Arimmora

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Advanced Research on Interaction Mechanisms of electroMagnetic exposures with Organisms for Risk Assessment

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Executive summary

1. Background: Exposure to extremely low-frequency magnetic fields (ELF-MF) was evaluated in an International Agency for Research on Cancer (IARC) Monograph as 'possibly carcinogenic to humans' in 2001, based on increased childhood leukaemia risk observed in epidemiological studies, while the evidence of carcinogenicity in experimental animals was considered "inadequate" and the supporting evidence from mechanistic studies "weak".

2. Objectives & Consortium: In response to the call FP7-ENV-2011.1.2.2.2, the project ARIMMORA was formed aiming to scrutinize the underlying biophysical mechanisms and to clarify a possible causal relationship between ELF MF exposure and cancer, especially childhood leukaemia. The consortium consists of ten world-leading competence centres in the fields of epigenetics, ERK signalling cascades, leukaemia *in vivo* models, *in vivo* toxicology, and EMF-sensitive animal models as well as in exposure assessment, biophysical modelling, and risk assessment.

3. Methods & Results: 1) Novel experimental and computational techniques were developed and applied to close knowledge gaps in the exposure assessment of children to ELF-MF. The personal exposure studies in Switzerland and Italy demonstrated that the mean exposure of the children is below 0.1 µT, and a small proportion, ca. 1 – 4% of children, are exposed to magnetic field levels >0.3 µT. The high exposure group is best defined by the bedroom exposure, i.e., neither daily activities nor exposures to near-field sources significantly contribute to the integrated exposure. To assess the induced E-field of near-field sources, a novel instrument that directly translates the measured amplitude and gradients to locally induced fields was developed. In addition, the transformation matrices for comparing *in vitro* and *in vivo* experiments with child exposures to facilitate the correct interpretation of experiments for this project and any future studies have been developed. 2) Novel and improved *in vitro* and *in vivo* exposure systems have been developed to maximise the exposure quality. 3) Novel instrumentation that allows not only assessment of the ELF-MF exposure but also the induced E-fields for any far- and near-field. 4) A major contribution was the development of a new transgenic mouse model in which the human gene associated with the most common childhood leukaemia (B-cell acute lymphoblastic leukaemia, B-ALL) is expressed. Results of preliminary experiments, in which one (of 30) of the ELF-MF exposed mice developed B-ALL — compared to none among the 65 control animals — allow the frequency of leukaemia development in the mouse model to be estimated. 5) Findings in several independent *in vivo* experiments showed decreases of CD8+ T-cells related to ELF-MF exposure. 6) Small differences in epigenetic modifications were observed in human haematopoietic stem cells exposed to ELF-MF. 7) A feasibility study based on the findings of the microscopic considerations showed that the radical pair mechanism is a possible candidate for the observed ELF-MF effects on signalling pathways.

4. Conclusions: Despite the several breakthroughs achieved, members of the ARIMMORA consortium concluded in the ARIMMORA risk assessment (applying the IARC Monograph program evaluation scheme) that that the relationship between exposure to the agent ELF-MF and the risk of childhood leukaemia is considered consistent with the "IARC Group 2B" classification of possibly carcinogenic to humans. This category is the result of the limited evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals. There was only weak supporting evidence from mechanistic studies. However, the new mechanistic insight from ARIMMORA experiments points to future research and could provide a step-change in future assessments that could be accomplished with one or two follow-up research projects.

Summary description of project context and objectives

Extremely low frequency magnetic fields (ELF-MF), associated with the use and transmission of electric power, have been classified as being possibly carcinogenic to humans, specifically childhood leukaemia, causing in humans, based on reasonably consistent results in population studies[1]. However, supporting evidence from laboratory studies in animals and cells for cancer-causing effects of ELF-MF at the microtesla level is weak.

To address the call FP7-ENV-2011.1.2.2.2, "Exposure to electro-magnetic fields (EMF): investigations of mechanisms to support risk assessment and reduce uncertainty", a consortium of world-leading competence centres in the fields of epigenetics, ERK signalling cascades, leukaemia *in vivo* models, *in vivo* toxicology, and electromagnetic-field-sensitive animal models, — joined by experts in exposure assessment, biophysical modelling, electrical engineering, and risk evaluation — was formed to investigate the association between ELF-MF and childhood leukaemia. After careful review of the available published studies, which did not reveal any predominant hypotheses of possible interaction mechanisms, the consortium identified open issues and knowledge gaps, and chose experimental directions aimed at providing EU policy makers and health authorities, the scientific community, standardization bodies, and the public with a firmer scientific basis for assessment of the risks associated with ELF-MF exposure. The ARIMMORA project was undertaken to use the most advanced tools in a comprehensive interdisciplinary approach to clearly detect and better understand the interaction mechanisms of ELF-MF with organisms or, alternatively, to clearly demonstrate the absence of an effect.

1. Recent advances in the molecular biology of leukaemia: Studies of ELF-MF interactions in cell cultures

Compared to well-known genotoxic agents, the reported extremely weak and often irreproducible effects of ELF-MF on DNA integrity make it questionable that ELF-MF can cause cancer. DNA integrity effects depend on cell type and cell proliferation. From a biophysical point of view, it is unlikely that magnetic fields are strong enough to directly damage DNA[2]. Findings from several studies on various types of cells conducted in many laboratories indicate that ELF-MF can alter cell-signalling pathways that control cell growth and division[3–5], but these results do not adequately explain a role in cancer, particularly for untransformed human lymphocytes[6]. There is also insufficient information about the impact of ELF-MF on the regulation of epigenetics and effects on gene stability to support that the reported weak gene expression changes and transformation of healthy to cancer cells can be caused by ELF-MF.

