Full Statement
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"The Health Effects of Cell Phone Use"

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Brief biographical sketch

My name is Dariusz Leszczynski and I am Research Professor at the Radiation and Nuclear Safety Authority, Helsinki, Finland. I am also Guangbiao Professor at the Zhejiang University School of Medicine in Hangzhou, China and Adjunct Professor of Biochemistry at the University of Helsinki in Finland. I have received M.Sc. (1978) and D.Sc. (1983) form the Jagiellonian University in Krakow, Poland and Ph.D. (1990) from the Helsinki University in Finland. I spent two sabbatical periods in the USA: 1990-91 as a Visiting Scientist at Georgetown University in Washington, DC and 1997-99 as a Visiting Assistant Professor at Harvard University in Boston, MA. I study the biological effects of mobile phone radiation using high-throughput screening techniques (HTST) of proteomics to identify the radiation-affected proteins. In 2005 I organized and conveyed the first ever scientific session on the topic of "Genomics, Transcriptomics and Proteomics" at the bioelectromagnetics meeting held in Rhodes, Greece. Since then, I have lectured on this topic around the world (Europe, USA, India, Japan, China, South Korea, Australia, and South Africa). I have co-organized and co-chaired two World Health Organization's (WHO) workshops and several other conferences around the world. I was an invited expert in the revision of the WHO Research Agenda on mobile phones in 2003 and 2006. I am a member of the Steering Committee of the Swiss National Science Foundation programme on non-ionizing radiation and the Management Committee of the European Cooperation in the Field of Scientific and Technical Research Action BM0704 "Emerging EMF (Electromagnetic Fields) Technologies and Health Risk Management". Within this Action I am chairing the Task Group on use of high-throughput screening techniques in mobile phone research. I was the Co-Chair of the Technical Program Committee for the joint meeting of the Bioelectromagnetics Society (BEMS) and European BioElectromagnetics Association (EBEA) - BioEM 2009, Davos, Switzerland, which is the largest gathering of bioelectromagnetics scientists. I am also the Co-Chair of the Technical Program Committee for the forthcoming 2010 Annual Meeting of BEMS in Seoul, South Korea. In 2006 - 2009 I was the member of the Board of Directors of the Bioelectromagnetics Society and in 2009 I received Leadership Award from the Bioelectromagnetics Society and the European BioElectromagnetics Association. I am an Associate Editor of the journal Bioelectromagnetics. I am reviewer of research grants in the field of bioelectromagnetics for various organizations in the United Kingdom, Holland, Switzerland, Austria, China and South Africa. I co-authored over 90 publications. I comment on current issues in bioelectromagnetics in my Science Blog: http://betweenrockandhardplace.wordpress.com/.

My research in the field of biological effects of mobile phone radiation

I and my research group have worked in the field of biological and health effects of mobile phone radiation for the past 10 years. The main focus of our research has been and is determining whether mobile phone radiation, at levels permitted by the current safety standards, induces biological effects. Proving or disproving this is of paramount importance because if this radiation can not induce biological effects then it can not cause any health effects either. On the other hand, the induction of biological effects does not automatically mean that these will cause a health hazard. Our research consists of both, laboratory experiments and as experiments on human volunteers.

The early sign of a living cell reaction to an external stress factor (e.g. chemicals, radiation, heat, etc.) is activation of stress response designed to protect cells from the damage to its vital functions. Activation of stress response by mobile phone radiation suggests that mobile phone radiation is recognized by the cells as a stress factor that might interfere with normal cellular physiology. Our published research suggests that mobile phone radiation might activate cellular stress response in human endothelial cells, cells that are lining blood vessels (1,2). Though, our yet unpublished research suggests that the activation of stress response depends much on the conditions of the experiment. Based on our observations we presented hypothesis that the activation of stress response in endothelial cells lining blood vessels in brain might impair function of blood-brain barrier. This barrier, consisting among others of endothelial cells, selectively regulates passage of molecules from blood stream to the brain. Impairment of function of blood-brain barrier might allow passage of such molecules, present in blood stream, that might be damaging for the brain cells. The issue of mobile phone radiation effect on blood-brain barrier is still unresolved, with several animal studies suggesting existence of an effect and several animal studies suggesting the lack of it.

