"Towards a mechanism-based framework in EMF research"

2nd international workshop in the framework of NRP 57 "Non-Ionising Radiation – Health and Environment"

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Organizer:	Swiss National Science Foundation, National Research Programmes
Date:	May 5 and 6, 2008
Venue:	Zurich, Hotel Zürichberg (www.zuerichberg.ch)
Chairs:	Alexander Borbély, Pierre Goloubinoff, Christian Hess, Dariusz Leszczynski, Meike Mevissen, Primo Schär
Invited Speakers:	André-Patrick Arrigo, Jean Cadet, David de Pomerai, Pierre Goloubinoff, Dariusz Leszczynski, Tomas Lindahl, Meike Mevissen, Günter Obe, Younousse Saidi, Primo Schär, Rony Seger

For the agenda with further information on the affiliations of the speakers and the titles of their respective talks, see www.nrp57.ch.

General Conclusions

The second scientific workshop "Towards a mechanism-based framework in EMF research" aimed at exploring the difficulties regarding ELF and RF electromagnetic fields and their effects at the cellular level, with a focus on DNA damage and repair, the stress response (with an emphasis on MAPK, ERK and Hsp27), as well as the role of temperature, such as thermal vs. non-thermal effects, temperature change sensing elements and down-stream signalling, and its role in induction of the stress response. The impact on biological systems is still a subject of intense ongoing scientific debate, as numerous findings remain isolated and controversial and their interpretation difficult due to the lack of a sophisticated mechanism-based framework. Particular shortcomings refer to the variety of cell types used, the non-standardization of measuring instruments and models applied, as well as the large concern of background noise.

These shortcomings, new results and the significance of the data as well as their potential effects on human health were presented and discussed in depth across the disciplines which led to a fruitful exchange during the one and a half days workshop. The following reflects the views and perspectives as expressed by the invited speakers and chairs in both day's final panel discussions.

Special and repeated emphasis was placed on the principle question whether a cellular effect of EMF exposure exists or not. While over the years evidence for a variety of weak effects has been accumulating, so far no well replicated set of data is unequivocally showing that EMF exposure affects cells. Accordingly, health risks and mutagenic, cancerogenic or other long-term effects cannot be deduced from the existing results. However, a lack of a reliable and robust effect in any *in vitro* or *in vivo* model does not necessarily mean that in fact it does not exist. So far, a sensitive method to prove or disprove EMF effects may simply not have been found or it may be possible that not the right factors have been regulated in

controlled experiments.

Consensus was reached that a reasonable methodology is most important to prevent a potential bias in the experiments and to assure comparability between outcomes of different laboratories. Problems may for example arise by using different types of cells, differences in cell treatment such as oxygen or by selecting different kinds of models and exposure set-ups. In addition, cells may differ in their sensitivity and may be differentially influenced by RF EMF exposure depending on the point in the cell cycle. A general suggestion was to experiment with cells in S-phase and to use intermittent exposure. A whole battery of methods may be necessary to assure the elimination of false negative and false positive results right from the start. Repetitions of experiments were considered as extremely important to substantiate possible outcomes and to prove the reliability of an effect under certain conditions. Yet, opinions were divided with regard to replications and whether to apply them in the strict sense, or to replicate a hypothesis in a different system and/or to follow-up on experiments by going one step further (e.g., including an additional exposure condition) to advance our knowledge. In either instance, studies should be documented and specified carefully, especially with respect to dosimetry, the lack of which was viewed as a major handicap in the published literature so far.

Another recurrent theme of the workshop was the importance of establishing a mechanism and the general need for a “dose”. Despite numerous studies during the last couple of years, EMF research is still at an early stage and arguments are all about early observations. So far, no reliable cellular effect could be unequivocally established and major pathways investigated do not seem to be influenced by low-dose exposure even though many key enzymes remain to be analyzed. Instead, only weak effects are reported and a consistent picture is difficult to establish. For example, it seems that RF EMF exposure does not cause direct mutations, but it cannot be excluded that it may cause mutations indirectly, e.g. by affecting cell metabolism and thereby cellular repair mechanisms. Here, small changes in signaling could have dramatic consequences. Some participants brought in the idea that toxic effects may be delayed (e.g., due to an accumulation of effects) and not seen immediately but only after long lapses of time, and even so at low-dose exposure (e.g., as established in the case of cadmium). Accordingly, research should proceed and input is needed from researchers outside the field. As intracellular pathways are sensitive even with low doses, the MAPK-pathway as well as the modulation of enzymatic activity seems to be worthwhile to investigate.

The scope of applicability and the significance of existing methods and models in EMF research on biological systems also was a matter of debate. It was pointed out that comet assays may be the measurement of choice when looking at tiny changes; yet, it only tells that DNA strand breaks occur but not where exactly. In general, one problem of multiple assays with different readouts lies in entirely disconnected observations so that nothing on the mechanism can be concluded anymore. To reproducibly measure something, the technique has to be reduced and a window needs to be identified of what to look at, how to look at it and from what perspective. The genetically uniform nematode *C. elegans* is generally viewed to be a useful *in vivo* model, but its suitability to study the effects of EMF exposure on the cellular level needs to be established. Especially long-range effects may be easier to investigate and by testing different mutants or applying different doses, questions may be approached in a variety of ways. Not much research in this direction has been performed so far and accordingly, more studies are needed.

There was general agreement that overall there seems to be a shift in common understanding that weak effects on the cellular level actually may exist and there are also some plausible ideas about which systems may be involved. A major problem lies in the interpretation of the results as research and results in cell lines are not directly transferable to higher organisms with more complex signaling systems; also, differences between genomes and proteomes may matter. With ELF EMF exposure, small and robust DNA strand breaks have been observed under non-thermal conditions. The mechanisms for RF EMF induced effects may be completely different, but could also have dramatic consequences. A future aim must be to define the threshold values at which effects occur and to investigate the molecular mechanisms underlying these effects. Different laboratories should aim for (better) cooperation and science needs to

be harmonized with regard to experimental models and exposure conditions. And most important, given that this is not a field in the limelight of science, that there are no clear solutions and that we are dealing with weak effects and unknown mechanisms, research should continue.