To address cell biology approaches to the investigation of mechanistic aspects of ELF-MF exposure, two of the world's leading research groups in the fields of cellular signalling and epigenetic signatures designed experiments to gain significant insight into the molecular effects of ELF-MF for leukaemia development. The objectives of the cell biology research were to: 1) investigate epigenetic changes in haematopoietic cells for possible importance in childhood leukaemia through study of the differentiation of healthy haematopoietic stem cells, with epigenetic stability analysed in leukaemic and healthy cells; 2) identify specific, inheritable epigenetic changes

in response to ELF-MF exposure that could be used as markers for bio-monitoring of short- and long-term exposure and in future molecular epidemiological studies; 3) explore how ELF-MF exposure impacts cellular signalling, for instance by short-term activation of mitogen activated protein kinase pathways and impact on oxidative stress responses; 4) conduct blinded investigations with well-controlled ELF-MF at 0.1 to >1000 microtesla under environmental conditions that closely simulate the characteristics of exposures to children to obtain dose-response data. 5) investigate whether observed cellular changes are directly due to incident magnetic field effects or are indirect effects of induced electric fields.

2. Recent Advances in the Molecular Biology of Leukaemia: Studies of ELF-MF Interactions in Animals

Before ARIMMORA, there were no suitable animal models available to study the effects of ELF-MF exposure on cellular components of blood and reveal the complex interactions that may lead to the fusion of genes in the development of B-cell acute lymphoblastic leukaemia (B-ALL), the most common form of childhood leukaemia. The objectives of the animal studies were to: 1) use cutting-edge genetic engineering technologies to generate a genetically modified mouse model engineered to develop a disease that mimics childhood B-ALL by expression of the *ETV6*-RUNX1 (formerly *TEL-AML1*) fusion gene; 2) comprehensively study pre- and post-natal exposure of *TEL-AML1* transgenic mice to ELF-MF with sampling of blood and immune system cells throughout maturation with comparison to appropriate unexposed control animals; 3) investigate effects of ELF-MF exposure on standard laboratory mice and in strains of rats known to have differential responses to environmental stressors in terms of maturation of blood cells and immune system response by: a) performing basic and differential blood counts and classical genotoxicity testing on blood samples, characterising expression of cell surface markers, quantifying patterns of cell proliferation, cytokine expression, gene expression profiles, and DNA methylation patterns in blood and immune system cells in CD-1 mice; b) sampling various tissues involved in the maturation of blood cells and the immune systems of pre- and postnatal female CD-1 mice; c) investigating blood, spleen, and bone marrow cells in terms of growth, division, activity, and programmed cell death pathways in F344 and Lewis rats; d) studying the impact of changes to cell surface adrenergic receptor proteins on development of blood cellular components, especially white blood cells, from F344 and Lewis rats.

3. State-of-the-Art Exposure Systems

To provide cost effective, high-quality control of exposure conditions, a novel flexible exposure system was developed for use in experiments with genetically modified mice; the monitoring systems of the exposure chambers for the studies of standard laboratory animals were upgraded with advanced systems to improve the level of exposure control. Good laboratory practice regarding blinding of investigators was followed[7].
In the course of the project period, it was decided to expand the effective exposure range of systems for studies of cell cultures into the nanotesla range and to install LED lamps to test the response to blue light[8].

4. Studies on ELF-MF Exposure of Children

Although there have been many studies on ELF-MF exposure of children, there has been insufficient investigation of levels and patterns of exposure according to daily activities in European children[9]. Previous personal measurement studies in children were mainly conducted in Asia; measurements made in North American and Europe have been mainly of adult exposures or of bedroom exposures of children. Daily activities may produce time-dependent variations in exposure patterns that may be more biologically relevant than time-averaged exposures. Although there have been recent advances in power electronics and an increase in the number of possible exposure sources, e.g., electric cars, trains, induction stoves, etc., near-field sources have been largely ignored due to a lack of suitable measuring devices. The intensity of electric fields induced in the various tissues had not yet been investigated in sufficient detail for effective design of laboratory studies and correlation with epidemiological studies. The objectives of the exposure studies were to: 1) develop new, improved equipment for measurement of exposure to near-field sources and accurate assessment of fields induced in the human body at relevant frequency ranges; 2) obtain personal data for exposure to ELF-MF of cohorts of children and adolescents in Switzerland and Italy characterised by subject location and behaviour; 3) compare contributions of near-field sources to those of power line fields; 4) use advanced numerical modelling methods to correlate incident fields with the intensities of fields induced in target tissues and organs, in particular blood and bone marrow, in pregnant women and in children of various ages and with different body postures; 5) develop and validate models that enable estimation of ELF-MF exposure of children in the past, present, and future .

5. Modern Numerical Models and Solvers for Informative Biophysical Modelling

There is a critical need in population studies for a means to systematically translate levels of exposure into degree of biological response, a field known as dosimetry, macrodosimetry for exposure of whole animals, organs, and tissues, microdosimetry to identify mechanisms governing the fields induced in cells and subcellular compartments. Advanced powerful numerical solvers were available to ARIMMORA researchers to allow correlation of state-of-the art macro- and micro-dosimetry concepts with findings from animal and cell culture experiments. The objectives for macro- and micro-dosimetry investigations were to: 1) quantify ELF-MF exposure in terms of fields induced at the tissue-, cellular-, subcellular- and molecular-levels for animal and cell culture experiments with advanced numerical models of cell cultures and rodents; 2) create a numerical exposure matrix to correlate exposure dosimetry in animals with that in humans; 3) use molecular dynamics simulations to investigate potential interaction mechanisms, for example, effects on reaction rates biochemical free-radical pairs in response to ELF-MF.

6. Mechanistic Hypotheses

There is a need for plausible hypothesis-based mechanisms to guide the experimental design of studies of ELF-MF exposure of animals and cell cultures. A thorough review of publications

relevant to mechanisms of interactions of biological matter with ELF-MF was undertaken, with focus on cryptochrome, a blue-light sensing protein implicated in animal magnetoreception[10], to seek evidence for a mechanism consistent with cancer from: 1) animal studies of magnetoreception; 2) biochemical investigations of cryptochromes; 3) theoretical studies of cryptochrome-based radical pair formation; 4) experiments on cellular responses to MF exposure.