The other part of my group's research is that we suggested that using high-throughput screening techniques of transcriptomics[1] and proteomics[2] could be used to identify potential molecular targets of mobile phone radiation. This so called "discovery science" approach seems to be particularly suited for elucidation of potential mobile phone radiation-associated health hazard issue because it might reveal effects that are not possible to predict based on the present knowledge of the biological effects of mobile phone radiation. Using high-throughput screening techniques of transcriptomics and proteomics we have shown that mobile phone radiation might alter gene expression and expression and activity of proteins. The number of affected genes and proteins appeared to be small and the confirmation of the impact of these changes on human physiology requires further studies (3,4,5). The changes in gene and protein expression appeared to be dependent on the genetic makeup of the cells. Furthermore, changes in protein expression that were induced by mobile phone radiation appeared to be induced not only in human cells grown in laboratory but also in the skin of human volunteers, as preliminarily suggested by our pilot study (6).

In summary, the basic finding of my group's research is that it appears that mobile phone radiation induces biological response in human cells and these responses might alter cell physiology. However, these findings do not yet prove that there exists health hazard. Further laboratory studies and studies using human volunteers are necessary to clarify this issue.

RELIABILITY OF THE SCIENTIFIC EVIDENCE

There is continuously ongoing controversy whether the users of mobile phones should be concerned about the health safety of the radiation (radiofrequency-modulated electromagnetic fields) emitted by these devices (7,8,9). The International Committee of Electromagnetic Safety (ICES) of the Institute of Electrical and Electronics Engineers (IEEE), the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the World Health Organization (WHO) Electromagnetic Fields (EMF) Project are assuring users that there is no proven health risk and that the current safety limits, on the radiation emitted by mobile phones, protect us all (10,11,12). However, based on the available scientific evidence, the situation might be not that clear.

1 transcriptomics examines in broad sense expression and activity of genes

2 proteomics examines in broad sense expression, structure and activity of proteins

When evaluating the possible health effects of mobile phone radiation, as with any other environmental factor, no matter naturally occurring or man-made, there are needed several types of scientific evidence such as (i) the possible mechanism how the effect is induced in living organism, (ii) *in vitro* laboratory studies that confirm the existence of the biophysical and biochemical mechanism of the effect, (iii) animal studies, including long term effects and toxicology, (iv) human volunteer studies, and (v) epidemiological evidence of the effect on human population at large.

Each type of the evidence is of different significance and value for the estimation and proof of human health effect. It is considered that the most important evidence is provided by epidemiology, followed by human volunteer studies and animal experiments. *In vitro* laboratory evidence does not directly inform about the possible health impact of any tested factor but it provides information about the possible cellular-level mechanism of the effect and it helps to understand whether the hypothesized biophysical mechanism of the effect is plausible. Knowing the mechanism of the effect increases reliability of human, animal as well as *in vitro* evidence. In the ideal situation, all five types of evidence point into the same direction. This is, however, not always the case. For example electromagnetic fields emitted by the power-lines were classified by International Agency for Research on Cancer (IARC) as a possible carcinogen (category 2B) based only on the epidemiology and there is no clearly supporting evidence for such effects from the animal and *in vitro* studies (13).

In case of the electromagnetic radiation emitted by the mobile phones the scientific evidence is contradictory. In each area of investigation (epidemiology, human volunteers, animal studies, laboratory *in vitro* experiments and biophysical mechanisms) there are both positive and negative studies and by the sheer numbers, the negative studies outweigh the positive ones. This is commonly referred as the “weight of the evidence” that is pointing out to the no-effect-conclusion because the outcome of the majority of published research studies is negative. This argument is used, and often abused, to support the notion that there are no proven effects on health below the present safety standard limits (10,11,12).

So far, the vast majority of the research examining the biological effects of mobile phone radiation has focused on the possibility of induction of genotoxic effects, cancer or impairments in embryonic development. At the same time, the discussion continues on whether mobile phone radiation could cause effects that, although not able to develop into life-threatening disease, could become detrimental to the quality of life. These non-life-threatening effects might include such ailments as e.g. sleep disorders, headaches or allergy-like symptoms. Furthermore, the vast majority of the presently conducted epidemiological, animal, and *in vitro* studies focus on the possibility of induction of cancer. Therefore, independently of their outcome, these studies will provide information only about the cancer and will be unable to neither give mobile phone radiation “a clean bill of health” or to reliably show whether mobile phone radiation exposure can be associated with any non-cancer health risk.

