Comment

Extremely Low-Frequency Magnetic Fields and Risk of Childhood Leukemia: A Risk Assessment by the ARIMMORA Consortium

Joachim Schüz,[1]* Clemens Dasenbrock,[2] Paolo Ravazzani,[3] Martin Röösli,[4] Primo Schär,[5] Patricia L. Bounds,[6] Friederike Erdmann,[1] Arndt Borkhardt,[7] César Cobaleda,[8] Maren Fedrowitz,[9] Yngve Hamnerius,[10] Isidro Sanchez-Garcia,[11] Rony Seger,[12] Kjeld Schmiegelow,[13] Gunde Ziegelberger,[14] Myles Capstick,[6] Melissa Manser,[5] Meike Müller,[2] Christoph D. Schmid,[4] David Schürmann,[5] Benjamin Struchen,[4] and Niels Kuster[6]

[1]Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France
[2]Fraunhofer ITEM, Hanover, Germany
[3]National Research Council of Italy, Institute of Electronics, Computer and Telecommunication Engineering, Milan, Italy
[4]University of Basel and Swiss Tropical and Public Health Institute, Basel, Switzerland
[5]Department of Biomedicine, University of Basel, Basel, Switzerland
[6]ITIS: Foundation for Research on Information Technologies in Society, Zürich, Switzerland
[7]Medical Faculty, Department of Pediatric Oncology, Haematology and Clinical Immunology, Heinrich-Heine University, Düsseldorf, Germany
[8]Spanish National Research Council (CSIC), Centro de Biología Molecular Severo Ochoa, Madrid, Spain
[9]University of Veterinary Medicine, Hanover, Germany
[10]Chalmers University of Technology, Gothenburg, Sweden
[11]Spanish National Research Council (CSIC), Instituto de Biologia Molecular y Celular del Cancer, Salamanca, Spain
[12]Weizmann Institute of Science, Rehovat, Israel
[13]University Hospital, Copenhagen, Denmark
[14]German Federal Office for Radiation Protection, Neuherberg, Germany

Exposure to extremely low-frequency magnetic fields (ELF-MF) was evaluated in an International Agency for Research on Cancer (IARC) Monographs as "possibly carcinogenic to humans" in 2001, based on increased childhood leukemia risk observed in epidemiological studies. We conducted a hazard assessment using available scientific evidence published before March 2015, with inclusion of new research findings from the Advanced Research on Interaction Mechanisms of electroMagnetic exposures with Organisms for Risk Assessment (ARIMMORA) project. The

Grant sponsor: European Commission; grant number: 282891.

Conflicts of interest: Prof. Kuster and Dr. Capstick report ownership of public utility company shares. Dr. Capstick also declares that he consults on research questions with SPEAG. Prof. Hamnerius declares that he consults privately on problems concerning electromagnetic fields, such as measurements and calculations.

*Correspondence to: Joachim Schüz, Section of Environment and Radiation, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, F-69372 Lyon, France. E-mail: schuzj@iarc.fr

Received for review 21 December 2015; Accepted 19 February 2016

DOI: 10.1002/bem.21963
Published online XX Month Year in Wiley Online Library (wileyonlinelibrary.com).

IARC Monograph evaluation scheme was applied to hazard identification. In ARIMMORA for the first time, a transgenic mouse model was used to mimic the most common childhood leukemia: new pathogenic mechanisms were indicated, but more data are needed to draw definitive conclusions. Although experiments in different animal strains showed exposure-related decreases of CD8+ T-cells, a role in carcinogenesis must be further established. No direct damage of DNA by exposure was observed. Overall in the literature, there is limited evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals, with only weak supporting evidence from mechanistic studies. New exposure data from ARIMMORA confirmed that if the association is nevertheless causal, up to 2% of childhood leukemias in Europe, as previously estimated, may be attributable to ELF-MF. In summary, ARIMMORA concludes that the relationship between ELF-MF and childhood leukemia remains consistent with possible carcinogenicity in humans. While this scientific uncertainty is dissatisfactory for science and public health, new mechanistic insight from ARIMMORA experiments points to future research that could provide a step-change in future assessments. Bioelectromagnetics.

