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## **Objective**

This four-day workshop was dedicated to an interdisciplinary exploration of engineering requirements and quality assurance in the main fields of bioelectromagnetics. The objectives were how to address uncertainties in technical and biological aspects and in the evaluation of research for health risk assessment in order to improve the quality of future research. Common aspects in the ELF to RF frequency range were discussed and specific recommendations were formulated in extensive panel discussions.

## **Technical Aspects**

Since many published studies suffer from inappropriate engineering implementations and a lack of dosimetric information, the objective of the first day was to propose the basic engineering and dosimetric requirements to conduct scientifically sound EMF experiments investigating biological effects and/or health responses. Basic experimental and numerical aspects of dosimetry were presented that are required to properly design, develop and evaluate the exposure systems needed to conduct such experiments. Subsequently, the minimal requirements regarding specific setups for the various research fields (in vitro, animal, human exposure and epidemiologic studies) were explored.

Consensus on the following points was reached:

- Since effects are expected to be small, the likelihood of evoking effects should be maximized, i.e., maximum exposure levels close to the thermal threshold, uniform tissue exposure, optimized modulation, minimization of the biological noise level and of artefacts possibly introduced by the setup without RF should be adopted. The latter should be verified by sham-sham experiments.
- The exposure system or setup must be designed to enable the intended experiments according to a standard protocol, meeting all dosimetric needs and avoiding any EMI/EMC issues. Since protocols differ from endpoint to endpoint, setups cannot be standardised.
- Blinding of the exposure is desirable for any setup but it is mandatory for human provocation studies. Regarding *in vitro* and *in vivo* experiments at least the evaluation should be blinded.
- True sham exposure is mandatory. Incubator controls for *in vitro* experiments and positive controls will depend on the experiment.
- In general, close collaboration between biological/medical and engineering parties is required throughout the design phase of exposure setups.
- The dosimetry characterisation of the exposure should include the distribution of the induced electric field or SAR as well as that of the magnetic field in space and time, including an experimental worst-case evaluation of temperature increase within samples. If the increase is not negligibly small from a biological point of view, arrangements for temperature control must be provided in the setup. The minimal requirements regarding SAR information should include the average value in the exposed volume (whole-body exposure vs. local exposure for *in vivo* experiments), spatial peak values averaged over appropriate masses, organ peak and average values for all tissues/cells exposed (whole-body and spatial peak values are only sufficient if global thermoregulatory responses are investigated). When micro-dosimetric information is of interest, a two-step procedure is appropriate, i.e., 1) characterization of the field distribution at the macroscopic level (macrodosimetry) from which 2) microdosimetry data can be derived.
- An important part of dosimetry is the analysis of uncertainty and variation. Uncertainty describes the uncertainty of the determined mean value of the exposure distribution (e.g., uncertainty of measurements and numerical tools, inappropriate average animal model,

dielectric parameters of tissue and setup components, secondary coupling effects, etc.). Variation describes the variations from the mean as a function of changes during the exposure (e.g., position within the exposure system, anatomy of animals/humans (size, weight, etc.) or amount of medium, posture, variations of dielectric parameters between samples, animals and setup, amplifier drifts, etc.). Uncertainties and variations should be provided for whole-body, spatial peak as well as tissue-specific SAR values, H-field and temperature increases (if not demonstrated to be negligible).