Epidemiological evidence

Epidemiological studies are considered as the most important in evaluation of human health risk. However, due to their low sensitivity in detecting health effects within the population, epidemiology is unlikely to be able to conclusively determine whether weak stimulus, such as mobile phone radiation, causes cancer. There are numerous biases involved in estimation of the health risk by epidemiology, such as: selection bias, misclassification bias, recall bias, and the effect of the developing disease on mobile phone use. Furthermore, there are methodological considerations in epidemiological studies that are unsolved at the moment, such as: no evidence based exposure metric, low duration of mobile phone use, and no evidence-based selection of end-points for epidemiological studies (14).

Further complication with the epidemiological evidence, used to examine the possibility of the increased incidence in brain cancer within the population due to mobile phone radiation exposure, is the long latency period (over 10 years) between the induction and possible diagnosis of brain cancer. Therefore, not surprisingly, majority of the to date executed epidemiological studies, covering at the longest the period of the first 10-years after the start of use of mobile phone, can not be expected to show link between brain cancer and mobile phone radiation, even if it would exist, because of the length of tumor latency period.

Great hopes for finding out the answers whether there is a link between brain cancer and mobile phone radiation exposure were with the European Union 5th Framework Programme-funded "INTERPHONE Project" (15). This project is a multinational case-control study that was set-up to investigate whether mobile phone radiation increases the risk of cancer and whether it is carcinogenic. The study focused on tumors development in brain and head tissues that are the most exposed to mobile phone radiation and can generate glioma, meningioma, acoustic neurinoma and partoid gland tumors. The study was conducted in 13 countries: Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the United Kingdom (divided in South and North). The hallmark of this project was supposed to be the common core protocol that would allow to pool the data obtained in all 13 countries and to perform one statistical analysis that would consist of sufficient numbers of cases and controls to be meaningful and informative (15). However, as it appears there were numerous exceptions from the common core protocol (Table 1) that put in doubt the reliability and to some extent the validity of the yet unpublished pooled-analysis.

Of particular concern are the differences in protocols between different INTERPHONE research groups that may lead to increased uncertainty of the exposure doses among the study subjects presented in Table below; "Areas of concern"-column.

Elements of common protocol	Exceptions of common protocol	Countries without (non-shaded boxes) and with exceptions (shaded boxes)	Comments	Areas of concern
Source population	major metropolitan areas	Australia, Canada, France, Germany, Italy, Japan, New Zealand	? differences in way of living in metropolitan, urban (small town) and rural areas ? strength of exposure differs between metropolitan, urban (small town) and rural areas	exposure dose
	nationwide	**Denmark, Finland, Israel, Norway, Sweden**		
	urban and rural	**UK-South, UK-North**		
Case eligibility	histology & diagnostic imaging	Canada, Denmark, France, Israel, Italy, New Zealand, Norway, Sweden, UK	? possible source for case misclassification	case assignment
	histology by confirmed only	**Australia, Germany**		
Monitoring ascertainment	interviews + secondary source	Australia, Canada, Denmark, France, Germany, Israel, Italy, New Zealand, Norway, Sweden, UK	? possible source for case misclassification	case assignment
	secondary source not used	**Finland, Japan**		
Collection of information	computer assisted personal interview (CAPI)	Australia, Canada, Denmark, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK	? possible source of bias - variability in responses to the same questions by persons with different social, economic and cultural background	social, economic and cultural background & "data manipulation"
	deceased subject - proxy respondent interview with full CAPI questionnaire	Canada, Denmark, France, Germany, Israel, Italy, Japan, Norway, Sweden, UK	? possible source of bias - not clear for unwanted "data manipulation"	
	deceased subject - proxy respondent interview with abbreviated CAPI questionnaire	**Australia, New Zealand**	? protocol does not describe how the inconsistencies were "corrected"	
	paper version of questionnaire	**Finland**		
History of mobile phone use	regular mobile phone user	Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK	? regular user definition by Interphone – at least 1 call per week for a period of at least 6 months; (this is rather occassional user !!)	exposure dose
Socio-economic status	country specific questions	Australia, Canada, Denmark, Finland, France, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK	? important bias source when comparing populations with different cultural and economic background	social, economic and cultural background
	algorithm	**Germany**		
Assessment of exposure	from history		? information reported by regular users - possible source of recall bias,	exposure dose
	absorbed RF energy		? model to estimate exposure - possible bias due to variety of mobile phone technologies available in all 13 Interphone countries	exposure dose
	missing data		? missing data was "created" based on the data of the adjacent periods - possible source of bias by "data manipulation"	"data manipulation"

