

GAPS IN KNOWLEDGE RELEVANT TO THE “GUIDELINES FOR LIMITING EXPOSURE TO TIME-VARYING ELECTRIC AND MAGNETIC FIELDS (1 HZ–100 KHZ)”

International Commission on Non-Ionizing Radiation Protection (ICNIRP)¹

INTRODUCTION

Abstract—Sources of low-frequency fields are widely found in modern society. All wires or devices carrying or using electricity generate extremely low frequency (ELF) electric fields (EFs) and magnetic fields (MFs), but they decline rapidly with distance to the source. High magnetic flux densities are usually found in the vicinity of power lines and close to equipment using strong electrical currents, but can also be found in buildings with unbalanced return currents, or indoor transformer stations. For decades, epidemiological as well as experimental studies have addressed possible health effects of exposure to ELF-MFs. The main goal of ICNIRP is to protect people and the environment from detrimental exposure to all forms of non-ionizing radiation (NIR). To this end, ICNIRP provides advice and guidance by developing and disseminating exposure guidelines based on the available scientific research. Research in the low-frequency range began more than 40 years ago, and there is now a large body of literature available on which ICNIRP set its protection guidelines. A review of the literature has been carried out to identify possible relevant knowledge gaps, and the aim of this statement is to describe data gaps in research that would, if addressed, assist ICNIRP in further developing guidelines and setting revised recommendations on limiting exposure to electric and magnetic fields. It is articulated in two parts: the main document, which reviews the science related to LF data gaps, and the annex, which explains the methodology used to identify the data gaps.

Health Phys. 118(5):533–542; 2020

Key words: International Commission on Non Ionizing Radiation Protection; health effects; safety standards; radiation, non-ionizing

SOURCES OF LOW-FREQUENCY fields are widely found in modern society. All wires or devices carrying or using electricity generate extremely low frequency (ELF) electric fields (EFs) and magnetic fields (MFs) (1–100 Hz), but they decline rapidly with distance to the source. High magnetic flux densities are usually found in the vicinity of power lines and close to equipment using strong electrical currents, but they can also be found in buildings with unbalanced return currents or indoor transformer stations. For decades, epidemiological as well as experimental studies have addressed possible health effects of exposure to ELF-MFs.

Research in the low-frequency range began more than 40 years ago, and there is now a large body of literature that has focused on the effects of MFs in this range, while only a few papers have investigated the effects related to EFs. Moreover, since few sources commonly found in society use frequencies of between 100 Hz and 100 kHz, fewer studies of these frequencies have been conducted.

There are scientifically substantiated acute effects on the functioning of the nervous system which can occur at high ELF MF levels as well as perception and annoyance relating to exposure to ELF-EFs. Exposure guidelines published by the International Commission on Non-Ionizing Radiation Protection (ICNIRP 2010) have been set to protect against such effects. Some epidemiological data suggest a possible association between exposure to ELF-MFs below guideline levels and health effects, although they are inconclusive. The International Agency for Research on Cancer (IARC) has classified ELF-MFs as a “possible carcinogen” (IARC class 2B; IARC 2002). This classification is based on epidemiological findings without support from experimental data (see below).

Comprehensive reviews of the scientific evidence and health risk assessments have been published by different international bodies, such as the World Health Organization (WHO) in its Environmental Health Criteria (EHC) monograph (WHO 2007) and more recently by the

¹ICNIRP c/o BfS, Ingolstaedter Landstr. 1, 85764 Oberschleissheim, Germany.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) collaborators are listed in the Acknowledgement section.

The author declares no conflicts of interest.

For correspondence contact Gunde Ziegelberger, Ingolstaedter Landstr. 1, 85764 Oberschleissheim, Germany. info@icnirp.org, www.icnirp.org. (Manuscript accepted 17 December 2019)

0017-9078/20/0

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the Health Physics Society. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/HP.0000000000001261

European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (50,51). The main objectives of these documents are to review the scientific literature on the biological effects of exposure to ELF-MF in order to assess any health risks, and to make recommendations to national authorities on health protection measures. Although the low frequency guidelines from ICNIRP were based on the WHO monograph (WHO 2007), ICNIRP recognized that there were some gaps in knowledge when formulating its guidelines (ICNIRP 2010), which had to be accounted for through the use of reduction factors.

Purpose

The aim of this document is to identify data gaps in research that would, if addressed, assist ICNIRP in further developing guidelines and setting revised recommendations on limiting exposure to electric and magnetic fields.

An algorithm was elaborated to identify the research needs; the details and the structure are described in the Appendix. The evaluation of certain research areas identified either a lack of knowledge in the literature or of inconclusive data where further research would be needed to improve knowledge about the biological effects of exposure from which guideline restrictions can be derived. Other areas provided sufficient information and were not considered to be in need of further research. Therefore, the topics that were considered not to be relevant are only briefly summarized, while the effects with potential relevance for setting guidelines are reported in specific sections.

Summary of research areas where further research is not considered necessary for guideline development

The ICNIRP 2010 guidelines indicated that effects of ELF-MFs on **neurobehavior** could be explained by scientifically substantiated mechanisms of induction of retinal phosphenes and nerve-stimulation. Other effects were not consistently shown. Since then, a limited number of methodologically heterogeneous studies have investigated brain electrical activity, cognition, sleep, and mood in volunteers and human populations. With the exception of nerve stimulation due to contact currents (see below), research with volunteers continues to indicate no substantiated neurobehavioral effects below the existing guideline values, nor does it point to any significant data gaps that require further research.

Very few studies since the publication of the ICNIRP 2010 guidelines have directly addressed the potential for effects of ELF-MF exposure on **inflammation and the immune system**. The ICNIRP 2010 guidelines concluded that there was no evidence for such effects. The few subsequent studies have been heterogeneous with respect to exposure conditions, biological model systems, and end-points (Rosado et al. 2018), and give no basis for drawing any different conclusions. No additional research is necessary on components of the **endocrine system**.