7. Risk Assessment & Dissemination

The results from the ARIMMORA investigations were used as the scientific basis for assessing the risks and associated uncertainties associated with exposure to ELF-MF. The ARRIMORA project closed with a workshop to perform a risk assessment to be used to better inform industry, media, and the public on the potential cancer causing effects of exposure to ELF-MF. The workshop was convened to: 1) perform the risk assessment on the basis of studies conducted within the project and correlated to recent studies conducted outside the consortium following the IARC Monograph program evaluation scheme on the level of evidence regarding carcinogenicity to humans; 2) evaluate the implications of recent modifications of the ICNIRP safety guidelines on standards/risk assessment; 3) disseminate the developed instrumentation and assessment procedures to relevant international standardisation groups (CENELEC, IEC, ICES, etc.) for distribution to academic, industrial, and governmental experts; 4) prepare a summary of the risk assessment for publication in an appropriate scientific journal.

8. Literature Database

To support the work of the consortium, a complete cross-disciplinary reference database was constructed and updated throughout the duration of the project. The database was compiled to: 1) provide a open repository for all consortium members accrue publications relevant to their own fields of expertise and make them available to consortium members in other fields; 2) serve as a ready resource of up-to-date insight for making amendments to the project plan and for drafting the ARIMMORA risk assessment; 3) be made available to the public at the end of the project

Description of the main scientific and technical results and foregrounds

1. Work Packages

To effectively obtain the scientific goal of ARIMMORA, the research was organised in ten workpages (WP):

WP1: Establish a frequently updated online literature database (pdf files) covering the topics of all WPs and accessible by all partners. This database (excluding all the articles protected by copyright) will be made available to the public for review and suggestions, and to improve the dissemination of the project's results.

WP2: Creation of an exposure matrix for children, including exposures from power lines, transformers, and near-field sources by personal exposure assessment and computational dosimetry. This matrix will be designed for epidemiological considerations and risk assessments; the findings will be used to develop the tools in WP4, the definitions of exposure scenarios in WP3, product standards WP8, and the risk assessment in WP9.

WP3: The exposure systems required in WP5 and WP6 will be developed based on input from WP1 and WP2. Preliminary dosimetry will serve as the basis for WP7.

WP4: Development of novel instrumentation and procedures to accurately assess exposure to ELF-MF from near-field sources. The outcome of WP4 is fundamental for WP2 and of global relevance for the industry and standardisation bodies (WP9).

WP5: Investigation of molecular mechanisms involved in development of childhood leukaemia, with a focus on cellular signalling cascades and epigenetic regulation in haematopoietic and leukaemia cells exposed to ELF-MF. The project directly exchanges with WP6, WP7 and relies on input from WP1, WP2, and WP3.

WP6: Assessment of the effects of ELF-MF on maturational changes on intact immune and haematopoietic systems by means of advanced immunotoxicological, genotoxicological, and gene-expression approaches in animal studies. Furthermore in this the work package, the best genetically modified mouse models are used to investigate the effect of ELF-MF on the genesis and/or course of childhood B-cell leukaemia. Also, endpoints related to diseases of mutagenesis are investigated animal strains known to be sensitive to ELF-MF exposure. This work package directly interacts with WP5 and WP7 and relies on inputs from WP1, WP2, and WP3.

WP7: Macro- and micro-dosimetry of the systems being investigated in WP5 and WP6 with comparison to the corresponding levels determined in WP2 and explorations of potential postulated interaction mechanisms (WP1) with the tools of molecular dynamics;

WP8: Dissemination of results from WP4 and WP2 to standardisation bodies towards empowering the industry to develop and analyse devices with scientifically sound instrumentation and procedures that could significantly improve future epidemiological studies

WP9: Creation of a risk assessment analysis following certain procedures of the IARC Monograph programme (especially the IARC evaluation scheme for hazard identification) with data from WP2 – WP8 and outside studies (WP1); utilise and compare with previous monographs related to EMF exposures.

WP10: Project management has been carefully structured to insure that all WPs stay focused on the research plan, that problems are identified early, and that appropriate contingency measures are taken.

2. Literature Database

The task of WP1 was to develop at the project website a literature database of publications relevant to each of the work packages. The database, which was accessible to all partners throughout the duration of the project, was continuously updated so that partners would have an up-to-date resource for guidance in making any necessary amendments to the project plan and to use in the final risk assessment. The database will be made available to the public, and experts in the fields of electromagnetic radiation and leukaemia research will be invited to critique and add to the database.

3. Exposure

3.1 Personal Exposure Measurements

Personal exposure measurements of children during their daily lives were performed in WP2 to obtain reliable input data regarding the exposure patterns and gain a better understanding of timing patterns and levels of ELF-MF exposures. Further, fields were characterised by spot measurements at locations of high exposure with both existing devices and new tools developed in WP4. The new devices were also used to assess exposures from potentially significant near-field sources such as house installations, household appliances, cars, trains, etc. The magnetic and electric fields and the electric current densities induced inside the body as defined by the standards were determined as functions of the field source, the amplitude and frequency of the field, transients, and time; it was also confirmed that the magnetic fields induced in the body are the same intensity as the incident magnetic fields. Exposure models were developed to evaluate the wiring configurations of power lines, the designs of transformers, and time-dependent variations in current distribution as a function of power consumption. In computational studies, exposures of anatomical models in various postures were considered as a function of the type of source. The exposure of pregnant women was also investigated computationally. Magnetic field source models were validated by comparison with experimental data. These tasks were undertaken to provide relevant exposure data for the risk assessment.

The measured typical average personal exposure of children is below 0.1 microtesla (μT), which corresponds approximately to a peak spatially averaged induced E-field over 2 × 2 × 2 mm of 20 μV/m[11]. Only a small proportion, ca. 1 – 4% of children are exposed to magnetic field levels >0.3 μT.

