15 years on biomedical mobile

A story of success

by Roland Glaser

It is worthwhile to take a look back at the past 15 years of research on potential health effects of high-frequency fields in order to draw conclusions and perhaps define new tasks. However, many of the topics and hypotheses investigated over the last 15 years have been identified earlier, therefore a look at older publications is inevitable. Most problems in the meanwhile were scientifically investigated and solved as required. Yet gaps and unclarities are repeatedly pointed out, generating discussion and uncertainty in the public sphere.

Even though the research on biomedical effects of high-frequency fields has not begun with the era of mobile phones[34], the annual number of publications in international scientific journals is distinctly increasing (fig. 1). In contrast, the number of publications on effects of alternate current low-frequency fields on biological systems is decreasing after a maximum in 1998.

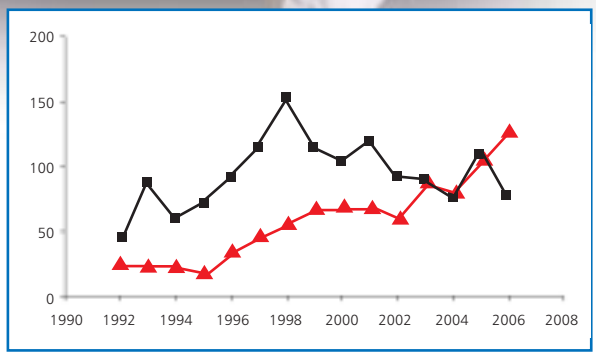

Fig. 1: Trend lines of the annual distribution of 960 publications on biological effects of EMF in the frequency range between 0.3 and 3 GHz (UHF) (red) and of 1446 investigations regarding the power frequency (50 and 60 Hz, respectively) (black) over the past 15 years.

# of research
effects of high-frequency communication fields
or an endless story?

Of course, this trend is mainly caused by the increasing relevance of the high-frequency issue as a consequence of the wide distribution of mobile phones and other forms of high-frequency data transfer. As a result, there was a corresponding reorientation of research funds.

This paper is not focused on the quantitative analysis of this situation but rather on the contents of research and the results that have become available over the past 15 years. This will be done exemplarily, related to the main trends of the development.

One specific trait of this field are the extremely high requirements to interdisciplinary competence – beginning at the proper handling of elaborate field application technology and dosimetry, knowledgeable experience in animal care and cell biology, knowledge of biomolecular aspects, and finally resulting in medical evaluation of the observed biological effects. Special knowledge is required, associated with an urgent need of interdisciplinary cooperation. Research in earlier years often suffered from the fact that biologically oriented working groups used primitive electronics, whereas groups with technical background had a naive understanding of biological concepts. Although such dubious experiments are published even to day, the faulty results of them making a huge splash, a distinct trend to high-quality multidisciplinary research has been observed over the last decades, which, increasingly, is based also on multinational cooperation.

The development of application systems and dosimetry

While there is no difference regarding biomedical analysis techniques in investigations between low-frequency and high-frequency EMF, the technical requirements are much higher regarding the RF range. Biological experiments in the GHz range require considerable technical and thus also financial expenditure, beginning with generators, via amplifiers up to defined transmission systems in a anechoic environment. It is not sufficient to place a mobile phone near a Petri dish, as, unfortunately, is done sometimes even in recent publications (e.g. 25, 79, 80, 99). Experimental data can only be taken seriously in research today, if technically accurate application conditions and a corresponding dosimetry are used.

There are several cases in the reporting period, where there was no evidence anymore for originally found biological effects in repeat studies after correction of application conditions. As an example, we should mention the investigations on the nematode *Caenor-*

habditis elegans. There was no evidence anymore of the expression of a heat shock protein (Hsp16) (termed "non-thermal") at SARs of 1 mW/kg[17] after correction of the application system[18]. The – correctly measured – effect was caused by heating of the extremely temperature-sensitive animals. Also the spectacular findings regarding tumor promotion at exposure to 900-MHz fields in transgenic mice[84] had to be revised after the method of field application had been made more precise[93].

In both cases, the working groups themselves revised their results. Unfortunately, these are exceptions. Mostly the results of one laboratory are denied by repeat studies of others. This frequently is interpreted as a case of conflicting opinions by outsiders. At best, a philosophical thesis can be "refuted". An experimental finding can raise doubts, if it is not reproducible, but it cannot be "refuted". It is only the evidence of methodological errors, as far as they can be recognized at all from the publication of results, that can explain the fruitless attempts to replicate an experimental finding and enhance the probability that the result is wrong. In spite of that – and unfortunately, there are many examples for that – faulty measurements frequently are used argumentatively by some campaigners. The neglect of methodological diligence still is a major source of false conclusions[46]. Unfounded concerns of citizens are repeatedly caused this way, intensified by corresponding press campaigns.