There have only been a few epidemiological studies since 2010 investigating whether exposure to ELF-MFs affects **reproduction and development**, the majority of which investigated maternal exposure and risk of miscarriage. Subsequent studies do not support the hypothesis that ELF-MFs are related to adverse pregnancy outcomes, and the older laboratory studies did not find an association between ELF-MFs and reproduction and/or development. There has been a lack of animal or mechanistic studies looking into this area since 2010. Overall, the evidence gathered so far does not indicate any data gaps that require research for guideline development. Also for **cardiovascular disorders** the research available at the time the ICNIRP 2010 Guidelines were drafted provided convincing null findings, which suggest there are no data gaps in this area that require research. Finally, looking at the knowledge on various **health effects from co-exposure with ELF-MF**, a meta-analysis concluded that the majority of the studies reviewed were positive, suggesting that ELF-MFs did interact with other chemical and physical exposures (Juutilainen et al. 2006). On the other hand, the review by SCENIHR (2015) concluded that more recent experimental studies indicated that findings from co-exposures to physical or chemical agents with ELF-MFs lacked consistency. Overall, ICNIRP does not see merit in further research in this area for developing guidelines.

Finally, it has been reported that **magnetite** deposits in the beaks of homing pigeons, combined with an intact trigeminal nerve, are essential for navigation (Mora et al. 2004). Deposits of magnetite have also been identified in most other animals, including humans (Hautot et al. 2003). However, their function is unknown, and whether there could be a response to ELF-MF fields below 5 μ T (WHO 2007) has not been established (see Mouritsen 2012 for a commentary). There is thus no indication that further research in this area would be useful for guidelines development.

PROPOSED RESEARCH AREAS

Several areas of research were identified and evaluated using the algorithm (Appendix) as being potentially relevant for setting guidelines. These data gaps, namely, pain associated with touching conducting objects in a magnetic or electric field; neurodegeneration; childhood leukemia; interaction mechanisms; and further refinements in dosimetry are outlined in Table 1 in terms of robustness of the available data and the consistency of the published results (as defined in the Appendix), and are expanded upon in the following sections.

Pain perception

Strong contact currents may result when a person touches a conducting object that is within an electric or magnetic field. This is caused by current flow between the person and object, which, depending on frequency, can

result in nerve stimulation or heating (Kavet et al. 2014). There is only one published study that assessed the relation between contact current strength and pain (Chatterjee et al. 1986). Although useful, it was only able to assess a limited range of contact configurations, and did not test the relation between the contact duration and pain. Significantly, it has not yet been replicated. These limitations are particularly important at the upper end of the low frequency spectrum, where the effects of contact currents on nerve stimulation are decreased, and heating plays a larger role. ICNIRP recommends that further research is conducted to replicate the study of Chatterjee et al. (1986), as well as to ascertain more clearly the thresholds at which contact currents cause pain as a function of both the frequency of the current and the duration of exposure. Further dosimetry research recommendations for contact currents are provided below.

Neurodegenerative disorders

The 2015 SCENIHR report reviewed new studies and several systematic reviews and meta-analyses on ELF-MF exposure and neurodegenerative disease published since

the 2009 evaluation (50,51). Weak associations between ELF-MF and the risk of amyotrophic lateral sclerosis (ALS) and Alzheimer's disease were reported in meta-analyses, but with evidence of publication bias, and statistically significant heterogeneity between studies. For ALS, associations were weaker with estimates of ELF fields than with assessments based on job-titles, which was not seen for Alzheimer's disease. Since the SCENIHR 2015 report, additional large cohort and case-control studies have been published on ALS, with contradictory results, and new meta-analyses have been published. All of these studies reported slight risk increases for both ALS and Alzheimer's disease, again with considerable heterogeneity between results (e.g., Gunnarsson and Bodin 2019; Huss et al. 2018; Jalilian et al. 2018; Koeman et al. 2017; Bozzoni et al. 2016). The majority of the available studies have focused on occupational exposure and have often had limitations in exposure assessment and lack of control of confounding from other occupational exposures. For instance, some ALS studies found associations with electric shocks but not for exposure to ELF-MF whereas others found the opposite (Peters

Table 1. Data gaps in knowledge related to low frequency electric and magnetic fields and health.

Topic	Robustness	Consistency	Comments
Pain perception	In general, limited and heterogeneous human research showing no effect for most endpoints. Contact current literature is limited to 1 study.	Inconsistent results between human and animal data in general. Contact current literature on pain consists of only one single study.	Data gap only identified in relation to contact currents. Further studies on contact currents are therefore recommended.
Neurodegenerative disorders	Research in this area is not robust.	Inconsistent results.	Further epidemiological and experimental studies on Alzheimer's disease and ALS would be useful.
Childhood leukemia	Limited research using adequate animal models is not robust. Substantial number of epidemiological studies of ELF-MF and childhood leukemia.	Generally no support for cancer induction or promotion from animal models. Consistent results from epidemiological studies on childhood leukemia indicate increased risk, but weaker findings over time.	Further studies on mechanisms and biological data from childhood leukemia experimental models are recommended. No further epidemiological studies unless a biologically based hypothesis can be formulated.
Neural network firing patterns	Well established phenomena.	Wide range of estimates of sensitivities.	Uncertainties in precise mechanism and derivation of tissue E-fields implies that actual thresholds could be lower (or higher) than current levels.
Free radical lifetimes	Effect of magnetic fields on free radical lifetimes well-established, but at higher field values than reference levels.	The radical pair mechanism is the only physically plausible way in which biological systems may be sensitive to low intensity magnetic fields. Observations are far from sufficient to explain predict health effects and to require consideration in terms of guidelines.	Ongoing research outcomes may motivate revision of conclusions regarding relevance to standard-setting.
Dosimetry & modelling	A certain number of reports on MF exposure, but not robust in some cases. Limited research on ELF exposure, contact current and non-sinusoidal wave exposures.	Some inter-comparison between models, but more needed. More critical examination of assumptions made required	Considerable gaps remain (see text for specific details)

et al. 2019; Huss et al. 2015; Fisher et al. 2015; Vergara et al. 2015). The systematic reviews and meta-analyses have, to a varying degree, made efforts to combine risk estimates based on comparable exposure levels and disease induction periods. However, comparability has not always been possible to achieve because of differences in choices made by the original investigators, which may increase influence of publication bias. Clinically-based studies have been prone to selection bias, whereas population-based studies often have had incomplete information on occupational history. In summary, it remains unclear whether occasionally observed increased risks for ALS and Alzheimer's disease reflect a true causal association or are due to bias.