3.2 Household Near-Field Sources

Analysis of household near-field sources shows that fields decay steeply with distance from the device or appliance, hence, the incident magnetic field exposure is relatively local. Furthermore, very few sources produce induced E-fields of significant intensity; those that do would normally either be relatively far from children or would be used only for a very short periods of time, i.e., fans, hair dryers, or vacuum cleaners. For example it is not normal behaviour to stand close to the motor at the rear of a fan or to lie on top of a vacuum cleaner, corresponding to the location of the radiated fields of highest intensity; further, the decay of the fields from domestic appliances is steep, thus, the fields tend to act only very locally on the body. Because these local sources act over relatively small cross sectional areas, induced E-field exposure for a given peak field strength is relatively much lower than that for fields of similar magnitude from more homogeneous sources such as power lines. Therefore in general, it is probable that localised very short-term exposures are of lower importance than long-term more uniform exposures from both incident and induced field perspectives.

3.3 ELF MF-Dosimetry

The knowledge about the induced field in exposed children has also been brought to a new level through application of the latest most powerful solvers, anatomical models children, and morphing and poser functions. The induced field increases roughly as a function of the cube root of the weight of the child, which increases as the child ages. The relative values of the E-fields in different tissues change as the children develop and grow, however the distribution of field values maintains the same characteristics. The tissues that are consistently more highly exposed in terms of induced E-fields are skin, subcutaneous adipose tissues (SAT), vertebrae, skull, and large intestine. The least exposed tissues include pineal body, hypothalamus, mid brain, adrenal gland, and pharynx and oesophagus. For foetal exposures, the most exposed tissues in terms of maximum E-field are skin and fat across all stages of pregnancy[12]. In all tissues, induced E-field exposure increases as the foetus matures and increases in size. Computational human models of pregnant women of the Virtual Population models developed by the IT'IS Foundation[13–15] were used in the simulations.

Harmonic components of the magnetic field add some contributions to the overall level of the E-fields induced in children and foetuses. Although these contributions increase with frequency and cannot be neglected, the amplitudes are low, even in the worst-case scenarios.

The consortium did not identify any urgent need to characterise the exposure of near-field sources beyond what has been achieved within ARIMMORA, as today's near-field sources expose children for only a very short time and only very locally for both the induced H-field and E-field. Furthermore, there are no indications from epidemiological studies today for an association of leukaemia with exposure to near-field sources.

3.4 Summary of the Exposure Studies

New measurements of ELF-MF exposure of children in Italy and Switzerland do not suggest any change in the exposure levels in comparison to earlier studies, but do highlight the importance of behaviour as a modifier of mean exposure levels, particularly in children living close to power lines. The measurements showed good agreement between the mean exposure levels from the child's bedroom and the personal measurements.

Measurements of domestic and household sources of ELF-MF show near-field characteristics with steep decays in the field strength that limit significant exposure to the immediate vicinity of a given appliance and relatively localised interaction with the body. The frequencies of fields emitted by devices with "universal" power supplies are in the intermediate frequency (IF) and not in the ELF range, and with that shifted increase in prevalence, the environment of the EM field is changing from that studied in earlier accounts. Whether IF exposure is relevant to leukaemogenesis, is, however, unknown.

4. Novel Exposure Systems for ARIMMORA

Optimised exposure systems specific for the *in vivo* and *in vitro* experiments of ARIMMORA had to be developed, manufactured, verified and validated, and installed. They meet all requirements and guidelines for well-controlled EM exposures and include capacity for uncertainty and variation assessments[7,16]. The exposure and the environmental parameters have been continuously monitored and documented.

5. Novel Exposure Measurements Devices To Assess Exposure and Induced Fields of Any Source

WP4 developed a new measurement device that can characterise the field present from a device, appliance, or power installation in terms of both field strength and homogeneity. The device is based on a new sensor paradigm in which, in addition to three orthogonal sensors of 100 cm^2 cross-sectional area, each sensor is divided into 4 equal segments. The combination of the 12 sensor segments results in eight 3D sectors formed between the planes of the sensor loops; each sector has on its 3 planar surfaces a field coil, and the vector sum of the fields measured by these three orthogonal loops provides a measure of the total field strength in that sector. With information on the field in the eight spatially distributed sectors, the direction and magnitude of the maximum field gradient can be determined.

The ability to measure both field strength and gradient is of particular importance when the fields induced in the human body during exposure are considered and for determination of compliance with standards designed to ensure public safety. Highly inhomogeneous fields, such as those generated by small household appliances, decay very steeply as the distance to the appliance increases; to assume that the field is homogeneous will result in incorrect evaluation of the likelihood of compliance or exceed a safety threshold for fields induced inside the body. The new instrument provides additional information that improves these evaluations.

6. In Vitro Studies

In WP5, blood cells and leukaemic cells were investigated for mechanisms of effects of ELF-MF absorption on cell signalling processes and epigenetic transformations. Specifically, the involvement of ELF-MF in short-term activation of mitogen-activated protein kinase (MAPK) signalling and other signalling pathways were investigated in cancer and non-cancer cell lines towards identification of upstream mechanisms of ELF-MF perception. Further, the effects of ELF-MF on the establishment and maintenance of epigenetic states during blood cell maturation and epigenetic stability in leukaemic cells was explored. Biological targets of ELF-MF exposure were tested and validated for use as potential biomarkers.

6.1 Signalling Processes

At the outset, it was important to determine whether and at what field strengths cells are able to sense ELF-MF. The effect of ELF-MF exposure on the activation of signalling pathways was tested in several cancer cell lines. The MAPK signalling cascade[17], which is very sensitive to environmental stressors, was used as the readout for ELF-MF response. For the upstream effects, the involvement of the blue-light sensitive protein cryptochrome[18], which has been implicated as a biological magneto-sensor, was assessed by testing the effect of exposure to light in combination with ELF-MF. Transient activation of the MAPK pathway was observed in some cell types with magnetic field of intensities as low as 0.15 µT; activation was decreased by co-exposure to blue light. That the magnetic field effect is modified in response to light is evidence for the involvement of cryptochrome and the radical pair mechanism. The level of activation of signalling pathways in all cell lines examined is likely too low for it to be involved in cancer initiation. Also, the mechanism by which cryptochrome could be involved in the activation of cell signalling pathways is not known.