Accurate knowledge through the use of modern biomedical analysis techniques

Of course there is clear methodological progress not only regarding RF technology, but also concerning methods of biomedical analysis. While the former has to be seen mainly as the use of already existing technical knowledge for the development of applicators and dosimetric methods, bioelectromagnetic research directly profits from the rapid development of biomedical techniques in general.

Examples are the development of HTS technologies (High Throughput Screening Technologies), a group of methods in biomolecular analysis allowing to get a huge number of biomolecular data from smallest samples[62] in very short time. However, great diligence regarding the statistical verification of results is required here as well. Premature conclusions regarding the possible expression of stress proteins and their potential cancer risk[61] had to be withdrawn later[45, 48, 94]. Only precise knowledge about the physiological variability of these complex parameters, associated with the conduct of positive controls allow to correctly interpret possible alterations in the exposed system. The fast determination of a large amount of data alone is not sufficient.

In this context also the discussion about the experiments should be mentioned, where it was concluded that DNA damages in human fibroblasts[20] were caused by RF fields near the upper limit. The authors of this paper referred to results obtained by the so-called comet assay, an electrophoretic test routinely used for the detection of DNA strand breaks. This test, especially if the evaluation is made manually and not automatically as in these experiments, is not per se sufficient for drawing far-reaching conclusions. It also indicates aberrations in the regular cell cycle[95]. Conclusions could only be legitimized by evidence of other consequences of this process. Attempts to reproduce the results by means of an improved technique had no result[89].

The investigation of possible effects of high-frequency electromagnetic fields on the cognitive performance of humans, their reaction time, but also their sleep behavior, profited a lot from the general development of neurophysiology and its methods. On one hand, this concerns EEG measurements, but also the possibility to make blood flow alterations visible by means of Positron Resonance Tomography (PET)[51, 52]. Unfortunately, by technical reason, many of those methods can not be used during RF exposure[14]. Surprisingly, many of such investigations show unreproducible effects. In some cases, the research groups failed to reproduce their own results (e.g. Röschke[85] versus Wagner[97]; Eulitz[24, 39] versus Hamblin[40]). In contrast to the examples above mentioned however, in most cases this does not seem to be a result of technical lacks or of lacking diligence of the

experimenters, but are caused by the system behavior itself. The conclusion was that not the exposure of a mobile phone base station near by, but sometimes the fields of a mobile phone at the ear can affect the brain. This influence however, obviously depends on the physiological state of the volunteer and keeps within neurophysiological day-to-day variations. Initial allegations that such measurements would show adverse health effects[56] are untenable, though. Nevertheless the mechanisms leading to such effects should be checked. Krause et al.[58] assume that responses to a slight cortical heating were behind this effect, indicated also by local changes in blood flow, as measured by PET[51]. Obviously, the sensitivity of the system of physiological thermoreception is still underestimated[33].

The road of epidemiological research

There has been a distinct increase in the number of epidemiological studies on possible effects of mobile radio fields over the last years, which, of course, is also due to the rapidly increasing use of corresponding devices. At the same time, there is also a clear trend to concretize results and eliminate wrong decisions.

Epidemiological studies on possible health consequences of high-frequency field exposure began by observation of occupationally exposed persons, like workers for broadcasting stations, radar and flight staff, especially in the military sector. So the study of Szmigielski[92] on alleged cancer cases in the Polish military due to field exposure, which was discussed very intensely and controversially. Surveys on occupational exposure to RF fields however did not show a clear association, mainly due to the lacking dosimetry as well as the different and, in part, very strong confounders, i.e. the influence of other specific occupational agents[11, 22, 23, 55].

It was only in the nineties that studies on the possible consequences of high-frequency exposure of the population were published. For example, a possible association between child leukemia and the vicinity of radio and television towers was investigated[21, 49, 69, 70]. Rothman et al.[86] for the first time stressed the need for epidemiological investigations of a possible link between RF exposure and brain tumors, at the same time pointing out the methodological problems of this endeavor.

It was only at the end of the nineties that epidemiological research directly focused on potential effects of mobile phones. The first case-control study on a possible association with the occurrence of brain tumors probably is that of Hardell et al.[43] from 1999. In the subsequent years some other case-control studies were published, but they did not allow to draw distinct conclusions[42, 43, 54, 72, 74, 75, 100]. Moreover there were publications addressing the lack of physical well-being and other general symptoms related to living in the vicinity of mobile phone base stations[7, 76] . These studies, however, often had serious methodological flaws.

A comprehensive summary of the situation was compiled by five members of the ICNIRP Standing Committee on Epidemiology[5]. They concluded that, until 2004, epidemiological findings did not provide conclusive and convincing evidence for a causal association between exposure to high-frequency fields and any serious health damage. At the same time, possible sources of error were pointed out both regarding statistics and dosimetry. Repeatedly, there is the problem of small numbers. If only about an average of 10-15 persons out of 100,000 per year get a brain tumor, this, naturally, is not sufficient for a statistically verified survey. Another problem are the so-called “confounders“, the wealth of mostly not detected and often not detectable causes of health disturbances our modern environment is known for.