Furthermore, the definition of the *regular user* is another major problem of the INTERPHONE protocol. A person who makes at least one phone call per week for the period of at least 6 months is defined as a *regular user*. This means that a person who makes 24-25 calls over 6 months period (one call per week) is put into the same category with a *regular user* who makes 24-25 calls per day - as e.g. many business people do. This means that the category of *regular users* consists of those who are only very little exposed to mobile phone radiation but also of those who are very heavily exposed. It means that, if we assume that the heavy exposure to mobile phone radiation could cause any health effects, then these effects will be down-graded by analyzing in the same group of very low- and very high-exposed study subjects. Therefore, the INTERPHONE's definition of "*regular user*" mixes "*heavy users*" with "*occasional users*". Therefore, considering the definition of "*regular user*" that might dilute the effect, it is somewhat surprising that there are INTERPHONE studies suggesting the increase in brain cancer among the long-term "*regular users*" (>10 years) (16,17). These results are still statistically uncertain and might either be showing a real link or might be just a statistical "glitch" due to small sample numbers. However, these results were obtained using definition of "*regular user*" as specified above - meaning that any effects induced by mobile phone radiation were, most likely, substantially "diluted" by the presence of very low exposed users among the so-called "*regular users*".

The results of the pooled analysis of the INTERPHONE results are still unpublished due to lack of consensus in interpretation of the results of all 13 national projects. The release of the final results is already delayed for several years (since 2006) due to the disagreements over the conclusions among the different research groups. *Summa summarum*, it appears that we have to wait for many years for the more reliable answers from epidemiologists. Therefore, the presently available epidemiological evidence has very limited usefulness for setting of human safety standards and for convincingly justifying them.

In my opinion epidemiological evidence is not sufficiently reliable to conclude that human health either is or is not at risk. I think that at this time any statement suggesting that there "is a health risk" or that there "is no health risk", based on the epidemiological evidence, is premature and not reliably supported by the available scientific evidence. However, even though the data are of insufficient quality to draw reliable conclusions, the existence of data suggesting the possibility of increased risk of brain cancer is, in my opinion, sufficient to advice precaution and to request further research to clarify this issue.

The epidemiological case-control studies so far have failed to provide reliable evidence. The new, currently ongoing European cohort study (COSMOS project) is again expected to provide more reliable answers than those of the INTERPHONE project. However, some scientists doubt it because we are dealing with a very weak stimulus and epidemiological approaches might have too low sensitivity to reliably detect small changes in the vast population of mobile phone users. Epidemiological studies are certainly needed but we should in parallel focus on human volunteer studies, using different sub-populations of mobile phone users. Such studies could determine whether mobile phone radiation has any significant effect on normal human physiology. This area has not been studied sufficiently so far.

Non-epidemiological human studies

The human volunteer studies have focused on mobile phone radiation effects on e.g. cognition, blood pressure, headaches, skin allergy-like symptoms, sleep disorders or direct recognition, by the exposed subject, whether mobile phone is on or off (18). In these studies the volunteers are not aware when they are exposed to mobile phone radiation and when not. One major set back of these studies, however, is that the experimental conditions and the exposure and measurement equipment may psychologically affect behavior of the volunteers during the experiments and the obtained information might become subjective and unreliable (18). There is only a single study which provides objective information - without asking the study subjects how/what they feel during the exposure. In this study effects of mobile phone radiation on human skin were examined at the molecular level (6). The outcome of this study suggests that it might be possible that mobile phone radiation alters expression of some proteins in human skin. This single available study has obvious limitations as well as advantages. The main limitation is that, because of the shortage of funding, only pilot study using 10 volunteers was possible to execute. The most obvious advantage of this study is that it has used proteomics approach - simultaneous screening of the expression of hundreds of proteins and, this way, it has shown that mobile phone radiation might affect physiology of human tissue in vivo.

It is certain that just such human volunteer studies, using methods of proteomics, transcriptomics and other biochemical analyses, are urgently needed to demonstrate whether human body (tissues, organs) responds, or not, to mobile phone radiation. Such studies will provide information as to which proteins and genes react to mobile phone radiation exposure. With this information it will be possible to formulate new, knowledge-based, hypotheses for health risk studies in humans (2,19).