6.2 Epigenetic Plasticity in Leukaemic and Differentiating Haematopoietic Cells

In another line of cell culture experiments, the epigenetic stability of leukaemic cells under ELF-MF exposure was assessed (epigenetics is the study of how environmental factors influence the ways genes control cells). In a first series of experiments, exposure of Jurkat cells, a line of human white blood cells used to study acute T-cell leukaemia, was investigated by examining levels of chemical alterations to the histone proteins that coat the nuclear DNA. Exposure to ELF-MF resulted in alterations at only few sites at barely above the detection threshold that could not be validated by other independent analyses. Similarly, ELF-MF exposure of REH cells, human white blood cells used to study B-cell leukaemia, did not reveal an effect on cell growth parameters. The effects of ELF-MF exposure on epigenetic aspects of blood cell maturation were also investigated. The stem cells from human umbilical cord blood cells were isolated, cultured, and tested for response to ELF-MF exposure. Differences between exposed and sham exposed cells in transient activation and repression of key developmental genes that regulate progression through the distinct

developmental stages of blood cell maturation were observed. The differential epigenetic modification of these sites needs to be validated in independent experiments before definitive conclusions can be formulated, and the biological function and down-stream functional consequences in terms of gene expression and chemical modification of DNA need to be clarified.

6.3 Summary of the *In Vitro* Studies

The work within ARIMMORA confirmed that most cells respond to ELF-MF by inducing ERK1/2 activation in a non-thermal manner. Contrary to expectations, the response was detected already at intensities as low as 0.15 µT. The duration and magnitude of the response is dependent on cell type. We also show that ELF-MF-induced ERK1/2 activation might be mediated, at least in part, by blue light under control by cryptochrome, for a new perspective on the perception of magnetic field by mammalian cells.

The activation of ERK1/2 in all cell lines examined was very low and is unlikely to support induction of proliferation and carcinogenesis. The magnitude of the effect varied significantly between cell lines. The mechanism by which cryptochrome is involved in ERK1/2 activation has yet to be determined.

The applicability of the signalling studies to carcinogenesis risk assessment is not direct, as the observed magnitude of ERK1/2 activation is probably not sufficient to induce carcinogenesis alone, and the involvement of cryptochrome in the processes remains to be confirmed. These preliminary results justify more efforts to investigate the low ERK1/2 activation as well as cryptochrome involvement to carcinogenesis through study of the signalling pathways that link these two systems.

The work of ARIMMORA also established a proof-of-concept that ELF-MF exposure (50 Hz, 1 mT) can affect the patterns of histone modifications. These effects are particularly notable in differentiating haematopoietic cells undergoing epigenetic programming. The identification of epigenetic footprints of ELF-MF exposure provides valuable information for future functional studies as well as the establishment biomarker panels for biological exposure assessment.
The analysis of epigenetic marks in a heterogeneous cell population is likely to average out small differences and thereby impacts the sensitivity. Thus, false negative results and conclusions cannot be completely excluded. The functional analysis of the identified ELF-MF-mediated epigenetic changes is beyond the aim of this project, thus the functional consequences of the alterations seen remain uncertain at this point.

The examination of activating and inactivating histone modifications in exposed and sham exposed Jurkat cells did not reveal evidence for a significant disturbance of global epigenetic patterns. There was no notable effect on cell proliferation or induction of cell death. Exposure of differentiating human haematopoietic stem cells revealed minor differences in apoptosis and cell cycle progression but not in lineage commitment. Programming of histone modifications was affected in a differentiation stage dependent manner. These data indicate that the ELF-MF exposure may have an effect on the epigenetic programming of differentiating haematopoietic cells. The functional relevance and the implication for carcinogenesis remain to be determined.

7. Animal Studies

The animal studies of WP6 included three sets of experiments. In one, an advanced constitutive susceptible laboratory mouse that expresses a gene (Sca1-*TEL-AML1*) associated with childhood pre-B-cell acute lymphoblastic leukaemia (pB-ALL)[19] was genetically engineered to study the effects of ELF-MF exposure on the genesis and/or the course of childhood B-cell leukaemia towards providing experimental evidence for cancer in test animals for use in the risk assessment. WP6 also included investigations with advanced biochemical methodologies of the effects of ELF-MF on maturational changes on the intact immune and blood cell systems in conventional laboratory mice. Finally, ELF-MF effects on the blood system components of laboratory rat strains with selective sensitivities to environmental stressors were investigated.

7.1 Transgenic Mouse Model

A new genetically modified laboratory mouse that expresses the fusion gene *TEL-AML1+* (also known as *ETV6-RUNX1+*) — found in children pre-disposed to develop B-ALL — was generated and tested for sensitivity to ELF-MF. The presence of the *TEL-AML1+* gene in a child's DNA only predisposes the child to leukaemia — not all children who have the gene develop leukaemia[20]. Samples taken from normal and modified mice for blood smear analysis show differences in the numbers of immature white blood cells consistent with predisposition to leukaemia. Of 30 exposed Sca1-*TEL-AML1+* mice, one animal developed pB-ALL; of 65 Sca1-*TEL-AML1+* non-exposed mice, none developed pB-ALL. The observation of a single case of leukaemia in the test mice provides proof-of-concept that mice carrying the *TEL-AML1+* gene can be used as proxies for human children to test the impact of ELF-MF and other environmental stressors on leukaemia development. The outcome was insufficient to support a change in the IARC classification of the cancer-causing potential of ELF-MF. In future studies with this or similar mouse strains, the statistical power of the results can be improved by increasing the number of Sca1-*TEL-AML1+* mice exposed; further, other exposure scenarios at various intensity levels should be explored. This test animal could also be used to investigate molecular and functional changes in immune cells and to address genomic and epigenomic aspects as well as the impact on the immune system associated with the development of pB-ALL.