Key words: risk assessment; hazard identification; electromagnetic fields; adverse effects; children; leukemia

INTRODUCTION

Exposure to extremely low-frequency magnetic fields (ELF-MF), related to power transmission and electrical appliance use, was judged in 2001 by the International Agency for Research on Cancer (IARC) Monograph program on the evaluation of carcinogenic risks to humans [Cogliano et al., 2011] as possibly carcinogenic to humans (Group 2B), based on limited scientific evidence for childhood leukemia [IARC, 2002]. For other cancers in children or cancers in adults (including leukemia), evidence was judged inadequate [IARC, 2002]. No re-evaluation has been performed by the IARC since then, but other assessments have referred to it when updating literature reviews, notably those by the World Health Organization (WHO) in its Environmental Health Criteria series [WHO, 2007] and the European Commission's (EC) Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [2007, 2009, 2015]. All of those systematic assessments were in agreement with the previous IARC classification of possible carcinogenicity for childhood leukemia and inadequate evidence for other cancers. In particular, all assessments commonly pointed to lack of convincing mechanistic data and lack of appropriate animal models when addressing childhood leukemia [SCENIHR, 2007, 2009, 2015; WHO, 2007]. To overcome these limitations, the European Commission-funded project "Advanced Research on Interaction Mechanisms of electroMagnetic exposures with Organisms for Risk Assessment" (ARIMMORA), which started on October 1, 2011, embarked on a series of experiments. These were targeted to find possible pathways to explain the association between ELF-MF and childhood leukemia, given that in more than 20 epidemiological studies, such an association had been observed with relatively high consistency [Schüz, 2011].

To conclude the ARIMMORA project, a risk assessment was conducted on the basis of available scientific evidence published before March 9, 2015 and including new results from ARIMMORA experiments. This risk assessment included, first, a hazard identification informed by the IARC Monograph program evaluation scheme on the level of evidence regarding carcinogenicity to humans and, second, an estimation of how many diagnoses of leukemia in children would be attributable to the agent, assuming causality. This is a summary of the ARIMMORA [2015] risk assessment.

METHODS

Importantly, this hazard identification was not an evaluation within the IARC Monograph program, but the IARC evaluation scheme (Fig. 1) was strictly followed, as the scientific community would be familiar with the interpretation of the outcome [IARC, 2002; Cogliano et al., 2011]. According to the IARC, in a first step two distinct types of evidence, namely cancer in humans (epidemiology) and cancer in experimental animals (in vivo studies), are evaluated separately as to whether there is sufficient evidence of, limited evidence of, or inadequate evidence of carcinogenicity, or evidence suggesting lack of carcinogenicity. Mechanistic and other relevant data are classified into weak, moderate, or strong, if appropriate, and address whether the mechanism is likely to be operative in humans. From the combination of these three lines of evidence, the agent is classified into Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), 2B (possibly carcinogenic to humans), Group 3 (not classifiable as to its carcinogenicity to humans), or Group 4 (probably not carcinogenic to humans), as outlined in the

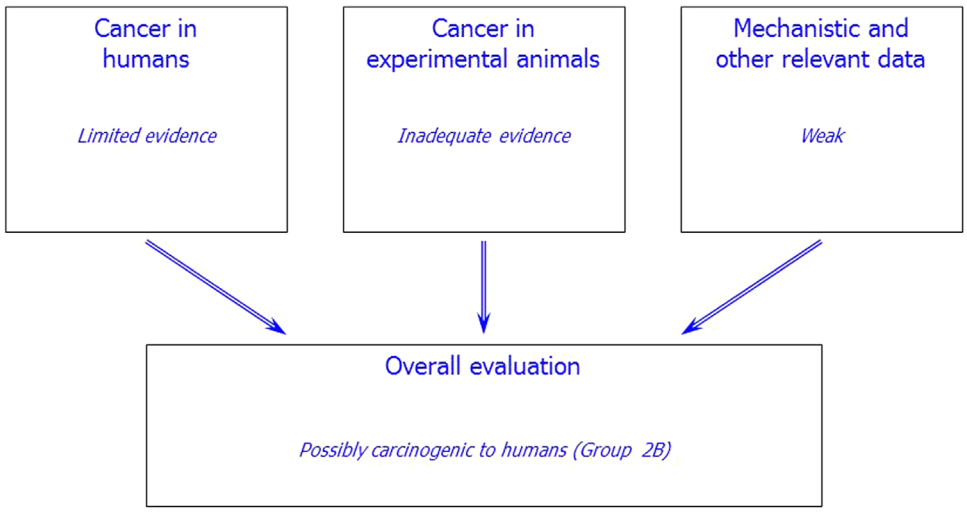

Fig. 1. ARIMMORA's evaluation of association between extremely low-frequency magnetic fields and risk of childhood leukemia according to the classification scheme of carcinogenicity from the IARC Monograph program on the evaluation of carcinogenic risks to humans.

preamble of the IARC Monographs program [2015]. In addition, and as in the IARC Monographs, human exposure data was reviewed.

