SWISS WORKSHOP FOCUSED ON QUALITY IN EMF RESEARCH

Niels Kuster of the IT'IS Foundation for Research on Information Technologies in Society, Zurich, a principal organizer of the conference, "EMF Health Risk Research: Lessons Learned and Recommendations for the Future," on November 21–24, 2005, opened by paraphrasing a remark that had caught his eye: "There is good science and bad science, and the difference is not simply a matter of opinion."

This theme—how to conduct careful, well-designed experiments with appropriate statistics, independent final evaluation, and following other principles for best quality—ran through all of the presentations over the four-day conference, the panel discussions and audience participation.

The international workshop was organized by the European EMF-NET project, the Swiss Agency for the Environment, Forests and Landscape (BUWAL), and the Swiss Federal Office of Public Health (BAG). It was also financially supported by the Swiss Federal Institute of Technology (ETHZ) and the Swiss National Science Foundation, the U.S. National Institute of Environmental Health Sciences (NIEHS), and the German Foundation for Behavior and Environment (VERUM). It was held at the Stefano Franscini Center on a hill known as Monte Verità, featuring vegetarian local specialty foods and glorious fall scenery, near the town of Ascona on Lago Maggiore in the Italian-speaking Ticino region of Switzerland.

More than 30 invited speakers discussed the proper handling of replication studies, dosimetry requirements and how to improve the quality and sharpen the focus of future research on possible health effects of EMF. Another organizer, Theo Samaras of the Aristotle University of Thessaloniki, Greece, said that bioelectromagnetics research seems to be at a crossroads now in Europe. Good quality scientific techniques and methods are needed not only for their own sake, but to show the European Commission that bioelectromagnetics research is mature enough to continue beyond Framework 6 (FP6), which ends soon. Samaras and others hope that the EC will decide to fund further EMF research in FP7. A major objective of the workshop, in the words of organizers, was how to address uncertainties in technical and biological aspects and in the evaluation of research for health risk assessment "in order to improve future research with respect to quality."

Organizers Jacqueline Pieper and Theo Samaras at the workshop in Ticino, Switzerland, sponsored by the IT'IS Foundation, Zurich.

The opening session featured talks on technical aspects of bioelectromagnetics experiments, because, as Kuster put it, "two of the major shortcomings in EMF health risk research resulting in inconclusive results on nonthermal effects are inappropriate engineering implementations and a lack of dosimetric information in many published studies." Talks on experimental and numerical dosimetry were given by Sven Kühn of IT'IS, by Samaras, by Georgio Lovisolo of ENEA, Rome, and Ferdinando Bersani of the University of Bologna, who spoke about ELF exposure setups. The speakers stressed the need for blinded protocols, for a true sham group, a positive control group, uniform exposure of the sample and good temperature and other environmental controls. Kuster spoke on exposure setups for animal EMF studies and Gernod Schmid of ARCS Siebersdorf Research, Austria, addressed engineering aspects of exposure setups for human laboratory studies. General discussion followed, on the topics of sample size and advantages of the repeated measures study design.

Among other things, EMF RF dosimetry experts said that studies should not use actual or modified mobile phones for human subjects research, because only generic and optimized exposure systems provide sufficiently small dependence of the locally induced tissue specific fields on anatomical differences.

The speakers were asked to identify key limitations of the existing studies, and as each session ended, Kuster and Samaras proposed a list of "Requirements"—quality assurance points that followed from issues raised in each topic area. Perhaps three White Papers will come out of this conference, drafted by scientific advisors of EMF-NET as part of their work for the European Commission. In part, these may help to set the agenda for future EMF study in Europe, according to Samaras and EMF NET Director Paolo Ravazzani of the Institute of Biomedical Engineering, CNR, Milan.

In the weeks since the workshop ended, Kuster and Samaras, with Sonja Negovetic of the University of Zurich, have prepared a an overview, an executive summary, of the four-day workshop. They list the points on which consensus was reached in four topic areas: Technical Aspects (dosimetry, engineering, etc.), Biological Requirements, Research Programs and Selected Endpoints.

The list is too long to be reproduced here, but the authors recommend that EMF investigators pay close attention to proper selection, characterization and calibration of the instruments for their specific use. The biggest emphasis in the planning of any EMF study should be placed on full characterization of the distribution of induced E and H fields, as well as temperature, and should include a full uncertainty and variation analysis of each reported quantity.

In later talks on the first day, Joe Wiart of the French National Research project, Adonis, and France Telecom and Georg Neubauer of ARCS, Siebersdorf, Austria, discussed strengths and limitations of the two new exposimeters now available for expo-

See Swiss Workshop, continued on p7

Swiss Workshop, Continued

sure assessment in epidemiology studies, the Antennessa and the Maschek meter. In their draft workshop report, Negovetic, Samaras and Kuster list 14 related consensus points. The first three are:

• "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, minimal noise level, optimized modulation, etc., should be adopted.