Only a small number of laboratory studies (in vivo/in vitro) since 2010 have investigated mechanistic pathways for an association between ELF-MF and neurodegenerative diseases. The evidence from these studies suggests that short-term ELF-MF exposure causes mild oxidative stress (resulting in modest ROS increases and changes in anti-oxidant levels) and possibly activates anti-inflammatory processes (with a decrease in pro-inflammatory and an increase in anti-inflammatory cytokines). In general, however, the existing experimental studies are not adequate in answering whether there is a causal relationship between ELF-MFs and neurodegeneration. More recently, since 2013, laboratory experiments have investigated the effect of ELF-MFs on animal models of Alzheimer's disease. In some cases, however, the model was inadequate, such as in those studies that used normal adult animals. The results available are so far inconclusive as various outcomes (protective, neutral or aggravating effects) have been reported (Jiang et al. 2013; Liebl et al. 2015; Liu et al. 2015; Zhang et al. 2013, 2015; Hu et al. 2016; Sakhaie et al. 2017; Akbarnejad et al. 2018; Bobkova et al. 2018; Zuo et al. 2018).

Thus, it still remains unclear whether exposure to ELF-MFs may affect the development or progression of ALS and Alzheimer's disease and further epidemiological and experimental studies are required. For a rare disease such as ALS, pooling of available population-based studies could be a way forward, to harmonize exposure definition, exposure cut-points, induction periods, and investigation of sensitive subgroups, while for Alzheimer's disease additional population-based cohort studies or nested case-control studies are recommended.

Childhood leukemia

Childhood leukemia is the only disease consistently reported in epidemiological studies to be associated with environmental exposure to ELF-MFs. This association was the principal motivation for the classification of ELF-MFs as "possibly carcinogenic to humans" by the IARC in 2002. This classification is based on epidemiological findings of an increased risk of childhood leukemia in domestic settings

with ELF-MF-levels higher than commonly found (daily averages exceeding 0.3–0.4 μT). However, there is no support from animal experiments and there are no mechanistic data that can provide an explanation for any effect on biological structures at the exposure levels that have been identified in epidemiological studies. Furthermore there is still a lack of adequate animal models of acute B-lymphoblastic leukemia (B-ALL), the main form of childhood leukemia. One study used an animal model (WKAH/Hkm male rats) for chemically-induced B-ALL (Bernard et al. 2008). In this study, exposure to a 50 Hz MF at 100 μT (with or without harmonics at 150, 250 or 350 Hz) did not significantly alter the incidence or the type of leukemia induced by the chemical.

Within the EU Seventh Framework Program ARIMMORA project, a transgenic mouse model expressing the human ETV6-RUNX1 (formerly TEL-AML1) fusion gene was engineered to develop B-ALL. This model, when fully characterized, will be valuable for further investigations of a potential effect of ELF-MFs on childhood leukemia. Moreover, data on other pathological processes identified in B-ALL are also missing, such as epigenetic changes and angiogenesis, especially in the bone marrow.

More recently, three studies were performed on rats exposed during gestation (12th day of pregnancy) to natural death, to 50 Hz MFs from 2 to 1,000 μT either alone (Bua et al. 2018) or combined with a single dose of γ radiation (0.1 Gy) when the pups were 6 mo old (Soffritti et al. 2016a), or formaldehyde in drinking water (50 mg L^{-1}) beginning at 6 wk of age (Soffritti et al. 2016b). The exposure groups consistently showed no effect when exposed to MFs alone, but an increase of tumor incidence was reported in co-exposure scenarios. The type of tumors differed according to the inducer agent: mammary gland in both males and females, lymphoma, leukemia and malignant heart Schwannoma in males with γ radiation and thyroid C-cell carcinomas and hemolymphoreticular neoplasias (lymphoma, leukemia, and histiocytic sarcomas) in males with formaldehyde.

Finally, a literature review published in 2016 evaluated a large data set and reported both negative and positive results for genetic damage on human cell lines after exposure to ELF-MFs (Maes and Verschaeve 2016). However, the human cytogenetic biomonitoring studies that were conducted in the past showed predominantly positive results, and it was reported that the observed cytogenetic damage correlated with increased cancer risk (Maes and Verschaeve 2016).

Epidemiological studies of residential exposure to power frequency magnetic fields have consistently found a modestly increased risk of childhood leukemia associated with ELF-MF levels in children's homes above 0.3–0.4 μT , but chance, confounding or other bias cannot be ruled out as alternative explanations. Furthermore, the size of the reported association has been decreasing in more recent

studies (Kheifets et al. 2010; Crespi et al. 2019; Swanson et al. 2019) and in re-analyses of older results (Bunch et al. 2016; Crespi 2016). A recent large pooled analysis of childhood leukemia and distance to power lines indicated that a small and imprecise risk increase in close proximity to highest voltage line is unlikely to be explained by magnetic field exposure (Amoon et al. 2018). Childhood leukemia is a very rare disease. Additional epidemiological studies of the same design are therefore unlikely to advance the knowledge, as they will potentially be affected by the same types of biases as the existing studies. Until further knowledge from other lines of research has provided evidence that gives insight into potential biological mechanisms, thereby providing the basis for hypothesis-driven research, identification of potentially susceptible subgroups and improved assessment of relevant exposure metrics, new epidemiological studies are unlikely to change the overall conclusion. The same argument applies regarding the potential effects of ELF-MFs on cancer in adults. Should epidemiological studies nevertheless be conducted, it is important that they report results for the exposure levels used in the published pooled analyses, i.e., $\geq 0.3 \mu\text{T}$ and $\geq 0.4 \mu\text{T}$ for residential exposure (Ahlbom et al. 2000; Kheifets et al. 2010), to allow pooling of risk estimates. Development of specific models for in vivo and in vitro studies to test the epidemiological data and to help in the identification of the possible transformation mechanisms should be promoted.

Interaction mechanisms

At the Task Group meeting for the WHO EHC monograph (WHO 2007) there was much discussion regarding plausible mechanisms for low-level effects (i.e., those that may occur within ICNIRP guideline levels). This discussion was reflected in the final text of the monograph, where three candidate mechanisms were reviewed. They were weak electric field effects on synaptic transmission in neural networks; magnetic field effects on radical pairs altering reaction rates; and magnetite crystals present in minute amounts in animal and human tissue (already described in the summary of the area where no further research is required). No additional hypotheses have been suggested since publication of that monograph.