To this time, we do not have available objective information whether human body recognizes mobile phone radiation (at levels permitted by the current safety standards) as an external stressor and responds to it at molecular level. Such responses are prerequisite for any physiological/health-related responses. Therefore, because of the lack of studies that would provide unbiased information whether the human body responds to mobile phone radiation, it is problematic to consider that the presently available scientific evidence and based on it current safety standards protect all users of mobile phones.

The effects of mobile phone radiation on children and recommendations of prudent use of mobile phones by children are one of the hottest topics in the discussion of the safety of mobile phones (7,8,9,20). According to ICNIRP and WHO EMF-Project, the present safety limits protect children: "...in the opinion of ICNIRP, there is neither need nor any justification for a specific approach to the protection of children or other special groups of the population." (21). However, the scientific basis of such assuring statements seems insufficient. There are no published studies where the effects of mobile phone radiation on development or health of children would have been examined, as revealed by search in the specialized EMF-Portal database (www.emf-portal.de). The scientific basis for such statement comes from the studies examining newborn or young animals. Such data, obtained with young mice or rats at low dose mobile phone radiation, is not sufficient to reliably assure that human children will not be affected.

In the spring of 2008, the European Union 7th Framework Programme for funding research had a specific call for research projects that would examine effects of mobile phone radiation on children. However, results of this research (epidemiological project MOBIKIDS) will not be ready for several years to come.

The presently used safety standards may very well protect the majority of mobile phone users. However, there likely exists a sub-population of people with different sensitivity to mobile phone radiation (not to confuse with the self-diagnosed so-called Electromagnetic Hyper Sensitivity - EHS). It is known that due to genetic variability among people, the same stimuli (medication, radiation, chemicals, allergens, environmental factors) may elicit responses of differing severity in different people (22). Finding out such sensitive subpopulation and defining it might be possible using the proteomics and transcriptomics (19). However, such studies are missing and, to my knowledge, no such studies are ongoing or planned or have received funding.

Animal studies

Another large group of studies used to determine human health risk are animal experiments. Especially the toxicology studies are of interest for establishing of human health risk and for setting human safety standards. In *sensu stricto* toxicology studies, animals are exposed to a large overdose of tested chemical, which would not be normally encountered by human being in real situation, and examined for any detrimental effects.

However, such toxicology studies are not possible to perform for mobile phone radiation (microwaves). Large overdose of this "agent" will heat animal and in extreme cases might simply "cook it". Thus, the so far performed and, so-called by the authors, "toxicology" studies are not exactly what they are claimed to be. These are studies where animals were exposed for different periods of time to levels of mobile phone radiation similar to those that are permitted by the human safety standards, and that do not cause heating of the animal. Thus, the usefulness of such studies to estimate human health risk, as compared with the *sensu stricto* toxicology is limited. What remains are studies where animals are long-term exposed to similar doses of mobile phone radiation as humans using mobile phones. However, direct extrapolating results of such long-term animal studies, performed at low doses of mobile phone radiation, to human health risk is almost impossible. It is known that although humans and animals possess many of the same genes, the functions of the same genes might differ and some of the same cancer types will be regulated by different genes in animals and in humans. This causes that some of the cancers that will appear in animal will not appear in humans and vice-versa (23). Thus, the animal "toxicology" studies seem to be of limited use for safety standards setting because they are not *sensu stricto* toxicology.

Laboratory *in vitro* studies

The majority of research on the biological effects of mobile phone radiation has been done in laboratory *in vitro* studies and the vast majority of the conducted research has focused on cancer. Some of the *in vitro* studies suggest, although do not prove, that mobile phone radiation might alter cell physiology e.g. by triggering cellular stress response, causing DNA damage, altering gene and protein expression (7,8,9). However, there are also studies that do not indicate such effects (7,8,9). One of the reasons for such discrepancy might be, as postulated in some studies, that the transcriptome- and proteome-dependency of the cell response to mobile phone radiation. It means that genes and proteins expressed (=active) at the time of exposure to mobile phone radiation might play a decisive role in the induction of the effects (4,5). Laboratory *in vitro* studies are of great value for discovering the biochemical mechanism of the effect. They provide support for human and animal studies, but can not be directly used in setting of human health safety standard.