All this critique has led to a clear improvement of new epidemiological surveys, partially using the data of cancer registries[13, 59, 67, 68]. The investigations of recent years are remarkable insofar as the international cooperation led to an increase in case numbers. An example is the INTERPHONE study involving 13 countries.

Though none of the studies so far has been able to give evidence of an influence of mobile communication base stations or mobile phones on well-being or health, nearly all of these publications end by stating

that "further investigations are necessary". This may be due to the principal uncertainty of all findings, but also the concerns still existing over longterm effects, although we are better able today to identify faults and give recommendations on the type of research to be done[77, 87, 96].

Models and hypotheses on possible biophysical interaction mechanisms of high-frequency electromagnetic fields

Others already reported in depth on primary processes of high-frequency electromagnetic field effects[34]. Here, the developments of the last two decades shall be outlined and tendencies shall be made visible.

"*Hypotheses non fingo*" – (I don't invent hypotheses) Newton said, thereby pointing out the relation between experiment and theory. In EMF research, this relation is obvious: Alleged field effects repeatedly encouraged biophysicians to think about mechanisms. On the other hand, new experiments were stimulated by theoretical models. This interaction between theory and experiment results either in a spiral, asymptotically approaching the point of reality or, if objective reality does not support the theory, an endless cycle, which gradually peters out.

In the case of dielectrophoresis and electrorotation there was a spiral of success: experiment and theory led to insights that have their firm place today in biotechnology[31, 35]. These two non-thermal processes of polarization caused by high-frequency fields however require field strengths, several magnitudes above the legally prescribed limits, and therefore are without relevance for the topic of this contribution. Unfortunately, the research on lower-intensity RF fields points in the other direction at present. This may be illustrated by two examples.

The first example is connected with the "cyclotron resonance" hypothesis of A. R. Liboff, first referring to the interaction of the static magnetic field and low-frequency EMF[63], later also to low-frequency modulated RF fields. The experiments of the laboratory of Ross Adey, due to which high-frequency fields (147 MHz) affected the calcium metabolism of the brain, if they were modulated with 16 Hz[8, 10], were especially spectacular. Already in 1982 however, Merritt and Shelton[71] had denied the findings of this group as being methodologically flawed and unreproducible. The impact of modulated high-frequency fields on the calcium signaling pathway in lymphocytes postulated by Bawin and Blackman could not be reproduced[15]. The hypothesis in the meantime was shown to be unrealistic, not only in experiment, but also physically[1]. Independent of this, it became clear that low-frequency cannot be the result of a demodulation of high-frequency fields by the biological system[28]. So this approach, promoted by many publications, petered out. The Bawin publication is still sometimes cited uncritically by certain outsider groups, if them seems useful.

The second example relates to the theory of coherent excitation of H. Fröhlich, to whom a special symposium was devoted in 1982 in Bad Neuenahr.[30] This theory and their predicted sharp resonance windows in the GHz range could neither be verified in experiment nor theoretically[36, 37], despite initial experimental evidence[38].

Related to these concepts are also the tests of T. Litovitz, who postulated a „coherence time", a short time that was needed to adapt the low-frequency coherence at HF-modulations in the biological system[66]. He still insisted on his concept of the impact of low-frequency window effects[73, 81] on ornithine decarboxylase (ODC), even after all attempts of other laboratories to reproduce this had failed [e.g.[6]] (especially on this controversy see[32, 65]).

Decisive progress made in the past decade is reflected in the statement – which was experimentally and theoretically confirmed – that there can be no resonant energy accumulation of high-frequency oscillations due to the strong viscosity reducing effects in the watery milieu[2, 3, 12, 26, 82, 83]. Thus the arguments for the existence of sharp frequency windows of high-frequency effects do not apply anymore either.

Neither the originally suspected induction of calcium signals nor the ODC findings[19, 45, 50] , nor the initially alleged changes in the melatonin metabolism[44, 90, 101] could be confirmed. Many of these findings were based on the methods of fluorescent microscopy. It is often

overlooked that the cells are sometimes exposed to UV radiation here, producing clearer effects than high-frequency fields[53].

In recent years, an influence of high-frequency EMF on the complicated system of the elimination of reactive oxygen species (ROS) of the cellular metabolism, suspected already in 1985[64], has been controversially discussed again[25, 29, 57, 60, 78, 88, 102]. There is no plausible biophysical mechanism supporting this hypothesis. The future will show whether the measurements can be verified or whether those will be right who see the biological variability of this system and the uncertainty of the analysis technique as the cause of to-date findings.