7.2 *In Vivo* Genotoxic Effects and Changes in Haematopoiesis

The exposure of standard laboratory mice to ELF-MF was also studied. Pregnant female mice and their female offspring were exposed, with sham exposed controls, over a range of magnetic field intensities. Samples of blood and from the spleen were taken to evaluate changes in the numbers and activation status of white blood cell types, T-cells and B-cells, and macrophages. The samples were examined for micronuclei formation as an indicator of general gene damage, and for chemical modification of the DNA of specific genes thought to be involved in the development of leukaemia. A moderate but significant decrease in the number of CD8+ killer T-cells in the blood samples

taken from 28-day-old mice was found at all levels of ELF-MF exposure. The reduction in the CD8+ T-cells was transient, and it is not yet clear whether the effect has any functional meaning for the development of leukaemia. If the effect is involved in leukaemia progression, it may prove to be useful as a biomarker for ELF-MF exposure.

7.3 *In Vivo* Effects in Blood, Spleen, and Bone Marrow of F344 and Lewis rats

Exposure studies were also carried out in two well-known strains of laboratory rats, Lewis and Fischer 344 (F344), which are genetically related to a common background strain but differ in terms of sensitivity to stress, carcinogens, and ELF-MF exposure. Both male and female rats were exposed for 14 days, were sacrificed, and blood, spleen, and bone marrow samples were analysed for effects on numbers and types of white blood cells and on a variety of biochemical markers of leukaemia. The findings indicate sex- and strain-related differences in response to ELF-MF exposure in biochemical markers for the progression of programmed cell death. Independently from rat strain and sex, ELF-MF exposure altered levels of some cytokines, cell-signalling molecules involved in the immune response, with impact on the numbers and functionality of T-cells.

7. 4 Summary of the *In Vivo* Studies

The aim of the ARIMMORA *in vivo* studies was to address causal relationships between ELF-MF exposure and childhood leukaemia. To this aim, a triple complementary approach was used. First, an advanced constitutive susceptible mouse model of ETV6-RUNX1+ childhood B-ALL was developed to study the effects of ELF-MF exposure on the genesis and/or course of childhood B-cell leukaemia. Second, the work package included investigation of the effects of ELF-MF on maturational changes on the intact immune and haematopoietic systems by means of advanced immunotoxicological, genotoxicological, and gene-expression approaches in mice. Finally, ELF-MF effects on the haematopoietic systems of susceptible rat strains were also investigated.
The main outcomes are as follows:

i) A new mouse model (Sca1-*TEL-AML1*+) of childhood pre-B-cell acute lymphoblastic leukaemia (pB-ALL) has been generated.

ii) One of 30 Sca1-*TEL-AML1*+mice exposed to 1.5 mT ELF-MF developed pB-ALL by 14 months of age, while of 65 Sca1-*TEL-AML1*+ non-exposed mice, none developed pB-ALL. Mice were observed for 24 months. Consistent T-cell-immunoalterations are identified in both mice and rats exposed to different exposure conditions regarding field strength (0.01 – 10 mT), duration, and harmonics.

iii) Transient reduction in the $CD8^+$ T-cells may serve as a biomarker for ELF-MF exposure in young CD-1 and B6CBA mice. Whether the observed reduction of CTL has a functional effect cannot be concluded from the present studies.

iv) Finally, there is no direct genotoxic effect observed in young and adult CD-1 mice at 10 µT, 1 mT, and 10 mT ELF-MF.

8. Macrodosimetry, Microdosimetry, and Biophysical Mechanisms

The biophysical mechanisms involved in biological responses to ELF-MF were addressed in WP7. Macrodosimetry — the measurement of the effects of radiation in the tissues and organs — was performed for free-running mice and rats to determine the levels of electric and magnetic fields induced for each tissue as a function of age, posture, and the location and incident directions of field in the exposure systems. The low frequency solvers of SEMCAD X (SPEAG) were used to numerically model the dosimetry with high-resolution computational animal models. The findings are correlated with respect to direct and indirect effects for the different exposure situations and with the fields induced in humans in real-life exposure situations. Approaches to macrodosimetry were considered for use in microdosimetry — the measurement of the effects of radiation at the level of the cell and sub-cellular structures — for exposure of living systems to electric and magnetic fields. Potential target molecules and systems to be considered as relevant for the biophysical mechanism were evaluated. The goal was to identify the most promising target molecules and the appropriate experimental approaches and exposure conditions to use to further elucidate the underlying biophysical mechanisms of ELF-MF exposure.

The ways that externally applied magnetic fields induce fields within biological tissues are influenced by the size, shape, anatomy, and material properties of the biological entity. Computational biophysical modelling was used to compare human exposure (WP2) with experimental evidence from exposure of cells (WP5) and animals (WP6) towards correlating cell culture studies with animal studies and extrapolating to exposure of children. Computational human and animal models of the Virtual Population were used to create a mapping algorithm for comparing rodent age and size with human age and size, and exposure assessments made with physical phantom models of rodents enable mapping of exposure levels between rodents and humans. The computational models were also used to determine exposure levels in tissues of interest: the blood, bone marrow, spleen, and thymus. Computer simulations were used to estimate the influence of the rodents' positions and postures.

The findings indicate that the level of magnetic field exposure may be taken directly as the incident field at the location of a given tissue or organ and is not significantly modified by the currents induced within the tissues or organs. Therefore, for a given magnetic field exposure, the correlation between incident and induced fields for rats and mice is directly the exposure field intensity. For the electric fields induced in the tissues and organs, significant differences in morphology and internal anatomy of humans and rodents dictate that the average electric field induced across all tissues should be used for comparisons. Ratio factors of 4.0 times higher exposure for rats and 7.4 times higher for mice compared to children were computed.

The resources available within the framework of the ARIMMORA project for the investigation of microdosimetry limited the work to a comprehensive review of the literature. Focus was given to the applicability of macrodosimetry concepts and definitions to microdosimetry applied to ELF-MF exposures. The review led to the conclusion that the only promising mechanistic model of interaction is the radical pair hypothesis; another possible interaction mechanism involves biomagnetite, a naturally occurring iron-containing crystal with magnetic properties, and the

potential near-field effects of biomagnetite on the radical pair mechanism. Magnetite has been detected in human heart, spleen, and liver[21]. Recommendations for future research on problems of microdosimetry include the use of experimental and numerical analysis approaches to improve models of the properties of cell membranes, to establish models of cell surface layers, and investigate the nonlinearity of magnetic field responses of cell membranes for understanding microdosimetry at the biomolecular level. The need for a non-thermal concept for specific absorption rate in microdosimetry has been identified.