Mechanisms: thermal vs. non-thermal effects of mobile phone radiation

In 1998, ICNIRP published the "Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300 GHz)." (11). In these guidelines, any biological effects of mobile phone radiation induced by temperature rise of up to 1 ^{o}C were considered as harmless and this approach became the basis for setting the safety standard that is still in force. At the same time the research field of non-thermal (athermal) effects was described as confusing, as stated in the ICNIRP guidelines: "*…Overall, the literature on athermal effects of AM electromagnetic fields is so complex, the validity of reported effects so poorly established, and the relevance of the effects to human health is so uncertain, that it is impossible to use this body of information as a basis for setting limits on human*

exposure to these fields.”.

According to the committees setting safety standard (ICES & ICNIRP) such small temperature increases of 0.1 - 0.3 ^{o}C induced by the mobile phone radiation exposure are meaningless when considering human health risk. The fact that the human body's temperature is in the morning ca. 1 ^{o}C lower than in the evening is commonly presented as a supportive piece of evidence. This is seen to suggest that the increase of the body temperature by up to 1 ^{o}C can not be hazardous to health because it is within the normal physiological range. However, entirely another question is if small temperature increases induced by mobile phone radiation could be meaningful, from the point of view of the potential induction of biological effects? And yes, the temperature increases are small but do we know enough about their nature and kinetics to be convinced that they are unimportant for the physiology of e.g. brain? I think that the issue might not be so simple. There are two "problems" to consider.

Firstly, the temperature of human body indeed rises over the course of the day by up to 1 ^{o}C and the process is harmless. However, this process can not be directly compared with the local temperature increases caused by the mobile phone radiation. Such comparisons are omitting the time-scale of the event, its location and the involved physiological factors. To increase the temperature of the whole body it takes time (even hours). The process is preceded and accompanied by the production of humoral mediators that inform tissues and organs that the temperature increase is happening and cells have time to prepare protective responses. However, in case of the mobile phone radiation, the microwaves act locally by penetrating deeply into the body tissue (e.g. brain) and the temperature increase happens "instantaneously" and without any humoral mediators' warning. The exposed brain cells are suddenly, without any warning, warmed up. This is a non-physiological event for the brain cells to which these cells have not been prepared throughout the evolutionary development. Thus, the direct comparison of the slow and uniform increase in body temperature by classical heating (e.g. sauna, hot-tube or sun-bathing) or by physiological processes (e.g. daily temperature fluctuations, physical exercises or fever) with mobile phone radiation-induced rapid and localized increase in temperature might not be justified.

Secondly, the radiation emitted by mobile phones might induce temperature hot spots within the exposed biological material, i.e. small areas where temperature might rise more than in the neighboring areas. We can detect and measure hot spots on the macro-scale but we do not have yet technology to measure whether hot spots are created on the micro-scale (sub-cellular-scale). Presently, dosimetry and modeling of the distribution and intensity of mobile phone radiation in the brain uses as a model plastic container molded in the form of half-head and filled with "physiological solution" consisting of water, salt and sugar. Such model represents human head with skull (plastic mold) and brain (water solution of salt and sugar). However, it is a great oversimplification of the reality.

Living tissues and cells are not homogenous environments but they are compartmentalized into cells and sub-cellular size volumes (organelles) that are delineated by lipid-containing hydrophobic membranes. Charged biological molecules and ions, unlike in the above mentioned "head model", are not distributed within the tissue or cell uniformly and can't travel freely. Thanks to the membranes and their selective transport mechanisms the distribution of molecules and ions in cells is non-uniform and produces electric gradients that play a paramount role in physiological functioning. Strong electromagnetic fields can disrupt the function of selective transport mechanisms of the membranes and cause profound physiological changes (e.g. electroporation).

The question to be answered is what happens when such hydrophobically compartmentalized environment is exposed to weak electromagnetic stimulus like mobile phone radiation. Will such exposure lead to formation of thermal hot spots on sub-cellular scale, because the free flow of charged molecules and ions is prevented by the selective transport mechanisms? Formation of such sub-cellular hot spots could cause changes in certain functional areas of the cell that eventually could lead to alterations in cell physiology. There have been identified the so-called temperature-sensing molecules in the cell membranes. When activated by temperature change these molecules send stress signals that may reach cell nucleus and may affect expression of genes and, as a consequence, alter cell physiology. However, we still do not know whether the activation of cellular stress response, observed in some studies, is caused by the activation of temperature sensing molecules in cell membrane by the mobile phone radiation or some another event.