Neural network firing patterns. The EHC Monograph stated: “A lower bound of 1 mV m^{-1} on neural network discrimination was suggested, but based on current evidence threshold values around $10\text{--}100 \text{ mV m}^{-1}$ seem more likely” (WHO 2007). Thus, additional data had suggested the possibility of effects below the basic restrictions recommended in the ICNIRP guidelines (100 mV m^{-1}). This appeared to be a fruitful area for closing a data gap, but little has been done to follow up [some references in addition to those in (WHO 2007) were considered in (Wood 2008), but these did not provide a definitive resolution]. The phenomenon of magnetophosphenes, which are thought to arise from magnetic induction of electric

fields in the neural networks of the retina, continues to be studied experimentally (Legros et al. 2012; Souques et al. 2014) and theoretically (Laakso and Hirata 2012a and b). However, the precise locus, frequency dependence, and mechanism of the generation of this phenomenon are still unclear.

Radical pair mechanism (including those putatively involving cryptochromes)

The view stated in the EHC monograph (WHO 2007) was that if these effects are involved in bird navigation and other magneto-sensory phenomena, it would be unlikely that static and ELF-MFs much less than $50 \mu\text{T}$ would have biological significance for the radical pair mechanism since the Earth’s magnetic field is about $50 \mu\text{T}$ and such effects produced by static and ELF-MFs are similar in nature. The work of several research groups on the possible role of retinal cryptochromes and associated free radical lifetimes in avian magneto-reception continues to provoke debate (Kattinig et al. 2016), and a link to reactive oxygen species (ROS) has been identified (Solov'yov and Schulten 2009). The relevance of this experimental work to possible ELF-MF interactions in mammals is less clear, while more work suggests that biological systems may be sensitive to lower static exposure levels (Maeda et al. 2008), and a very recent study has investigated magneto-reception in fish (Fitak et al. 2017). ‘The radical pair mechanism is the only physically plausible way in which these observations can be reconciled with magnetic interactions that are more than 6 orders of magnitude weaker than the thermal energy’ (Kattinig et al. 2016). However, no substantiated health effect has yet been demonstrated.

Overall, of these possible interaction mechanisms, only further study of magnetophosphenes would seem to hold promise for guidelines development.

Dosimetry and modeling

A number of uncertainties relating to modeling and dosimetry that were mentioned in the ICNIRP 2010 Guidelines (ICNIRP 2010) have not yet been clarified, and dosimetric uncertainties have also been highlighted in related publications. These uncertainties are considered below.

The estimate of the threshold in terms of the internal electric field strength for neural stimulation effects in the retina (between 50 and 100 mV m^{-1}) could usefully be clarified. Since the basic restriction for the central nervous system of the head ($1 \text{ Hz--}1 \text{ kHz}$) is derived from this estimate, the statistical distribution of the thresholds obtained experimentally should be assessed, together with a computational approach. A review of the experimental data on both electro-phosphenes and magneto-phosphenes reported a value of 56 mV m^{-1} , but with a wide confidence interval of $2\text{--}1,330 \text{ mV m}^{-1}$. From that review, a model based on the classical excitable membrane physiology was suggested as one of the best candidates from available data (Wood 2008).

There is also uncertainty regarding the derivation of reference levels of external magnetic field strength from the basic restrictions in the ICNIRP 21010 guidelines (ICNIRP 2010). Kavet (Kavet 2015) has estimated an “implicit” conversion factor (or coupling coefficient) for internal electric field in the peripheral nervous system (PNS) and has suggested that the reference level values are overly conservative in the ICNIRP 2010 guidelines. It was found that at the general public reference level, the “Head and Body” exposure is far less than the basic restriction by a factor of 2.5 or more. The disparity exists across the frequency range and is due, in most part, to the different body models used. The precision of voxel modeling has improved over time, with early differences across research groups approximately 200% (Stuchly and Gandhi 2000), reducing more recently to approximately 20–30% (Hirata et al. 2010). One of the most significant sources of uncertainty associated with the use of anatomical models is the electrical conductivity values used in the models (including anisotropy and age dependency) (Gabriel et al. 2009; Wake et al. 2016). However, the available data are not sufficiently comprehensive to detail the uncertainty in dielectric properties of tissues, and further studies are necessary in order to improve the accuracy and validity of relevant dosimetry studies. Inter-comparison between models by experts would be particularly useful for determining the conversion factors.

The external electric field reference level in the low frequency guidelines is derived using numerical calculations. The relation between the internal and external electric field strength has been investigated only at 50/60 Hz (Hirata et al. 2001; Dimbylow 2005), and contains a large uncertainty. In order to improve the reference levels of the external electric field at 1 kHz or higher, it is recommended that detailed numerical calculations considering variations in the target population and tissues be performed.

The issue of nerve excitation modeling has been recently compared in (Reilly 2016) for the PNS and substantial variability has been found for pulses shorter than 100 μ s. This is mostly attributable to variation in the chronaxie values, characterizing the frequency dependency of the threshold, and it would be useful to determine the most appropriate values to use. It is recommended that excitation modeling as well as threshold assessment be conducted in order to improve the accuracy of restrictions at frequencies where actual threshold data have not yet been determined.

Further research is also required to better clarify the most appropriate averaging volumes and distances for setting basic restrictions. A related issue is the choice of percentiles in deriving these values. The 99th percentile value used in the definition of the basic restrictions was originally introduced by Dawson and Stuchly (2001) for uniform exposures to spheres and then applied to anatomical

models (Hirata et al. 2001), where the main purpose was to derive the relationship between the basic restrictions and the reference levels. Recently, the weakness of the metric has been suggested, especially for non-uniform exposure (e.g., Kos et al. 2011; Laakso and Hirata 2012a and b), and it is recommended that further research be conducted to clarify this issue.

The relationship between internal electric fields and contact currents also requires further clarification. The poor understanding of this indirect coupling phenomenon is one reason that no basic restriction has been developed for the contact current stimulation effect. That is, since stimulation effects are assumed to be related to internal electric field, and there are only data relating the contact current (and not internal electric field) to health effects, it is not possible to determine the relation between health effects and the internal exposure itself. The issue of non-uniform distribution of current over the area of contact (which was not addressed in the ICNIRP 2010 guidelines) also needs clarification through additional experimental data.

The method of evaluation for non-sinusoidal waves, including pulses, is also an important topic worth investigating. In the low frequency guidelines, the Fourier transform analysis has been introduced based on the assumption that the interaction between internal fields and the nervous system can be represented with a simplified model. The relative conservativeness and appropriateness of this approximation have not been determined, and data gaps remain that could usefully be addressed in order to assist future development of guidelines.