• "The setup must be designed in such a way as to enable the intended experiments according to standard protocol, meeting all dosimetric needs and avoiding any EMI/EMC issues. Since protocols differ from endpoint to endpoint, setups cannot be standardized."

• "Blinding of the exposure is a plus for any setup but mandatory for human provocation studies. Regarding *in vitro* and *in vivo* experiments at least evaluation should be blinded."

The goal of the second day was to identify basic guidelines on quality assurance with respect to statistical analyses and biological aspects of the different fields including animal, *in vitro*, human provocation and epidemiologic studies. "A significant conclusion was that experiments should not be standardized, as their design and operation specifications depend on the biological endpoints to be examined," organizers noted. They also recommend that because RF EMF health effects research is in the early stages, this area should be a focus of new research, specifically with respect to chronic exposure. Also, health risk should be assessed in a broad context taking into account the evidence from epidemiologic, mechanistic and toxicologic studies.

One invited expert in biostatistical techniques was Christopher Portier, director of the U.S. National Toxicology Program (NTP) at NIEHS in Research Triangle Park, N. Carolina. He began with the provocative statement that EMF researchers should avoid performing simple replication studies because these do not advance science. Portier said that simple replication may fail to repeat the finding of the original study, leaving those who must weigh the evidence for health risk assessment with one positive and one negative result and no guidance on the overall meaning. To avoid this, Portier recommended that "challenge studies" should be performed. A refined kind of replication, they improve on the original design and challenge the implications of the results, he said. In his opinion, the same or new investigators should analyze the original design and make every improvement possible in sample size and precision of exposure categorization, for example, to challenge the implications of the first study.

Ravazzani said he is not sure whether Portier's advice on replication is useful in bioelectromagnetics research because there we lack a biological mechanism. Portier conceded the point, but repeated that the best solution is to improve on the original study wherever possible. "You may want to replicate the result in your own lab before publishing," he suggested. "The challenge has to be to go beyond the original assay, to get better." Later in a wide-ranging discussion with the audience, Portier surprised some by stating that so-called "fishing expeditions" or exploratory studies can be of value in some cases.

In the rest of his talk, Portier reviewed the design of his agency's lifetime bioassay of RF exposure starting *in utero* in two rodent species. He said that NTP decided to double the group size for this two-year assay because with RF it is impossible to give animals a near-toxic threshold exposure. During the discussion, Samaras asked Portier what, as a reviewer, is the first thing he evaluates in a review paper. Portier replied that he checks sample size first, to see whether the study had statistical power to detect a difference between groups if one existed.

In the wrap-up session, the audience, invited speakers, Samaras and Kuster agreed on several statistical points, including that sample size is crucially important and that appropriate statistical analysis should be chosen *a priori*. Other speakers on Day 2 included Martin Röösli of the University of Bern, who spoke on types and goals of epidemiology studies. The afternoon speakers were Dariusz Leszczynski of Finland's Radiation Protection Authority, and Meike Mevissen of the University of Bern on *in vitro* EMF studies. Clemens Dasenbrock, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, and Larry Anderson of the U.S. Pacific Northwest Laboratory, spoke on animal toxicology studies; while Peter Achermann of the University of Zurich and Maila Hietanen of the Finnish Institute of Occupational Health addressed methods and design of human provocation studies. They also tried to critically assess the literature of their respective fields and summarize the main problems encountered when conducting experiments, as well as pointing out the general weaknesses from which many studies suffer. This greatly contributed to the formulation of requirements for quality assurance, in the organizers' view.

Larry Anderson and Clemens Dasenbrock

For each subject area, there was general discussion on these guidelines. The executive summary by Kuster, Samaras and Negovetic lists five consensus statements for *in vitro* work, three for human provocation studies and three for epidemiology.

One of the debates on the second day took place between Portier and Leszczynski. Once again provocatively, Portier suggested that statistically, if a researcher does not specify a pathway of interest before starting genomics screening, he or she has a 100 percent chance of identifying a random set of gene expressions that are not part of a meaningful pattern, because each screen is statistically a single sample, with multiple comparisons evaluated within it. He added that without evidence-based guidance on where to look for combinations of up and down-regulated genes related to a valid pathway, it is nearly impossible to overcome the statistical problem of making 20,000 comparisons, Portier added.

See Swiss Workshop continued, p8

Swiss Workshop, Continued

Leszczynski strongly objected to this characterization of genomics. Whereas he agreed that you should not attempt to use high-throughput screening techniques if not having enough resources for proper replication, he argued that they save time and can be repeated more easily than animal bioassays and toxicology studies. Further, it is still cheaper and faster to use genomics research to generate data from which hypotheses can be developed, he said. Genomic techniques can produce new endpoints for further study of possible health-related effects, Leszczynski added.