- Dosimetry should be based mainly on numerical dosimetry. Numerical dosimetry must be verified by experimental measurements, the agreement between which must be within the combined uncertainty of both techniques. Numerical dosimetry also constitutes an essential part in the development and optimization of exposure setups.
- Basic procedures to obtain minimal dosimetric data as described in the literature are considered to be sufficient for most exposure setups. More guidelines are needed to address large scale *in vivo* studies.
- The current, commercially available numerical tools are sufficient for dosimetric studies. Since most dosimetric evaluations involve greatly non-homogenous structures, FDTD was defined as the most suitable technique (FIT is considered to be equivalent). Other methods, e.g., FEM, are also appropriate if the required discretisation can be obtained.
- The current, commercially available experimental and dosimetric tools are sufficient for the characterization of the exposure setup and the validation of numerical dosimetry.
- Animal and human models with enhanced resolutions have become available. Nevertheless, models still pose the largest limitations for dosimetry and therefore enhancements should be of top priority, such as improved animal models or the generation of a “virtual family”.
- Shortcomings have been identified regarding sound procedures and equipment for exposure assessments in epidemiological studies of the general population. Substantial progress has been made in the last years, especially regarding dosimeters and the estimation of exposure from handsets. The assessment of low-level *in situ* exposure is more difficult and a consensus about suitable techniques could not be found, regarding, in particular, how to combine SAR with time, and how to combine different exposure sources.
- In general, retrospective dosimetry is difficult to conduct and aggravates the difficulty of evaluating past studies with insufficient dosimetric data.

### **Biological Requirements**

The goal of the second day was to obtain basic guidelines on quality assurance with respect to statistical analyses and biological aspects in the different research fields. A significant conclusion was that experimental setups should not be standardized, as their design and operation specifications depend on the biological/health endpoints to be examined. Further, the focus should lie on RF EMF research since it is still at its beginning and observations are in general sparse, specifically with respect to chronic exposure. Health risks should be assessed in the broader context taking into account the evidence from epidemiologic, mechanistic and toxicological studies.

### *Statistical issues*

- The purpose of a study and its appropriate statistical analysis need to be determined prior to commencing the experiment. Whether a study is hypothesis-driven, an exploratory expedition ('a fishing expedition'), a standardised study according to testing guidelines (e.g., for chemicals), or whether it aims at the estimation of an effect has bearings on the minimal requirements regarding design, power, dose placement etc.
- When designing a study, appropriate statistical tools must be used to evaluate the statistical properties (power, bias, variance) either for the specific case or based on tables.
- Sample sizes are of crucial importance and should be based on the expected variation. It was argued that e.g., in human exposure studies 16 subjects per group would constitute the minimal requirement.
- From a theoretical point of view, pure replication studies without any new aspects should be discouraged, as new studies challenging the consequences of the original work will improve our understanding more efficiently.

#### *In vitro studies*

- With respect to *in vitro* experiments, it is necessary to balance mechanistic vs. toxicity studies. Genotoxicity studies should address DNA strand breaks, DNA repair, chromosomal aberrations, micronuclei, apoptosis and cell cycle; dose-response for different exposure levels should be performed and time of exposure and exposure parameters (e.g. continuous - intermittent) should be tested. It is important to define new endpoints in addition to DNA damage and brain cancer and subsequent studies should be performed with a step-by-step approach investigating different levels of complexity (genes, proteins, regulation at the cell level and metabolism).
- The necessity of positive controls in *in vitro* research was emphasized repeatedly.
- Since current methodologies (e.g., comet assay, cytogenetic techniques) continue to give contradictory results, protocols, exposure setups, etc. need to be harmonised as much as possible to allow for proper comparison between studies. Also, new approaches may need to be envisaged (e.g., high throughput screening techniques). However, when new and emerging techniques (e.g. proteomics and transcriptomics) are used, a combination of them should be attempted along with a physiological approach. As no direct link to health effects can be established, data need to be interpreted carefully in the context of physiological and biochemical events.

#### *Animal studies*

- Evidence regarding biological effects is mixed. Future challenges comprise good dosimetry, consistency in the selection of biological endpoints, variance in the sensitivity to exposure (e.g., in different tissues or organs; temporal variability), adequate sample sizes and power.
- When designing animal studies, the biological model should be validated for the experiment, at least justified. In general, at least three exposure levels should be used and RF doses justified. GLP (-like) conditions should be secured for the experiment and the animals' health status should be checked with microbiological/ parasitological examinations. If applicable, cage and positive controls should be used.