It is also noted that the evaluation method for non-sinusoidal waves is applicable up to 100 kHz in the ICNIRP 2010 guidelines, while the restrictions are set up to 10 MHz in the same guidelines. Because the evaluation method is based on the Fourier transform analysis or pure mathematics, the evaluation method can be expanded to frequencies higher than 100 kHz. The degree of conservativeness and appropriateness of the evaluation method for non-sinusoidal waves should therefore be investigated up to 10 MHz.

CONCLUSION AND REMARKS

Although some areas provide sufficient information and do not suggest that any specific deficiencies exist related to low frequency electric and magnetic fields and health, there are clear gaps in knowledge in other areas. This paper has provided a list of these gaps in knowledge for which additional research would greatly assist ICNIRP and others in the future development of low-frequency exposure guidelines. These research needs were identified using a predefined algorithm, but they were not classified with respect to priority. They have been presented with the explicit intention that

researchers and relevant funding bodies will consider addressing these important issues with the overall goal of helping to improve non-ionizing radiation protection.

Acknowledgments—Collaborators: Carmela Marino, ICNIRP and Agency for New Technologies, Energy and Sustainable Economic Development, Italy; Rodney Croft, ICNIRP and Australian Centre for Electromagnetic Bioeffects Research, Illawarra Health & Medical Research Institute, University of Wollongong, Australia; Maria Feychting, ICNIRP and Karolinska Institutet, Sweden; Adèle C Green, ICNIRP and QIMR Berghofer Medical Research Institute, Brisbane, Australia and CRUK Manchester Institute, University of Manchester, Manchester, UK; Akimasa Hirata, ICNIRP and Nagoya Institute of Technology, Japan; Guglielmo d'Inzeo, ICNIRP and La Sapienza University Rome, Italy; Sharon Miller, ICNIRP; Gunnhild Oftedal, ICNIRP and Norwegian University of Science and Technology; Tsutomu Okuno, ICNIRP; Martin Röösl, ICNIRP and Swiss Tropical and Public Health Institute, Basel, Switzerland; Zenon Sienkiewicz, ICNIRP; Eric van Rongen, ICNIRP and Health Council, The Netherlands; Soichi Watanabe, ICNIRP and National Institute of Information and Communications Technology, Japan; Isabelle Lagroye, ICNIRP SEG and IMS Laboratory, University of Bordeaux I, France; Ken Karipidis, ICNIRP SEG and Australian Radiation Protection and Nuclear Safety Agency; Mats-Olof Mattsson, ICNIRP SEG (until 2017) and SciProof International AB, Sweden; Andrew Wood, ICNIRP SEG and Swinburne University of Technology, Melbourne, Australia.

Additionally, the SEG members Jukka Juutilainen and Anssi Auvinen are gratefully acknowledged for the time devoted in the development of the general strategy of the document.

The views expressed by the authors and collaborators do not necessarily reflect the views or policies of the organizations they are professionally affiliated with. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by ICNIRP or any of the organizations with which the collaborators are affiliated.

The support received by the German Federal Ministry for the Environment (BMU), the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020), the International Radiation Protection Association (IRPA), the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), and the New Zealand Ministry of Health is gratefully acknowledged.

In regard to the EU funds, for further information please consult: <http://ec.europa.eu/social/easi>. The information contained in this publication does not necessarily reflect the official position of the European Commission, or any other donors. All information concerning the support received by ICNIRP is available at www.icnirp.org.

REFERENCES

- Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen JH, Tynes T, Verkasalo PK. A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer* 83:692–698; 2000.
- Amoon AT, Crespi CM, Ahlbom A, Bhatnagar M, Bray I, Bunch KJ, Clavel J, Feychting M, Hemon D, Johansen C, Kreis C, Malagoli C, Marquant F, Pedersen C, Raaschou-Nielsen O, Röösl M, Spycher BD, Sudan M, Swanson J, Tittarelli A, Tuck DM, Tynes T, Vergara X, Vinceti M, Wunsch-Filho V, Kheifets L. Proximity to overhead power lines and childhood leukaemia: an international pooled analysis. *Br J Cancer* 119:364–373; 2018.
- Akbarnejad Z, Esmaeilpour K, Shabani M, Asadi-Shekaari M, Saeedi Goraghani M, Ahmadi-Zeidabadi M. Spatial memory recovery in Alzheimer's rat model by electromagnetic field exposure. *Int J Neurosci* 128:691–696; 2018.
- Bernard N, Alberdi AJ, Tanguy ML, Brugere H, Helissey P, Hubert C, Gendrey N, Guillosson JJ, Nafziger J. Assessing the potential leukemogenic effects of 50 Hz magnetic fields and their harmonics using an animal leukemia model. *J Radiat Res* 49:565–577; 2008.
- Bobkova NV, Novikov VV, Medvinskaya NI, Aleksandrova IY, Nesterova IV, Fesenko EE. Effect of weak combined static and extremely low-frequency alternating magnetic fields on spatial memory and brain amyloid- β in two animal models of Alzheimer's disease. *Electromagn Biol Med* 37:127–137; 2018.
- Bozzoni V, Pansarasa O, Diamanti L, Nosari G, Cereda C, Ceroni M. Amyotrophic lateral sclerosis and environmental factors. *Funct Neurol* 31:7–19; 2016.
- Bua L, Tibaldi E, Falcioni L, Lauriola M, De Angelis L, Gnudi F, Manservigi M, Manservigi F, Manzoli I, Menghetti I, Montella R, Panzacchi S, Sgargi D, Strollo V, Vornoli A, Mandrioli D, Belpoggi F. Results of lifespan exposure to continuous and intermittent extremely low frequency electromagnetic fields (ELFEMF) administered alone to Sprague Dawley rats. *Environ Res* 164:271–279; 2018.
- Bunch KJ, Swanson J, Vincent TJ, Murphy MF. Epidemiological study of power lines and childhood cancer in the UK: further analyses. *J Radiol Prot* 36:437–455; 2016.
- Chatterjee I, Wu D, Gandhi OP. Human body impedance and threshold currents for perception and pain for contact hazard analysis in the VLF-MF band. *IEEE Trans Biomed Eng* 33:486–494; 1986.
- Crespi CM. Childhood leukemia and distance from power lines in California: a population-based case-control study. *Br J Cancer* 115:122–128; 2016.
- Crespi CM, Swanson J, Vergara XP, Kheifets L. Childhood leukemia risk in the California Power Line Study: magnetic fields versus distance from power lines. *Environ Res* 171:530–535; 2019.
- Dawson TW, Stuchly MA. Evaluation of modeling accuracy of power frequency field interactions with the human body. *Appl Comput Electromagnet Soc J* 16:162–172; 2001.
- Dimbylow P. Development of the female voxel phantom, NAOMI, and its application to calculations of induced current densities and electric fields from applied low frequency magnetic and electric fields. *Phys Med Biol* 50:1047–1069; 2005.
- Fitak RR, Wheeler BR, Ernst DA, Lohmann KJ, Johnsen S. Candidate genes mediating magnetoreception in rainbow trout (*Oncorhynchus mykiss*). *Biol Lett* 13(4):20170142; 2017.
- Gabriel C, Peyman A, Grant EH. Electrical conductivity of tissue at frequencies below 1 MHz. *Phys Med Biol* 54:4863–4878; 2009.
- Gunnarsson LG, Bodin L. Occupational exposures and neurodegenerative diseases—a systematic literature review and meta-analyses. *Int J Environ Res Public Health* 16(3):337; 2019. doi:10.3390/ijerph16030337.
- Hautot D, Pankhurst QA, Khan N, Dobson J. Preliminary evaluation of nanoscale biogenic magnetite in Alzheimer's disease brain tissue. *Proc Biol Sci* 270(Suppl 1):S62–S64; 2003. doi:10.1098/rsbl.2002.0012.
- Hirata A, Caputa K, Dawson TW, Stuchly MA. Dosimetry in models of child and adult for low-frequency electric field. *IEEE Trans Biomed Eng* 48:1007–1012; 2001.
- Hirata A, Yamazaki K, Hamada S, Kamimura Y, Tarao H, Wake K, Suzuki Y, Hayashi N, Fujiwara O. Intercomparison of induced fields in Japanese male model for ELF magnetic field exposures: effect of different computational methods and codes. *Radiat Protect Dosim* 138:237–244; 2010.
- Hu Y, Lai J, Wan B, Liu X, Zhang Y, Zhang J, Sun D, Ruan G, Liu E, Liu GP, Chen C, Wang DW. Long-term exposure to ELF-MF ameliorates cognitive deficits and attenuates tau hyperphosphorylation in 3xTg AD mice. *Neurotoxicol Mar* 53:290–300; 2016.
- Huss A, Peters S, Vermeulen R. Occupational exposure to extremely low-frequency magnetic fields and the risk of ALS: A systematic review and meta-analysis. *Bioelectromagnetics* 39:156–163; 2018.