Portier agreed that genomic techniques offer a powerful research tool, but he believes researchers will always get more information from studying 10,000 samples on one endpoint than from 10,000 comparisons from a single sample. In his opinion, high throughput screening has no clear use for public health decisions. Leszczynski agreed that genomic screening must be followed by target validation on the protein level and or example in an animal model, to look for evidence from the genomic screen in target tissues.

Public Meeting Was Part of the Program

On the evening of the second workshop day, following a tradition of the Centro Stefano Franscini conference center on Monte Verità, people from local towns were invited to a public forum on "Mobile Phones and Health." The event was popular, with standing-room-only in a hall that seated 100. The Franscini Center's director said that Monte Verità had a rather notorious past from 1900–1930 because guests of the baron who owned the estate embraced health food, nudism and free love. To counteract the elitist and rather scandalous past image, the Center now regularly opens its doors to the public.

Organizers assembled a panel of speakers and offered translation to Italian. Speakers included Jürg Baumann of the Swiss Agency for the Environment, Forests, and Landscape; Kuster; Portier; Ravazzani; Kjell Hansson Mild of Sweden's Institute for Working Life; Chiyoji Ohkubo, formerly director of Japan's National Institute of Environmental Science and now with the World Health Organization's International EMF Project; Lawrie Challis, Director of the UK Mobile Telecommunications and Health Research (MTHR) Program, and Claude George of Swisscom Mobile AG.

The panel was moderated by a local journalist who spoke Italian and English. He translated questions from the audience to the panelists, most of whom could not understand the question. Portier later said he was impressed with how well-informed the audience appeared to be and with the quality of the questions. He felt the tone was similar to what he would have heard in the USA. Ravazzani agreed that the public seemed to be fairly well-educated about EMF health-effects issues. Several scientists attending the workshop said they were pleasantly surprised that the meeting did not become extremely emotional.

Research Agenda, Evaluation

On the third day of the workshop, the focus was on the EMF research agenda, on research evaluation, on various quality control methods used by national research programs in Europe, the U.S. and Japan, and on the role of EMF-NET and the World Health Organization's International EMF Project in coordinating them and helping to set future goals.

Jürg Baumann of the Swiss Agency for the Environment, Forests, and Landscape, at left, with Alexander Borbély of the University of Zurich, at Monte Verita.

"Lessons learned and recommendations for the future" that emerged from this day recognized that despite efforts to coordinate, some duplication of research effort has occurred. A few voiced the opinion that this is not always wasteful—having a question examined from different viewpoints can be instructive.

Many participants spoke appreciatively of the value of holding such meetings such as the Ticino workshop itself, where the goal is to share experiences and where investigators can share protocols, exposure systems and even arrange to share samples. There was also "much appreciation" expressed, according to the organizers, for the idea of establishing a central agency in Europe for coordinating and evaluating research programs and funding. There was some talk of lobbying the European Commission to establish a new European Academy of Sciences. "Lessons" from this discussion, among other things touched on the importance of having strong firewalls between researchers and industry to protect study independence and on the need for focused projects that yield data relevant to health risk assessment.

Finally, the last day was devoted to discussing three endpoints that some researchers believe indicate the existence of EMF-induced biological responses below the established interaction (thermal or induced current) pathways. These are DNA strand breaks reported with 50-Hz intermitted magnetic fields and pulsed and intermittent RF exposure and assessed by the comet assay, evidence for pulse-modulated RF effects on sleep EEG in human studies, and gene expression changes with RF exposure.

Franz Adlkofer of Verum, Munich, coordinator of the REFLEX Program, summarized the ELF REFLEX experiments, which he said provide evidence that intermittent (5 min. on, 10 min. off, ramped) exposure to a 1-milliTesla 50-Hz magnetic field for up to 24 hours causes DNA single- and double-strand breaks in human fibroblasts.

The next speaker, Maria Rosaria Scarfi of the Interuniversity Center for Interaction between Electromagnetic Fields and Biosystem Studies (ICEmB) at University of Genoa, Italy, reported that she and colleagues were not able to confirm the DNA strand breaks. They repeated Rüdiger et al.'s experiments as closely as possible four times using the same modified comet assays, but

saw no increase in any of the parameters tested, Scarfi said. She suggested that when one laboratory fails to replicate the original finding, a confounding factor may be present at both labs, or a subtle but undetected difference in procedure or methods could be present. Primo Schär of the University of Basel said he and colleagues recently repeated an experiment by Rüdiger *et al.* at the University of Vienna for the REFLEX Program, confirming the DNA strand breaks in human cells intermittently exposed to ELF EMF.