The evidence base for the ARIMMORA risk assessment consisted of three sources. First, the SCENIHR [2015] update of their systematic literature review with collected evidence up to July 2014 was used to not duplicate other work commissioned by the EC; however, disagreements with this evaluation in terms of individual studies or conclusions would be noted [ARIMMORA, 2015]. Second, a review of individual studies published between July 2014 and March 9, 2015 was performed. Third, a review of outcomes from the ARIMMORA experiments, irrespective of whether they were accepted for publication at time of the risk assessment was performed [ARIMMORA, 2015].

RESULTS

Exposure

Measured typical daily mean personal exposure of children in Europe is below 0.1 μT, while only a small proportion (1–2% of children) are exposed to ELF-MF daily means >0.3 μT, corresponding to >60 μV/m induced fields. An association between ELF-MF and childhood leukemia risk has been observed mainly at daily mean levels >0.3 μT [Schüz, 2011]. New measurements of ELF-MF exposure of children in Italy and Switzerland within ARIMMORA confirmed those typical exposure levels of earlier studies, but highlighted the importance of child's behavior as a modifier of daily mean exposure levels, particularly for children living close to power lines [Struchen et al., 2015]. Nevertheless, measurements show good agreement between daily mean exposure levels from the child's bedroom and personal measurements, confirming that stationary bedroom measurements in epidemiological studies are good proxies of personal exposure.

Within ARIMMORA, measurements of household near-field sources showed that fields decay steeply with distance dropping to common household background levels <0.1 μT within centimeters to normally much less than a meter; most sources are used normally either relatively far from children or for only short periods of time, for example, fans and vacuum cleaners, and tend to act locally on the body in contrast to large sources such as power lines. The frequencies of fields emitted by devices with "universal" power supplies are intermediate frequency (IF) and not in ELF range, but whether IF exposure is relevant to leukemogenesis is unknown. Harmonic components of 50 Hz ELF-MF contribute somewhat to overall exposure, but although these contributions cannot be neglected, amplitudes are low, even in the worst-case scenarios. Measurement of ELF-MF at 50/60 Hz in bedrooms, as done in epidemiological studies, therefore appears to be an appropriate approach.

In addition, the ARIMMORA findings fill some gaps of knowledge about exposure assessment of pregnant women by means of a computational approach. For fetal ELF-MF exposure, the most exposed tissues in terms of maximum electric field have been found to be skin, fat, and subcutaneous adipose tissue across all gestational ages; and, in all tissues, induced electric field exposure increases with increase in gestational

age [Liorni et al., 2014]. Harmonic components also add some contributions to the overall level of electric fields induced in fetuses, but again are low, even in worst-case scenarios [Fiocchi et al., 2015].

Epidemiology

A positive association between residential exposure to ELF-MF and childhood leukemia has been observed in several epidemiological studies in various settings at different points in time. Combining those studies in pooled analysis showed relative risks of 1.5–2 at daily mean exposure levels exceeding 0.3/0.4 μT [Ahlbom et al., 2000; Kheifets et al., 2010; Schüz, 2011]. Despite data from more than 20 studies, there were small numbers of highly exposed children, hence, some uncertainty in risk estimates remained and precision to explore exposure-response relationships was limited. As an alternative to causal interpretation of epidemiological findings, methodological shortcomings such as information bias, selection bias, confounding, and publication bias are of concern, although no strong support for such alternative explanations had been obtained from either validation or simulation studies [IARC, 2002; Schüz, 2011; SCENIHR, 2015]. Results from more recent studies were broadly comparable with those from earlier studies [Ahlbom et al., 2000; Kheifets et al., 2010], but similar case-control designs and methods of exposure assessment were used, and it is therefore unclear whether consistency points to a consistent association or consistent underlying biases. Among the recent studies, one notable large register-based study from the United Kingdom indicates that observed association is present only in cases occurring before 1990 [Bunch et al., 2014] and suggests that factors other than ELF-MF may play a role.