- Huss A, Spoerri A, Egger M, Kromhout H, Vermeulen R. Swiss National Cohort. Occupational exposure to magnetic fields and electric shocks and risk of ALS: the Swiss National Cohort. *Amyotroph Lateral Scler Frontotemporal Degener* 16:80–85; 2015.
- IARC. Non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 80. Lyon, France: International Agency for Research on Cancer, IARC Press; 2002.
- International Commission on Non-Ionizing Radiation Protection. Guidelines on limits of exposure to time-varying electric, magnetic and electromagnetic fields (1 Hz–100 kHz). *Health Phys* 99:818–836; 2010.
- Jiang DP, Li J, Zhang J, Xu SL, Kuang F, Lang HY, Wang YF, An GZ, Li JH, Guo GZ. Electromagnetic pulse exposure induces overexpression of beta amyloid protein in rats. *Arch Med Res* 44:178–184; 2013.
- Jalilian H, Hosseini Teshnizi S, Rösli M, Neghab M. Occupational exposure to extremely low frequency magnetic field and risk of Alzheimer disease: a systematic review and meta-analysis. *Neurotoxicol* 69:242–252; 2018.
- Juutilainen J, Kumlin T, Naarala J. Do extremely low frequency magnetic fields enhance the effects of environmental carcinogens? A meta-analysis of experimental studies. *Int J Radiat Biol* 82:1–12; 2006.
- Kattnig DR, Solov'yov IA, Hore PJ. Electron spin relaxation in cryptochrome-based magnetoreception. *Phys Chem Chem Phys* 18:12443–12456; 2016.
- Kavet R. Dosimetric uncertainties: magnetic field coupling to peripheral nerve. *Health Phys* 109:556–565; 2015.
- Kavet R, Tell RA, Olsen RG. Radiofrequency contact currents: sensory responses and dosimetry. *Radiat Protect Dosim* 162:268–279; 2014.
- Kheifets L, Ahlbom A, Crespi CM, Feychting M, Johansen C, Monroe J, Murphy MFG, Oksuzyan S, Preston-Martin S, Roman E, Saito T, Savitz D, Schüz J, Simpson J, Swanson J, Tynes T, Verkasalo P, Mezei G. A pooled analysis of extremely low-frequency magnetic fields and childhood brain tumors. *Am J Epidemiol* 172:752–761; 2010.
- Koeman T, Slottje P, Schouten LJ, Peters S, Huss A, Veldink JH, Kromhout H, van den Brandt PA, Vermeulen R. Occupational exposure and amyotrophic lateral sclerosis in a prospective cohort. *Occup Environ Med* 74:578–585; 2017.
- Kos B, Valic B, Miklavcic D, Kotnik T, Gajsek P. Pre- and post-natal exposure of children to EMF generated by domestic induction cookers. *Phys Med Biol* 56:6149–6160; 2011.
- Laakso I, Hirata A. Reducing the staircasing error in computational dosimetry of low-frequency electromagnetic fields. *Phys Med Biol* 57:25–34; 2012a.
- Laakso I, Hirata A. Computational analysis of thresholds for magnetophosphenes. *Phys Med Biol* 57:6147–6165; 2012b.
- Legros A, Corbacio M, Beuter A, Modolo J, Goulet D, Prato FS, Thomas AW. Neurophysiological and behavioral effects of a 60 Hz, 1,800 μ T magnetic field in human. *Eur J Appl Physiol* 112:1751–1762; 2012.
- Liebl MP, Windschmitt J, Besemer AS, Schäfer AK, Reber H, Behl C, Clement AM. Low-frequency magnetic fields do not aggravate disease in mouse models of Alzheimer's disease and amyotrophic lateral sclerosis. *Sci Rep* 5:8585; 2015.
- Liu X, Zuo H, Wang D, Peng R, Song T, Wang S, Xu X, Gao Y, Li Y, Wang S, Wang L, Zhao L. Improvement of spatial memory disorder and hippocampal damage by exposure to electromagnetic fields in an Alzheimer's disease rat model. *PLoS One* 10:e0126963; 2015.
- Maeda K, Henbest KB, Cintolesi F, Kuprov I, Rodgers CT, Liddell PA, Gust D, Timmel CR, Hore PJ. Chemical compass model of avian magnetoreception. *Nature* 453:387–390; 2008.
- Maes A, Verschaeve L. Genetic damage in humans exposed to extremely-low frequency electromagnetic fields. Review. *Arch Toxicol* 90:2337–2348; 2016.
- Mora CV, Davison M, Wild JM, Walker MM. Magnetoreception and its trigeminal mediation in the homing pigeon. *Nature* 432:508–511; 2004.
- Mouritsen H. Sensory biology: search for the compass needles. *Nature* 484:320–321; 2012.
- Peters S, Visser AE, D'Ovidio F, Beghi E, Chiò A, Logroscino G, Hardiman O, Kromhout H, Huss A, Veldink J, Vermeulen R, van den Berg LH. Euro-MOTOR Consortium. associations of electric shock and extremely low-frequency magnetic field exposure with the risk of amyotrophic lateral sclerosis. *Am J Epidemiol* 188:796–805; 2019.
- Reilly JP. Survey of numerical electrostimulation models. *Phys Med Biol* 61:4346–4363; 2016.
- Rosado MM, Simkó M, Mattsson MO, Pioli C. Immune-modulating perspectives for low frequency electromagnetic fields in innate immunity. *Front Public Health* 6:85; 2018.
- Sakhaie MH, Soleimani M, Pourheydar B, Majd Z, Atefimanesh P, Asl SS, Mehdizadeh M. Effects of extremely low-frequency electromagnetic fields on neurogenesis and cognitive behavior in an experimental model of hippocampal injury. *Behav Neurol* 9194261; 2017.
- Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Opinion on: Health Effects of Exposure to EMF. 2009. Available at https://ec.europa.eu/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_022.pdf. Accessed 27 February 2020.
- Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Opinion on: Potential health effects of exposure to electromagnetic fields (EMF) [online]. 27 January 2015. Available at http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihhr. Accessed 27 February 2020.
- Solov'yov IA, Schulten K. Magnetoreception through cryptochrome may involve superoxide. *Biophys J* 96:4804–4813; 2009.
- Soffritti M, Tibaldi E, Padovani M, Hoel DG, Giuliani L, Bua L, Lauriola M, Falcioni L, Manservigi M, Manservigi F, Panzacchi S, Belpoggi F. Life-span exposure to sinusoidal-50 Hz magnetic field and acute low-dose γ radiation induce carcinogenic effects in Sprague-Dawley rats. *Int J Rad Biol* 92:202–211; 2016a.
- Soffritti M, Tibaldi E, Padovani M, Hoel DG, Giuliani L, Bua L, Lauriola M, Falcioni L, Manservigi M, Manservigi F, Belpoggi F. Synergism between sinusoidal-50 Hz magnetic field and formaldehyde in triggering carcinogenic effects in male Sprague-Dawley rats. *Am J Ind Med* 59:509–521; 2016b.
- Souques M, Plante M, Ostiguy G, Goulet D, Deschamps F, Mezei G, Modolo J, Lambrozo J, Legros A. Anecdotal report of magnetophosphene perception in 50 mT 20, 50 and 60 Hz magnetic fields. *Radioprotect* 49:69–71; 2014.
- Stuchly MA, Gandhi OP. Inter-laboratory comparison of numerical dosimetry for human exposure to 60 Hz electric and magnetic fields. *Bioelectromagnetics* 21:167–174; 2000.
- Swanson J, Kheifets L, Vergara X. Changes over time in the reported risk for childhood leukaemia and magnetic fields. *J Radiol Protect* 39:470–488; 2019.
- Wake K, Sasaki S, Watanabe S. Conductivities of epidermis, dermis, and subcutaneous tissue at intermediate frequencies. *Phys Med Biol* 61:4376–4389; 2016.
- Vergara X, Mezei G, Kheifets L. Case-control study of occupational exposure to electric shocks and magnetic fields and mortality from amyotrophic lateral sclerosis in the US, 1991–1999. *J Expo Sci Environ Epidemiol* 25:65–71; 2015.

