on human response to radiation spectrum of 6 GHz – 100 GHz that will be used in the 5G technology (millimeter waves)
- Above 6 GHz the energy of radiation will be deposited solely in the skin; other human tissues and organs will not be directly affected by the exposures. However, because skin forms the largest organ of human body that is involved in regulation of the immune response, it is of paramount importance to determine if depositing 5G energy in the skin will have any impact on this vital function
- There is only a single study examining biochemical response of the skin of human volunteers (protein expression) to GSM exposure. There are no studies on spectrum of 5G technology
- The research on biological effects of millimeter waves is scarce and very haphazard. There are only less than 200 studies and majority of them is useless for human health risk estimation.
- **Apart of human volunteer studies it is important to perform NTP-like study, a standardized animal toxicology study, to examine effects of 5G on mice and rats. Even though the radiation will be absorbed in skin only, there might be indirect effects, by factors produced by the skin cells, on internal organs, including brain function, and standardized toxicology is needed to resolve this issue, especially at high exposure levels and long periods.**
- **Because radiation emitted by the 5G wireless communication devices will be absorbed solely by the skin, there is need to launch comprehensive examination of the possible effects using both, skin obtained from exposed human volunteers as well as artificial human skin models. Experiments need to evaluate physiological, structural and biochemical changes (including high-throughput screening of proteins and gene transcripts) in human skin and skin models exposed for prolonged time to 5G radiation.**

Development of standardized testing methods

- Use of a broad variety of biological models and very diverse exposure protocols results in problems of comparing results obtained in different studies. Standardization of the experimental protocols is much needed. The advantages of standardization would be two-fold:
  - ✓ **Easing comparison of results obtained in different laboratories** when the experiments will be performed, among others, using the same biological models and the same exposure protocols;

- ✓ **Determining whether new radiation frequencies and modulation will, or will not, induce biological effects and how these differ from those induced in earlier exposure conditions**. Idea of developing such fast screening test was presented at the WHO conference in Helsinki. However, this far, it did not 'take off', predominantly because the approach involved use of high-throughput screening techniques - *omics*.
    - 2006, Leszczynski & Meltz. Questions and answers concerning applicability of proteomics and transcriptomics in EMF research. Proteomics 6(17):4674-7