Summing up this paragraph, the conclusion must be that the 15 years of this reporting period were a time of clearing up unrealistic hypotheses. Recalling Newton's "*Hypotheses non fingo*", the question is allowed: What undeniable experimental effects do still require a biophysical explanation today?

"Non-thermal" or "subtle thermal" effects?

When looking at the neurological measurements initially listed, including their variability, as well as the repeatedly published results on the occurrence of heat shock proteins[16, 91], one comes back to thermal effects of high-frequency fields, even if they are not always measurable as a temperature increase. It seems very clear regarding heat shock proteins, as many recent findings show, that this cellular response in fact can be expected only when thermal stress occurs[47, 88, 98].

The term „non-thermal effect" has a populist undertone, as it suggests that there were secretive, still undiscovered adverse health effects of electromagnetic fields, not having been considered in the setting of limits. Laypersons can be easily convinced that electrical oscillations may attack all kinds of charges, thereby causing unimaginable damage in the biological system. But the problem are not these effects per se, which undeniably exist, but rather the dosimetry and the question whether these oscillations disappear to the noise and unspecifically dissipate to heat, i.e. eventually are "thermal", or whether these smallest amounts of energy could have specific biological effects before their dissipation.

This question is as old as the research on the impact of electromagnetic fields itself, going back to the end of the 19th century[34]. The past years have greatly contributed to clarification through scientific publications and, especially, through discussion during special conferences.

Initially we reported that some "non-thermal" effects disappear after correction of the application system, because they were just the results of uncontrolled heating. But even when neglecting the results of publications providing evidence of heating effects or at least corresponding suspicions, a number of findings remain which are not as easily explained by measurable heating. Progress made in the field of thermosensitive ion channels and so-called "riboswitches" however has shown in the past decade that, in many cells, these molecular thermometers respond so sensitively in certain temperature ranges, possibly releasing biochemical signal chains, that macroscopically changes in temperature are not measurable[27, 33]. The result of such responses can be both special protein expressions, as well as local changes in blood flow, which could lead to measurable alterations in the EEG. As these responses however are also dependent of different other physiological parameters, the difficulty to reproduce these neurological effects becomes clear.

Hence "non-thermal" effects really are to be termed „subtle thermal", i.e. minimal thermal day-to-day effects. They even occur when a man is sweating on a summer day, enjoying the relaxing warm water of a shower, or his thermoregulation is otherwise activated. Of course, the biophysicist is interested in each effect of high-frequency fields on the biological system for which there is clear evidence, the radiation protection scientist on his part must notice only influences which are health-relevant. The statement of Bernhardt published already in 1999 was corroborated[9]: "A possible pathological relevance of to-date available reports on so-called non-thermal effects is purely speculative at present."

Conclusions

It seems obvious to come to the following statement: "The problem is solved. Science has proved that there are no adverse health effects of mobile communication fields within legal limits." – Unfortunately, this is true only to a certain extent: science cannot prove the non-existence of a process or phenomenon. So, the conclusion would have to be: "Last decade's research, could clear up many errors regarding effects of high-frequency fields, and despite global efforts to date no reproducible evidence could be found for a health risk from these fields within valid limits."

As EMF is no agent which concerns only a minor percentage of the population, but each citizen of the civilized world is exposed to nowadays to a different degree qualitatively and quantitatively, we cannot be content with this conclusion.

The following activities in this field seem of future relevance to the author:

- The technical application of high-frequency fields is developing rapidly, thus qualitatively und quantitatively increasing the general exposure. Although narrow window effects for special frequencies and intensities of high-frequency fields could not be found until now, certainly different interaction mechanisms can be expected for the broad frequency range of 0.1 to 10 GHz at greater intensities. This results in the obligation to reassess all technological innovations regarding health consequences of applied intensities, frequencies and modulations and, possibly, initiate new research projects in order to exclude potential health-relevant effects.
- The quantitative increase in the number of scientific publications shown in fig. 1 requires greater attention. As repeatedly experiments are published, which were performed without reliable dosimetry, double-blind evaluations and positive control, i.e. which are of lacking quality regarding modern technology and therefore are often faulty, attentive quality control is required. Unfortunately, there are many examples for results of superficial experiments or flawed performance of experiments that, accentuated by the press, led to spectacular reactions in the public. Research projects worth millions were needed, eventually failing to disqualify these results, even if they were not confirmed and sources of error were pointed out. Permanent control and instruction are needed to prevent this. Diligent observation of research activities and a well-coordinated international cooperation are a means to this end.
- It is an important and continuing task to counter unfounded concerns of citizens over possible dangers of high-frequency fields by objective information. In this respect it is even important to check the above-mentioned effects, which really are within day-to-day alterations without any health-relevance. Only by knowing the mechanism of such day-to-day effects a scientific extrapolation and assessment of exposures in general can be done.

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