- World Health Organization. Extremely low frequency fields, Environmental Health Criteria No. 238. Geneva: World Health Organization; 2007.
- Wood AW. Extremely low frequency (ELF) electric and magnetic field exposure limits: rationale for basic restrictions used in the development of an Australian standard. *Bioelectromagnetics* 29:414–428; 2008.
- Zhang C, Li Y, Wang C. Extremely low-frequency magnetic exposure appears to have no effect on pathogenesis of Alzheimer's disease in aluminum-overloaded rat. *PLoS One* <https://doi.org/10.1371/journal.pone.0071087>(8); 2013.
- Zhang Y, Liu X, Zhang J, Li N. Short-term effects of extremely low frequency electromagnetic fields exposure on Alzheimer's disease in rats. *Int J Radiat Biol* 91:28–34; 2015.
- Zuo H, Liu X, Wang D, Li Y, Xu X, Peng R, Song T. RKIP-mediated NF- κ B signaling is involved in ELF-MF-mediated improvement in AD rat. *Int J Med Sci* 15:1658–1666; 2018.

APPENDIX

INTRODUCTION AND PURPOSE

The main goal of ICNIRP is to protect people and the environment from detrimental exposure to all forms of non-ionizing radiation (NIR). To this end, ICNIRP provides advice and guidance by developing and disseminating science-based exposure guidelines that provide a framework to limit exposure. Where necessary, ICNIRP uses detailed reviews of the scientific evidence and health risk assessments from other expert groups to help it form a consensus opinion regarding established and potential health effects. This ensures the robustness of its guidelines. However, relevant knowledge gaps can be identified during this process, and ICNIRP recognized that there were some gaps in knowledge when formulating its previous guidelines (ICNIRP 2010, 2013, 2014) but gave few specifics. Thus ICNIRP has now organized a project group that is charged with drafting a research agenda that highlights the gaps in knowledge that have been identified during the development of its guidelines for each frequency range of the NIR spectrum.

This Appendix describes the structured approach that was developed by the project group in order to encourage both transparency in methodology and consistency across NIR domains. This methodology provides a means to select

the issues considered relevant to guidelines when the results are considered weak or not strong enough or when there are no data with which to characterize a particular phenomenon.