While no epidemiological study was conducted within ARIMMORA, epidemiology played an influential role in hazard identification and risk assessment. It was consistency of epidemiological findings supporting evaluation of possible carcinogenicity in various previous hazard identification and risk assessments [IARC, 2002; SCENIHR, 2007, 2009, 2015; WHO, 2007]. However, doubts about methodological limitations remain, and bias and confounding cannot be ruled out with reasonable confidence. Therefore, the evaluation of the evidence was considered "limited" by the ARIMMORA consortium.

Experimental Animals

In the previous hazard identification and risk assessments by the IARC, the WHO, and the SCENIHR, evidence from studies in experimental animals was considered inadequate [IARC, 2002; SCENIHR, 2007, 2009, 2015; WHO 2007]. A major limitation was, however, that no human-based leukemia predisposed animal model was used.

One goal of ARIMMORA was therefore to study the possible role of ELF-MF in a transgenic mouse model in which the first genetic lesion associated with childhood precursor-B acute lymphoblastic leukemia (pB-ALL), namely *ETV6-RUNX1*, was constitutively expressed in the hematopoietic stem/progenitors compartment with potential to mimic initiation of human pB-ALL [Wiemels et al., 1999; ARIMMORA, 2015; Martín-Lorenzo et al., 2015]. Initially, 34 mice were exposed to 1.5 mT ELF-MF, while 27 were unexposed and monitored for a maximum of 24 months. Four exposed and two unexposed were found dead during the course of the experiment, but cause of death could not be determined. Excluding these dead animals at month 22, of a total of 30 exposed mice, one developed ETV6-RUNX1-positive pB-ALL at 14 months of age, while none of 25 non-exposed animals plus an independent cohort of 40 animals developed pB-ALL. It should be noted that this first experiment in which this transgenic mouse model was used was set up without any prior knowledge of frequency of leukemia development in mice and therefore provides data on the baseline leukemia rate in unexposed mice, to allow more informed statistical power calculations in future experiments.

The main outcome of animal studies within ARIMMORA is therefore that a new pB-ALL mouse model was successfully established and utilized for ELF-MF exposure studies. More data are required, as in this first experiment only one exposed mouse and no unexposed mice developed leukemia. Overall, from totality of the literature and new ARIMMORA results, evidence of carcinogenicity in experimental animals is considered "inadequate."

Mechanistic Data

Previous hazard identification and risk assessments describe lack of support from mechanistic data as a major weakness in causal interpretation of epidemiological findings that suggest an association between ELF-MF and childhood leukemia [IARC, 2002; SCENIHR, 2007, 2009, 2015; WHO 2007; Schmiedel and Blettner, 2010]. Without identification of relevant mechanisms of action, it is impossible to integrate all reported positive and negative experimental outcomes into a consistent picture [Santini et al., 2009]. Nevertheless, the body of evidence that ELF-MF can modulate cellular responses to chemical or physical agents is steadily increasing and, in some areas, gaining robustness, although underlying mechanisms, which are likely to be diverse and

complex, remain to be clarified [ARIMMORA, 2015]. These findings indicate that multiple cellular processes that depend on interactions of distinct molecular pathways may be affected in a similar fashion. In respect to neoplastic diseases, use of stem cells for mechanistic studies should provide better relevance for risk assessment, as non-terminally differentiated cells that escape control mechanisms are believed to be central to carcinogenesis. So far, studies in which stem cells were used are rather sparse [SCENIHR, 2015].

As one ARIMMORA goal on mechanisms, the impact of ELF-MF exposure on the immune system was analyzed for changes in hematopoiesis and gene expression profiles as well as for genotoxic and epigenetic effects [ARIMMORA, 2015]. Female CD-1 mice were exposed to 50 Hz ELF-MF at 10 μT, 1 mT, and 10 mT (controls were sham exposed), starting with pregnant dams and continuing to female offspring up to 90 days of age. Most importantly, on day 28 diminished numbers of CD8+ cytotoxic T-lymphocytes were seen in peripheral blood in all ELF-MF groups. Although the effect was moderate, it is statistically significant; however, the effect did not become stronger with increasing exposure level and was not observed after 60 and 90 days. Furthermore, number of B-lymphocytes was significantly increased in blood after 60 days of 1 mT and 10 mT exposure, and number of monocytes was diminished at exposure to 10 mT. Finally, no significant induction of micronuclei in peripheral blood erythrocyte fraction was observed, which would indicate profound and direct DNA-damaging potential of ELF-MF exposure.