Another emerging area is magnetic field sensing by biological tissues, and hypotheses regarding biophysical mechanisms of electro-magnetic field interactions with biological tissues need further development. The biophysical interaction mechanism identified as the most plausible to explain biological responses to ELF-MF exposure is the radical pair mechanism, which has been investigated in terms of magnetosusceptability responses in animals, e.g., in geo-orientation of migratory birds[22]. Magnetosusceptability is thought to be conferred by light-sensitive generation of pairs of radicals — molecules having an unpaired electron — in cryptochrome, a blue-light-sensitive protein related to photolyase DNA repair enzymes[18]. The involvement of the superoxide radical ascorbate (vitamin C), a potent antioxidant, in the radical pair mechanism could indicate a connection with oxidative stress mechanisms associated with cancer. Cryptochrome is known to be involved in circadian rhythms, which have been suggested to impact cancer[23].

9 ARIMMORA Risk Assessment

9.1 Carcinogenicity in Humans

There is limited evidence in humans for the carcinogenicity of extremely low frequency magnetic fields in relation to childhood leukaemia. A positive association has been observed for which a causal interpretation is considered by the ARIMMORA group to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence because of the low number of exposed cases.

The observed association is considered credible because it is fairly consistent across a large number of studies in different settings and time periods. The applied methodologies are state-of-the-art for case-control studies. Since the evaluation by the IARC in 2001, several new studies have been published and chance is less likely to be a plausible explanation. Nevertheless, the number of exposed cases >0.3 μT from all available studies is low (<100 out of ten thousands).

All of the evidence arises from case-control studies. For this type of study the representativeness of controls for the population from which the cases emerged is crucial. In studies using field measurements response rates were often low and thus selection bias may have occurred. The main concern is that the number of exposed individuals in controls had been underestimated, which would produce an overestimation of the risk. Only a few studies were nested in population settings and, thus, not dependent on consent for participation.

Another concern is publication bias, which could occur because the number of exposed cases is expected to be small in most settings. Thus, it is conceivable that in some studies by chance no or very few exposed cases occurred. Such studies might be less likely to be published. This may be less of a concern for studies of ELF-MF measurements but rather for studies of distance to power lines as the exposure measure.

There are few established risk factors for childhood leukaemia. Studies in which ELF-MF and other possible risk factors for childhood leukaemia are simultaneously monitored have not found evidence for confounding. While the possibility of confounding due to an unknown risk factor cannot be ruled out, there is currently a lack of convincing candidates.

As the ARIMMORA measurements have shown, some exposure misclassification is unavoidable in epidemiological studies. Since this type of error is expected to be similar for cases and non-cases (non-differential), risk, when it exists, is rather underestimated than overestimated.
In conclusion, despite several new studies on the topic, the evidence for human studies on childhood leukaemia has hardly changed since the assessment by the IARC in 2001.

9.2 Carcinogenicity in Experimental Animals

There is inadequate evidence for either direct or indirect leukaemogenic effects of ELF-MF in animal models.

There is a lack of data from studies outside the ARIMMORA consortium, and the studies performed within ARIMMORA have insufficient statistical power.

The predisposed leukaemia Sca1-*TEL-AML-1*+ transgenic mouse model developed in the ARIMMORA project provides the proof-of-concept, and the quantitative statistical limitations could be overcome with future investigations of ELF-MF effects on this or a similar mouse model performed with larger numbers, in additional laboratories, and under additional exposure conditions.

9.3 Mechanistic and Other Relevant Data

Recent studies in the literature have addressed aspects of cell signalling, genotoxicity and growth control. Advances are in general small and point towards consistent effects of co-stressing conditions and cell type dependency. The magnitude of effects is marginal, and the impact on carcinogenesis is uncertain. Thus, the evidence for the contribution to carcinogenesis overall is weak.

Although there is some evidence for the effects of ELF-MF on the immune system of both mice and rats, mostly observed within ARIMMORA, the immune system alteration data cannot be directly linked to ELF-MF-associated leukaemogenesis. Therefore the evidence for the contribution to carcinogenesis at this point is weak.

Newly emerging topics include cell differentiation and reprogramming. While the reported effects of cell differentiation and reprogramming are substantial, the number of studies is small. Although interesting, the impact of these effects on cancer development at this stage is weak.
Another emerging area is magnetic field sensing. There are wide range of studies that point to the involvement of cryptochrome and the radical pair mechanism in animal magneto-reception. Cryptochrome is known to be involved in circadian rhythms, which have been suggested to impact cancer. However, the evidence for the contribution of ELF-MF to carcinogenesis at this stage is weak.

Pertinent findings of the ARIMMORA project indicate that ERK1/2 activity is increased in response to ELF-MF in all cell lines tested. Notably, effects were detectable within minutes of exposure to sub-µT fields (50 Hz, 0.15 µT – 1 mT). The data indicate possible involvement of cryptochrome in the mechanism. These effects are cell line dependent and the level of ERK response may not be sufficient to play a role in carcinogenesis. The evidence for the contribution to carcinogenesis at this point is weak.

The examination of chromatin modifications in exposed and sham exposed human haematopoietic stem cells revealed minor differences in epigenetic programming. Programming of activating and inactivating histone modifications was affected in a cell differentiation stage-dependent manner. The functional relevance needs to be determined. The evidence for the contribution to carcinogenesis at this point is *weak*.

9.4 Overall Evaluation

The ARIMMORA Risk Assessment classifies the relationship between exposure to extremely low-frequency magnetic fields and the risk of childhood leukaemia as:

Group 2B: The agent is possibly carcinogenic to humans

This category of the hazard identification is the result of the limited evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals. There was only weak supporting evidence from mechanistic studies.