Primo Schär

Schär reviewed his laboratory's replications, first reminding the audience that in the normal course of life, cells in the human body may see tens of thousands of DNA single strand breaks each day during routine cell division. The vast majority of these breaks, however, are fixed by routine DNA repair processes. DNA double-strand breaks are more serious and more unusual, he added. Using the same exposure system as the Vienna group and the same human fibroblasts, he and colleagues got similar results as Rüdiger—no ELF effect with continuous wave exposure, but an increase in DNA strand breaks after 15 hours of intermittent exposure, Schär said.

He cautioned that the genotoxic effects detectable by the comet assay are small, although statistically significant. Also, this early, single experiment in Basel has brought up more questions than it has answered, Schär said, and he is convinced of the need to investigate further. The functional meaning of the result, if any, also is not clear, in his opinion. He outlined plans to carry out further tests that would allow pinpointing the origin of the DNA damage observed at a molecular level.

Schär said a problem with this preliminary work is that he and colleagues have been unable to add an optimal positive control group to the experimental design to improve study quality. Genetic toxicologist Vijayalaxmi of the University of Texas Health Science Center, San Antonio, also expressed concern that cell cycle effects have not been taken into account in the original REFLEX or replication studies. Actively dividing cells cycling through normal mitosis in culture are undergoing "scheduled DNA synthesis," she said. In her opinion, this is the most likely source of DNA strand breaks detected by the comet assays. She and Scarfi, with James McNamee of Health Canada, have a letter to the editor in a recent issue of *Mutation Research* listing their concerns. A reply by Rüdiger et al. is included.

In the last session of the workshop, Peter Achermann of the University of Zurich summarized his results from various controlled human sleep studies showing an effect on the sleep EEG in response to pulse modulated RF EMF. He also presented preliminary data from an investigation on a possible dose-response relationship by applying pulse-modulated RF EMF at two intensities (0.2 and 5 W/kg), revealing a dose dependent increase of power in the spindle frequency range in the non-REM sleep EEG. Sarah Loughran of the Swinburne University of Technology, Australia, who was preceding his talk, confirmed the findings of the Zurich group regarding the observed changes in the sleep EEG, and also reported an effect on sleep architecture showing a reduction of REM sleep latency. She stressed the importance to carry on with investigations regarding the effects of RF EMF on brain and sleep physiology for their potential to become a crucial issue in health risk assessment.

Organizers of the scientifically stimulating four days in Ticino have published a summary of the Monte Verità Workshop on EMF Health Risk Research that is now available at www.itis.ethz.ch/mv Click on "Results" to read this or to download many of the talks presented. They may also be contacted at: IT'IS Foundation, Zeughausstrasse 43, 8004 Zurich, Switzerland. Tel:+411 245 9696; Fax:+411 245 9699. E-mail: mv@itis.ethz.ch

– Janet Lathrop, with thanks to Sonya Negovetic, a research assistant at the University of Zurich, and Theo Samaras of the Aristotle University of Thessaloniki.

EMF NET EVIDENCE EVALUATIONS PUBLISHED

Paolo Ravazzani of the Istituto di Ingegneria Biomedica, Milan, Italy, the director of EMF-NET, the European Commission's four-year project intended to provide "policy-relevant interpretation and advice" on EMF scientific issues to health, environment and regulatory authorities, recently released three reports on the strength of evidence from recent laboratory studies for selected biological effects of exposure to extremely low frequency (ELF), intermediate frequency (IF) and radio frequency (RF) EMF.

The EMF NET scientific advisors who formed Working Groups to produce these reports used the International Agency for Research on Cancer's (IARC) 4-level scale for classifying the strength of evidence to evaluate the *in vitro* and *in vivo* evidence for various endpoints. Ravazzani said that the three reports should be available soon in pdf format at <http://emf-net.isib.cnr.it/>.

FGF PAPERS AVAILABLE

Forschungsgemeinschaft Funk e.V. (FGF), The Research Association for Radio Applications in Germany, recently announced that three rapporteurs reports of its workshop held in Stuttgart on November 21–23, 2005, "Subtle Thermal Effects of RF-fields *in vitro* and *in vivo*," are available for download at www.cost281.org/documents.php?node=121&dir_session=

Also, a summary report by Prof. Roland Glaser will be published in the next FGF Newsletter at www.fgf.de/fup/publikat/newsletter.html in the coming months.

Finally, a new issue of FGF's "Edition Wissenschaft" (Science Edition) No. 21, by Roland Glaser, has been published on the topic of the workshop: "Are thermoreceptors responsible for 'non-thermal' effects of RF fields?" It is available at www.fgf.de/english/fup/fgfpub/edition.html