Analysis of peripheral blood of ELF-MF-exposed transgenic mice from the experiment described above (see "Experimental Animals") showed a small, but statistically significant decrease in numbers of CD8+ T-cells in exposed mice at 2 months of age. There were no significant changes in populations of myeloid cells.

As another ARIMMORA goal on mechanisms, two well-known inbred rat strains, Lewis and Fischer 344 (F344), which are genetically related to the same background strain but differ in terms of sensitivity to stress, carcinogens, and ELF-MF exposure, were used to determine effects of in vivo ELF-MF exposure in blood, spleen, and bone marrow. Cell proliferation and apoptosis, cell cycle, cytokine secretion, and possible ELF-MF targets, expression and functionality of adrenergic receptor were investigated in animals exposed at 50 Hz 0.1 mT magnetic fields [ARIMMORA, 2015]. Effects of ELF-MF exposure on hematopoietic cell signaling were observed, and these confirmed differences between the two rat strains and sex. ELF-MF affected cellular regulation with distinct functional consequences. Apoptotic cascade and expression of cytokines related to cell death and cellular activation were altered in a strain- and sex-dependent manner and corresponded to alterations in peripheral blood and affected proliferative capacities after mitogen stimulation. Independent of rat strain and sex, the majority of cytokines altered by ELF-MF exposure impacted number of T-cells or were involved in T-cell functions.

In in vitro studies within ARIMMORA [2015], key regulatory mechanisms of carcinogenesis, namely signaling processes and epigenetic regulation were addressed. Pertinent findings indicated that ERK1/2 activation increases in response to ELF-MF in most cell lines tested. Notably, effects were detectable within minutes of exposure to low μT fields, comparable to residential levels. Additional data indicated possible involvement of the photoreceptor cryptochrome in the mechanism of ELF-MF perception. However, these effects were cell-line dependent, and signaling response level may not be sufficient to play a role in carcinogenesis.

Cell identity and fate is defined by the epigenetic landscape. As cells change their phenotype during carcinogenesis, the pattern of the chromatin modifications are dramatically altered. These aberrations are therefore a hallmark of cancer but may also be a driving force for carcinogenesis [Morgan and Shilatifard, 2015].

Examination of activating and inactivating histone modifications in exposed and sham exposed leukemic Jurkat cells at 50 Hz 1 mT did not reveal evidence for a significant disturbance of global epigenetic patterns but yielded some candidate regions for future investigation. Also, no effect on cell proliferation or induction of cell death was detected. Exposure of differentiating human hematopoietic stem cells revealed minor changes in apoptosis and cell cycle progression but not in lineage commitment. Activating and inactivating histone modifications were affected at a small number of loci in a differentiation-stage-dependent manner. These data establish a proof-of-concept that ELF-MF exposure can affect patterning of histone modifications. This appears to be particularly notable in differentiating hematopoietic cells undergoing differentiation but less so in leukemic cells, suggesting that ELF-MF affect programming rather than stability of epigenetic marks. Functional relevance and implication for carcinogenesis remain to be determined.

In summary, despite different exposure conditions, consistent T-cell immuno-alterations were identified in both mice and rats. However, biological

consequences of observed reductions of CD8+ T-cells remain to be determined. Finally, no direct genotoxic effects were observed in young and adult CD-1 mice. Some possible mechanistic effects on signaling processes and epigenetic regulation were observed, but their functional relevance and role in carcinogenicity is unclear at present.

Taken together with the body of evidence from outside ARIMMORA, no mechanism was identified from mechanistic studies to confirm epidemiological findings for childhood leukemia. Hence, overall, mechanistic evidence for specific cellular responses to ELF-MF exposure from the literature and ARIMMORA experiments can be considered moderate while evidence for contribution to carcinogenesis remains weak.