Potential impact and main dissemination activities and exploitation results

1. Impact

1.1 Impact on Science

While the overall evidence has not changed compared to the previous assessments by the IARC in 2001 and the three SCENIHR opinion statements from 2007, 2009, and 2015, the ARIMMORA project still added important knowledge on the possible carcinogenicity of exposure to ELF-MF.

Most importantly, a mouse model for predisposed childhood leukaemia has been successfully established and used. Although the impact of EMF-MF exposure on the development of leukaemia is uncertain at this point, this achievement is considered an important step towards providing a relevant disease model. If used with larger numbers of mice and applying several different exposure levels, it has the potential to provide major future insights. Mechanistic findings related to the immune system also have the potential to provide a future insight if a role in the development of childhood leukaemia is identified. Other mechanistic effects were observed at the levels of cell signalling and epigenetic programming. Although their biological significance and contribution to carcinogenicity is currently unclear, the findings implicate novel, as yet unexplored, mechanisms of interaction of EMF-MF with cell behaviour.

1.2 Impact on Risk

The findings of ARIMMORA are insufficient to impact decisions on safety policy at present but mandate that the research effort be accelerated as they point to future research that could provide a step-change in future assessments. The consortium recommends that future investigations be addressed with one or two 3-year research programs of similar size.

The results also encourage the current policy of 'prudent avoidance'. The policy in view of the current state of knowledge regarding the risk of childhood leukaemia from ELF-MF exposure might include deciding to locate newly built schools at sufficient distance from high voltage power lines, or, conversely new lines far from existing schools. However, there is as yet insufficient scientific evidence to justify the relocation of existing schools and power lines.

1.3. Impact on Measurement Standards

Measurement standards are likely to change as the instrumentation and procedures developed in ARIMMORA empower more reliable demonstration of compliance in the close vicinity of ELF-MF sources with the basic restrictions. This can be considered a breakthrough, in particular in the context of with the EU directives on EMF exposure. However, also NIOSH and Industry Canada have shown great interest.

2. Dissemination

The ARIMMORA dissemination aimed to promote knowledge sharing among the scientific community and standardisation bodies and to increase awareness of the project results on the part of the public. Various instruments were and are used to reach that goal.

2.1 Project Website

A project website was established at the beginning of the ARIMMORA project and was continuously updated during the course of the project. The purpose of the website was to exchange information and share confidential data within the consortium as well as to promote the project and its activities to the wider scientific and user communities. It, therefore, consisted of public and private sections. The public section comprised all material accessible to the general public, whereas

the private section is intended for the internal organisation of the project and could only be accessed via login with a username and password. The structure of the ARIMMORA website at http://www.arimmora-fp7.eu was designed in a clear and consistent way so that visitors and users could easily locate all information intended for them. The main sections were listed in the left navigation pane.

2.2 Project Leaflet

A project leaflet written in generally understandable language, containing a summary of the main objectives and methodology and the project partners, was developed. The leaflet aimed not only to promote the project to the public, but was also used to inform people who were affected by the studies, e.g., pupils (and their parents) of the schools and other facilities where measurements were performed. The leaflet is available for download from the project website and was distributed in printed form at conferences and other events during the lifetime of the project.

2. 3 Dissemination to the Scientific Community

Dissemination activities of ARIMMORA to the scientific community included various channels, such as participation in scientific meetings, conferences, and workshops, publications, and liaisons with other research projects. The ARIMMORA project and its results have been presented at around 20 national and international scientific meetings, conferences, and workshops in the form of posters and oral presentations and distribution of the project leaflet.

Dissemination of the project results to the scientific community and industry and general public has also been established via a workshop. The IT'IS Foundation, coordinator of ARIMMORA, organized a scientific workshop covering, among other topics, ARIMMOA-related research results. The workshop "EMF Health Risk Research - Lessons Learned and Recommendations for the Future – 7 years later" took place in Autumn 2012 (October 21 – 26, 2012) at the Center Stefano Franscini, in Monte Verità, Ascona, Switzerland. The workshop brought together world-renowned researchers in the field of EMF and health as well as government health protection experts and standardization committees to analyze and synthesize newly available research results. It provided a forum for extensive discussions that has been available neither at scientific meetings nor at official standard/assessment group meetings, namely, to focus on those experiments that are not in line with current understanding of EMF interaction with biological systems.

2.4 Dissemination to Standards

The objective of Work Package 9 ("Dissemination to Standards") was the direct dissemination of the results of ARIMMORA. The results have been disseminated to the following authorities defining safety guidelines and public policies:

The results of the exposure assessments research and development has been disseminated to IEC, ICES, Industry Canada, NIOSH, FDA. The work will have a direct impact on measurement standards for complex near-field exposures situation, in particular in the occupational environments.

2.5 Expoitable Results

A transgenic mouse in which the expression of the first B-ALL genetic lesion (*TEL-AML1*+ human oncogene) is targeted to haematopoietic stem/progenitor cells was developed. A potential risk of this strategy was that the transgenic expression of the human TEL-AML1 oncogene might cause a leukaemic process in the mice too rapid to allow the to the possible ELF MF effect on B-ALL progression *in vivo* to be addressed. However, like in humans, the leukaemic process followed by the Sca1-*TEL-AML1*+ mouse model is not rapid, and this transgenic mouse is an ideal model for *in vivo* modeling of the possible effects of ELF-MF exposure on B-ALL. A patent application to describe the Sca1-*TEL-AML1*+ mouse model developed within the project has been filed.

A number of innovative research tools were developed and used in addition to the patented *TEL-AML1*+ laboratory mouse, namely, 1) an improved device for measuring the properties of ambient electromagnetic fields was designed and constructed, and the prototype was validated and used to collect data. 2) Exposure systems for cell cultures and for humane housing of rodents were developed, manufactured, and installed. In the course of the project, one of the cell culture exposure systems was adapted for exposures and sham exposures at sub-µT levels of ELF-MF and for co-exposure to light, to test for the involvement of the light-sensitive protein cryptochrome in the cell signalling response. 3) Novel children models posed in typical realistic postures were developed. These tools will eventually become commercially available for the benefit of future investigations.

Address of project public website and relevant contact details

Public website: http://arimmora-fp7.eu

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