In my opinion, it is possible to expect that the mobile phone radiation might affect cells by the combination of thermal and non-thermal (if they exist) mechanisms. Thermal effects, induced by mobile phone radiation, should not be automatically regarded as unimportant in context of health risk evaluation because their occurrence and kinetics are different from the harmless physiological warming up of the body. Unfortunately, the presently available technologies do not yet permit to measure temperature or mobile phone radiation distribution on sub-cellular scale. On the macro-scale of groups of thousands of cells, that are presently measurable, such sub-cellular hot spots would not be detectable.

From the point of view of the safety of mobile phone users, the issue of induction of biological (and possibly health) effects by thermal or non-thermal mechanisms should be put to rest. Continuous talk of the harmlessness of thermal effects induced by temperature rise up to 1 ^{o}C and the continuous dispute whether non-thermal effects exist is misdirecting science and is taking attention from the important issue - if there are any effects induced by mobile phone radiation at levels permitted by the present safety standards that can alter normal physiology.

Negative vs. positive studies and the "weight of evidence" issue

It is not only my personal observation that the negative studies seem to be accepted as such, without too much scrutiny, whereas the positive studies are examined in every detail to determine why the result is positive. Hence, the positive studies are not treated equally with the negative ones, even though also the negative studies might include erroneous results or interpretations. Moreover, only the positive studies are demanded to be replicated before they can be accepted as valid scientific evidence.

This replication requirement is of course the correct approach, but it should be applied, at least to some degree, also to negative studies. At least the negative studies that are considered as providing the crucial evidence of no-effect should be replicated. An error in study design, execution, data analysis or interpretation might lead not only to positive but also to negative result. Furthermore, many of the positive studies are not even being attempted to be replicated and of course negative studies are not replicated at all. However, if the replication of the positive study is attempted then, commonly, the protocol of the replication study has so many modifications, introduced to improve the quality. That causes that the outcome of such "replication" study is difficult, if not impossible, to compare with the original one. As often happens, the outcome of the so-called replication study differs from that of the original study. However, the failed replication might be either because of incorrect (unreliable) result of the original study or because of the modifications introduced in replication study. Usually, this question remains unanswered but the final result is often claimed to be: in summary, the original study has not been replicated (= is not valid evidence).

Another important issue that comes up when analyzing positive and negative studies is the "weight of evidence". To me this term is often abused by those who wish to disregard scientific studies showing that mobile phone radiation can induce biological effects. We continuously hear that there were done thousands of studies on mobile phone radiation. However, this number is grossly exaggerated because it refers to research at all microwave-frequencies. For example the applicability of the results obtained using radiation frequency of microwave ovens might not necessarily be directly applicable to the mobile phone-emitted microwaves. There is still ongoing discussion whether it is possible to transpose results of experiments done with one frequency of microwaves to other frequencies. To me, in order to be relevant, the studies should be performed using actually mobile-phone-emitted microwaves. The number of such studies, which were done using mobile phone-emitted microwaves, is available from the EMF-Portal database (http://www.emf-portal.de/) that is maintained by the Research Center for Bioelectromagnetic Interaction at the University Hospital of the Aachen University in Germany. This specialized database lists as of September 8th, 2009, total of 631 studies that explicitly investigated the biological and health effects of mobile phone-related microwave frequencies. Therefore, in my opinion, the number of the executed studies is not sufficiently large to create reliable basis for any conclusive statements about the existence or the absence of the health risk associated with the use of mobile phone. These 631 studies include studies that do not show any biological effects of mobile phone radiation but also studies that show induction of such effects. However, because the majority of the published studies show no effect, it is commonly suggested that this "weight of evidence" supports the notion that there are no biological effects and no health risk.

In this context, the newly designed, and about to start in the USA, large animal study is considered by some scientists as unlikely to have impact on science concerning mobile phone effects because of the "weight of evidence" provided by the earlier published studies. In short it means that, even well designed, well executed state-of-the-art study with best available radiation exposure dosimetry, might not be sufficient to cause any change in thinking about mobile phone radiation effects. The reason is that the earlier published studies, of which many were poorly designed or executed or had poor dosimetry design, provide "weight of evidence" against any effects. Single well done study is not enough to provide sufficient proof but also a large number of scientifically weaker studies should not be outweighing it.