Potential Risk at Population Level

A recent estimate of incidence of childhood leukemia attributable to ELF-MF in Europe showed proportions of 0.30% (95% confidence interval (CI), −0.12% to 1.12%) for a categorical threshold exposure model, 1.53% (CI, −0.41% to 4.03%) for a categorical non-threshold model, and 1.86% (CI, −0.27% to 18.61%) for a continuous non-threshold model when the exposure-response relationship between ELF-MF and childhood leukemia risk was assessed, suggesting that, under an assumption of causality, up to 2% of childhood leukemia may be caused by ELF-MF exposure, which would correspond to 10–61 cases annually in the European Union (27 states at that time) [Grellier et al., 2014]. With confirmation of exposure levels from ARIMMORA, this estimate appears to be the most accurate and finds support from the ARIMMORA group.

DISCUSSION

The outcome of hazard identification within the ARIMMORA risk assessment is that the relationship between exposure to the agent ELF-MF and risk of childhood leukemia is considered consistent with "IARC Group 2B" classification of possibly carcinogenic to humans (Fig. 1). This category is the result of limited evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals. There was only weak supporting evidence from mechanistic studies.

While overall interpretation has not changed compared to previous assessments by IARC [2002]; the WHO [2007]; and the SCENIHR [2007, 2009, 2015]. Opinion statements, the ARIMMORA project still adds important knowledge on the possible carcinogenicity of exposure to ELF-MF. Most importantly, a transgenic mouse model for predisposed childhood leukemia has been successfully established and utilized. This is considered a major step forward. In future experiments, larger numbers of animals should be used with a range of exposure levels. Some possible mechanistic effects were observed, the functional relevance and role in carcinogenicity of which are unclear at present. Findings related to the immune system have potential to provide future insight if a role in development of childhood leukemia is identified. ARIMMORA confirmed that exposure levels at which increased risks of childhood leukemia were observed in epidemiological studies are very uncommon in Europe, and it may be estimated that, under an assumption of causality, up to 2% of childhood leukemia may be caused by ELF-MF exposure in Europe.

In conclusion, the ARIMMORA risk assessment considers evidence on ELF-MF and childhood leukemia as being consistent with the classification of possibly carcinogenic to humans (IARC Group 2B). The continuing existence of major scientific uncertainty since 2001 is a dissatisfactory situation in terms of public health and prevention [Maslanyj et al., 2010] as well as for science, given the large number of studies and the large bulk of additional scientific data collected over the last decades. It highlights, however, the challenge of establishing convincing evidence for a presumably weak association between a rare exposure and rare disease as causal. Nevertheless, some notable progress has recently been made, such as establishment of an animal model that mimics the commonest form of childhood leukemia and findings of ELF-MF effects on the immune system.

Therefore, research on this topic needs to continue. Should the association observed in epidemiological studies turn out to be spurious, we could gain general methodological insight into limits of such studies in detecting small risks related to rare exposures. Should the association be causal, we could gain more insight into physiological pathways leading to childhood leukemia with preventive potential extending beyond ELF-MF, as there is at present little known about the etiology of childhood leukemia.

ACKNOWLEDGMENTS

We would like to thank colleagues who participated in the ARIMMORA consortium (and their studies), but not in risk assessment: Achim Bahr, Elena Campos-Sanchez, Mark Douglas, Serena Fiocchi, Yijian Gong, Roman Halter, Einat Kapri-Pardes, Sven Kühn, Geertje Lewin, Ilaria Liorni, Marta Para-

zzini, Davnah Payne, Katja Pokovic, Stella Reamon-Büttner, Mohamad Sater, Katharina Sewald, Carolina Vincente-Dueñas, Martin Wild, and Christina Ziemann. Special thanks to Iris Szankowski from IT'IS Foundation for her skillful support of ARIMMORA as project manager.

This risk assessment was part of the ARIMMORA project and therefore performed by those conducting the ARIMMORA experiments, with support of some external advisors. The task was to put new results from the ARIMMORA project into the context of overall scientific evidence. It is thereby inherent in the setup that results were used where scientific publications are still under way. All those participating in risk assessment had access to those results but risk assessment therefore reflects assessments made by the authors that were unanimous.

This risk assessment reflects the position of the authors (not representing their institutions) and is not an official report by the IARC and was not part of the IARC Monographs program on the evaluation of carcinogenic risks to humans.

ARIMMORA is a collaborative project funded by the European Commission within the 7th Framework Program (282891). The ARIMMORA Risk Assessment is fully supported within the collaborative project (Work Package 9 and additional travel resources for individual project partners).

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