#### *Human provocation studies*

- Scientific quality of human provocation studies is often questionable with respect to exposure, blinding and physiological measures. Hence, standardization of exposure including assessment of its variation during the experiment, of exposure duration and of environmental conditions (e.g., light, temperature), as well as double-blinding pose the most prominent challenges. In addition, inclusion/ exclusion criteria, homogeneity of the study group, confounders (e.g. sufficient sleep, alcohol consumption) and adequate

measuring techniques (e.g., test batteries for cognitive performance) should be addressed.

- Minimal exposure duration may be needed to induce effects; effects may outlast exposure up to hours; carry-over effects must also be considered.
- Studies on response time and cognitive parameters have so far produced conflicting results. Studies addressing sleep physiology have produced more consistent results and may therefore be interesting to pursue further; especially studies of long-term low-level exposure may need to be considered as effects on sleep could have important health implications.

#### *Epidemiologic studies*

- The various categories of epidemiologic studies (e.g., cohort, case control and cross-sectional studies) with their strengths and weaknesses and frequent types of errors were presented. Publication bias and data mining were identified as common problems. Sample size considerations are also crucial and the STROBE list was proposed as a starting point to guarantee quality.
- It was agreed that mixed exposures from various exposure sources (e.g., base station and handset) necessitates the careful formulation of hypotheses when designing epidemiologic studies. In general, the focus should be turned to the highest exposure levels encountered and to individual exposure vs. time, incorporating good dosimetry in the design.
- The discussion was also concerned with the definition of 'dose'. Important questions that remain to be answered are how to combine SAR with time, whether exposures from different sources are equivalent in their effect and how to combine them, whether dose-response is gradual, whether there is a cumulative effect of exposure and whether there may be biological reset times.

#### **Research Programs**

During the third day, the focus was on the many and diverse national research programs in Europe, the U.S. and Japan, and on the role of the EC, EMF-NET and WHO in helping to coordinate them and in setting the research agenda. Achievements and limitations of completed programs were discussed and the goals of future programs and cohort studies presented. Main topics in the discussion included measures that have to be taken to (1) appropriately manage national programs, (2) secure quality in funded research, (3) disseminate results, and (4) evaluate program outcomes or benefits.

##### Lessons learned and recommendations for the future

- A large variety of projects, programmes and strategies are found throughout Europe, but despite efforts to coordinate research, work is often inefficiently duplicated. The need to foster collaboration, i.e., share experience among groups, protocols, or even resources (such as exposure systems or samples) was acknowledged.
- In order to coordinate research in Europe, a database needs to be established and the role of the EC needs to be clarified. The call for a central "agency" that would evaluate programmes, set research priorities, and coordinate research and funding on a Europe-wide level was met with much appreciation by the participants.
- With respect to funding, the installation of firewalls between researchers and stakeholders to ensure independence of research, to improve public trust and to maintain credibility appears mandatory. When funding of a program is supported by industry, stakeholders must be contractually prevented from interfering with the publication of the results.



- The main criteria for the selection of projects should be based on a rigorous scientific risk assessment and the quality of the proposed research, not on the public nor any other stakeholder's direct concerns. Each project must be evaluated regarding its potential to assess health risks. To ensure transparency, aims and results need to be communicated clearly to all stakeholders.
- Instead of fragmenting resources, programmes should be focused and should limit the number of projects in order to ensure high quality of projects that would generate data relevant to health risk assessment. It was generally agreed that e.g., cohort studies come at a large cost but have to be regarded as very informative.
- During the selection process and in the evaluation of prospective projects, external committees should engage in a proactive dialogue with the respective researchers to help improve and modify promising projects for the greater benefit of the programme. Further, projects should be monitored by independent experts.
- The general consensus on whether standardized exposure systems and protocols should be used was a clear "no". However, minimal requirements to ensure quality are very important and needed. Strong quality control on dosimetry is necessary as good dosimetry is crucial, and GLP/GCP rules should be followed as far as applicable.
- Programme management should ensure that results are submitted for peer reviewed publication.
- An additional point in the discussion addressed the lack of research regarding mobile phone and environmental exposure of children and the need for more work in this area, both in the low-frequency (<100KHz) as well as in the RF range.