Conclusions on the reliability of scientific evidence

In the present situation of the scientific uncertainty, the statements assuring that there are not proven health effects and, because of it, the use of mobile phones is safe are premature. In my opinion the current safety standards are not reliable in the context of the lack of studies on human volunteers, children and on effects of long-term exposures in humans.

The purpose is not to discourage people from using the mobile phone technology. However, we should remember that we have still remaining large gaps in the knowledge of the mobile phone radiation effects on humans. We urgently need well designed comprehensive molecular level human volunteer studies to close these gaps in the knowledge. In the meantime, it is wise to support the use of precautionary measures in every day dealings with mobile phones in order to, whenever reasonably possible, limit the body exposure to mobile phone radiation.

Advisories for mobile phone users in Finland

The Finnish Radiation and Nuclear Safety Authority (STUK) is a regulatory authority, research centre and expert organisation whose mission is to protect people, society, the environment and future generations from the harmful effects of radiation (www.stuk.fi). STUK belongs to the administration of the Ministry of Social Affairs and Health in Finland.

STUK has issued two advisories for mobile phone users. The first one in 2004, as part of the Nordic countries advisory, and the second one in 2009 as STUK's own advisory focused on children using mobile phones. Both advisories mention the uncertainty of the scientific evidence that causes the need for precaution in the use of mobile phones.

Excerpt from the Common Nordic Countries View:

> "The existing knowledge gaps and the prevailing scientific uncertainty justify a certain precautionary attitude regarding the use of handsets for mobile telephony. Due to the widespread use of mobile phones even a very small risk could have consequences for public health. Because of the lack of knowledge in certain fields of research the Nordic authorities find it is wise to use, for instance, a hands-free kit that reduces the exposure to the head significantly. This information should be addressed both to adults, young people and children. It is important that parents inform young people and children about how to reduce the exposure from mobile phones."

Excerpts from the STUK advisory "Children's mobile phone use should be limited":

> "In relation to mobile phones children are given special consideration. They will have more time to use a mobile phone for a longer period of time than adults who started using mobile phones more than 10 years ago. The long-term risks from the use of mobile phones can not be assessed before the phones have been in use for several decades. Additionally, children's brains are developing up to the age of 20 years."
>
> ...
>
> "...Children's mobile phone use could be, restricted in the following ways:
>
> favoring the use of text messages rather than calls,
>
> parents limiting the number of calls and their duration,
>
> children can be advised in the use of hands-free devices, which reduces the exposure significantly. When communicating on the hands-free device the phone should be kept a couple of centimetres away from the body,
>
> talking in an area with low connectivity or in a moving car or a train should be avoided.
>
> However STUK does not deem it justified to ban children's use of mobile phones altogether. As mobile phones also promote security, since it facilitates easy communication with parents.
>
> If an adult is concerned about their own exposure, it can be reduced in the same way as mentioned above for children."

The future research needs

We need a few well-designed studies, executed by consortia of scientists, not by single research groups. These studies should be aimed at proving or disproving whether human body responds to mobile phone radiation and whether the response is of a sufficient magnitude to alter normal human physiology. In spite of years of research into human health risk of mobile phone radiation, we still do not have the answer to the fundamental question: whether human bodies (tissues, organs) react to mobile phone-emitted microwaves. If human bodies do not react to mobile phone radiation on molecular level, then there will never be any health problem. But, at present, we are still missing science to prove it. We need studies where human volunteers will be exposed to mobile phone radiation and, thereafter, examined for changes on molecular level looking at gene and protein expression and activity changes using methods of transcriptomics and proteomics. Furthermore, we need to look if there are any changes in internal organ physiology by e.g. sampling various body fluids.

The other area that needs urgent attention is the search for mechanisms of the observed biological effects. In particular, the sub-cellular level mobile phone radiation dosimetry needs to be developed to answer the question whether absorption of energy by sub-cellular structures could be a trigger mechanism for some biological effects.

Such studies should be well funded so that scientists will not need to make short-cuts in science because of the lack of funds to perform all of the needed experiments and in a sufficient number of replicates. This is often the case now and that is why so many of inadequate quality and non-informative studies have been published; and provide the distortion to the "weight of evidence". However, getting funds is a problem. Continuous

assurances from ICES, ICNIRP and WHO, that thousands of studies have been done and that mobile phone radiation does not cause any known health risk and the safety standards protect us all, have caused that the funding agencies are not interested to sponsor new projects. However, these assurances are weakened by the lack of sufficient scientific evidence to support them.

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