METHOD FOR DETERMINING “RESEARCH NEEDS OF RELEVANCE FOR GUIDELINE DEVELOPMENT”

ICNIRP sees merit in highlighting NIR research needs so that studies may be conducted that would be beneficial for future guideline development (as distinguished from benefitting science more generally). The Data Gaps Project Group (DG-PG) was formed to identify such research gaps in the different frequency regions of the NIR spectrum, starting with low frequency fields (see main text).

In considering how the process should best operate to identify data gaps, it was decided that a structured approach would be useful. For this purpose, a two-step algorithm was developed to identify research needs (Fig. A1). The algorithm was intended to maximize transparency, consistency with other NIR guidelines, relevance to guidelines setting and to avoid recommending research that does not benefit guidelines. However, no attempt has been made to prioritise the recommendations.

Step 1 shows how to evaluate issues related to biological endpoints that have been assessed for the current guidelines (Fig. A1), while Step 2 questions whether there are biological endpoints related to thresholds and dosimetry (Fig. A2); in Fig. A3 the last Step allows to evaluate the relevance of endpoints that have not yet been considered, but might be important to explore for future guidelines.

The main goal of these steps is to better identify and so clarify biological endpoints or mechanisms from which guidelines restrictions are derived. In this context, the term “relevant to health” is only used to signify that the biological endpoints or mechanisms have some known association to an adverse health outcome or have been used as a biomarker for a particular disease.



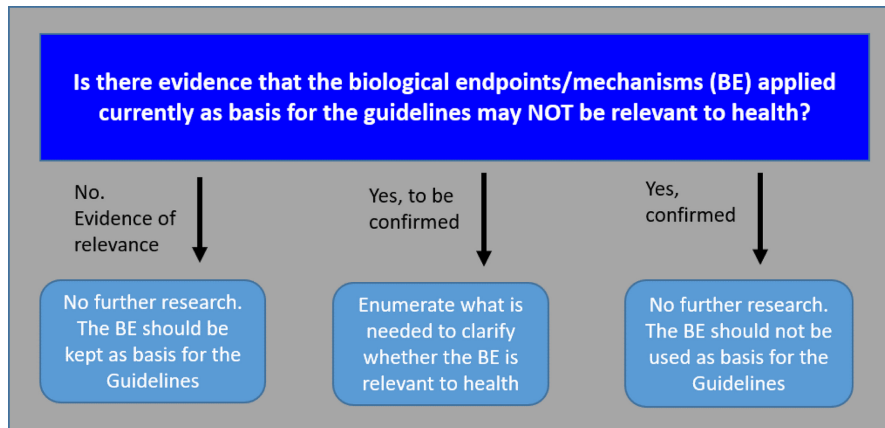


Fig. A1. Step 1 of the algorithm used to identify research needs; assessing relevance of currently included endpoints. *Note, BE: Biological endpoints/mechanisms.*

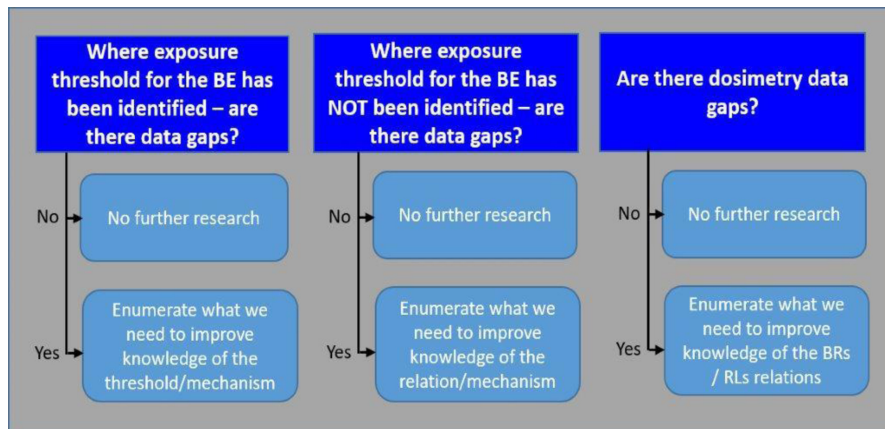


Fig. A2. Step 2 of the algorithm used to identify research needs; assessing data gaps related to thresholds and dosimetry. *Note, BE: Biological endpoints/mechanisms; BR: Basic restrictions; RLs: Reference levels.*

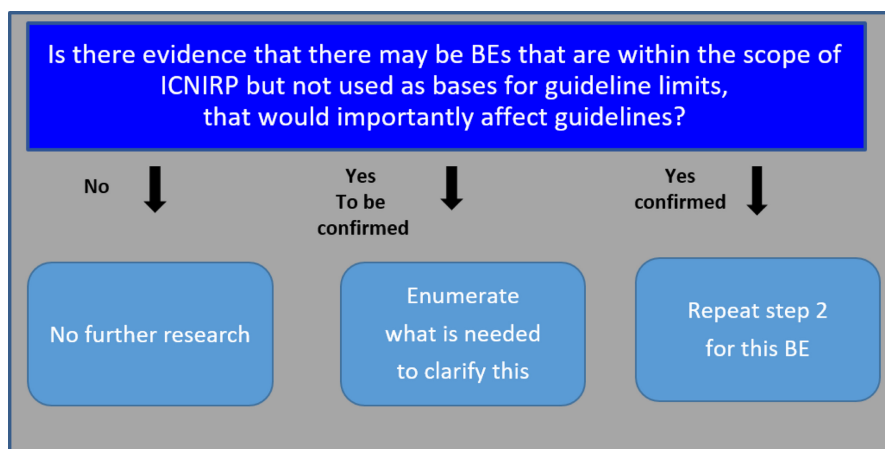


Fig. A3. Step 3 of the algorithm used to identify research needs; assessing relevance of endpoints that are currently not used as basis for the guidelines. *Note, BE: Biological endpoints/mechanisms.* It is important to note that although this algorithm will provide the direction and justification for the process, it was not intended to do so at the expense of the primary objective, which is to encourage research that will inform guideline development. Thus, the members of the DG-PG were also encouraged to think outside of this structure, and to include research recommendations even if they did not precisely fit within the algorithm. However, should any inconsistencies between the algorithm and research recommendations be identified, the DG-PG required that justification should be provided as to why the research recommendations are given despite not satisfying the algorithm, and a reconsideration of the algorithm would be considered to improve its applicability for future use.