Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

Potential health effects of exposure to electromagnetic fields (EMF): Update with regard to frequencies between 1Hz and 100 kHz

The SCHEER adopted this document on 17 May 2024

ABSTRACT

The exposure of the general population in Europe, as reported in the published literature reviews, remains below the exposure limits recommended in Council Recommendation 1999/519/EC. There are no systematic reviews and meta-analysis available for melatonin hypothesis, radical pair mechanisms, oxidative stress or epigenetic effects in connection with exposure low frequency electromagnetic fields (EMF). There is weak evidence regarding the involvement of interaction mechanisms (oxidative stress, genetic/epigenetic effects) in health risks from extremely low frequency (ELF) magnetic fields (MF) that were observed in epidemiological and *in vivo* studies.

More research is needed to establish interaction mechanisms between low frequency EMF and living matter, making use of standardised exposure conditions and optimised *in vitro* cell lines, with the possibility to extrapolate to *in vivo* models where the metabolic processes play an important role for the interpretation of the biological responses relevant to human health.

The SCHEER could not identify recent (post 2015) systematic reviews or meta-analyses on low frequency EMF exposure and self-reported symptoms to update the previous SCENIHR assessment in the current Opinion. It is noted that in the SCENIHR Opinion (2015) it was concluded there was no convincing evidence for a causal relationship between ELF-MF exposure and self-reported symptoms.

Published systematic reviews concerning leukaemia and ELF-EMF exposure, based mainly on case-control studies, revealed that ELF-MF exposure showed consistent but moderate risk estimates, but there was too little evidence to establish a dose-response curve. With respect to childhood leukaemia, there is weak to moderate weight of evidence from epidemiological studies (the primary line of evidence). However, the animal models used in the majority of studies were not appropriate for studying childhood leukaemia, therefore there is weak evidence from this line of evidence. Moreover, there is weak evidence from interaction mechanisms on the induction of neoplasia by ELF-MF exposure. Consequently, overall, there is weak evidence concerning the association of ELF-MF exposure with childhood leukaemia.

Overall, there is moderate evidence (mainly from human studies) on the association between occupational exposure to ELF-EMF and amyotrophic lateral sclerosis, weak evidence for the association of occupational ELF-EMF exposure with Alzheimer’s disease, and dementia, but only uncertain to weak evidence for residential exposure and these neurodegenerative diseases. No significant association can be established between EMF exposure and Parkinson's or multiple sclerosis disease.

No systematic reviews or meta-analyses could be identified on exposure to ELF-EMF and neurophysiological outcomes. Therefore, it is still not possible to draw a definite conclusion on potential effects.

The available systematic reviews and meta-analyses have not shown an association between ELF-EMF exposure and pregnancy or reproductive outcomes.

The weight of evidence on the health effects of IF-EMF exposure is uncertain due to contradictory information from different lines of evidence. No conclusive results can be reached based on human studies, either.

The exposure of animals and plants to ELF-EMFs may reach higher levels than that of humans if they are close to anthropogenic sources in the environment. Moreover, animals and plants possess receptors and structures not existing in humans, which could give rise to species-specific biological effects.

Keywords: Electromagnetic Fields, Low frequencies, Intermediate Frequencies, Powerlines, Health effects, Biological effects, Interaction mechanisms

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Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). The Scientific Committees review and evaluate relevant scientific data and assess potential risks. Each Committee has top independent scientists from all over the world who are committed to work in the public interest.

In addition, the Commission relies upon the work of other Union bodies, such as the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHEER

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- health and environmental risks related to pollutants in the environmental media and other biological and physical factors in relation to air quality, water, waste and soils.

- complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health, for example antimicrobial resistance, nanotechnologies, medical devices and physical hazards such as noise and electromagnetic fields.

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1 MANDATE FROM THE EU COMMISSION SERVICES

The following part is provided by the requesting Commission services.

1.1 Background

Council Recommendation of 12 July 1999[1] (hereafter Recommendation) on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz) sets out basic restrictions and reference levels for the exposure of the general public to electromagnetic fields (EMFs). These restrictions and reference levels are based on the guidelines published by the International Commission on Non-Ionizing Radiation Protection in 1998 (ICNIRP)[2]. In response to the Recommendation, all Member States have implemented measures to limit the exposure of the public to EMF, either by implementing the provisions and reference levels and limits proposed by the Recommendation, or by implementing more stringent provisions[3]. In particular, twenty (20) Member States follow the Recommendation/ICNIRP Guidelines, while seven (7) impose stricter limits than those of the Recommendation.

In relation to the protection of workers' health and safety, Article 153 of the Treaty on the Functioning of the European Union foresees that the European Parliament and the Council can adopt by means of directives minimum requirements for the improvement, in particular, of the working environment to protect workers' health and safety, in order to support and complement the activities of Member States. In this context, the Council and the Parliament adopted Directive 2004/40/EC of 29 April 2004[4] on the minimum health and safety requirements regarding their exposure to the risks arising from physical agents such as electromagnetic fields which was repealed by Directive 2013/35/EU[5]. Member States had to transpose Directive 2013/35/EU by 1st July 2016. It lays down minimum requirements including action levels and exposure limit values for electromagnetic fields. In accordance with Article 153 of the TFEU, Member States are allowed to maintain or adopt more stringent protective measures for the protection of workers.

The Recommendation also invites the Commission to "*keep the matters covered by this recommendation under review, with a view to its revision and updating, taking into account possible effects, which are currently the object of research, including relevant aspects of precaution (paragraph 4)".* The ICNIRP guidelines were endorsed by the Scientific Steering Committee (SSC)**[6]** in its Opinion on health effects of EMFs of 25-26 June 1998. The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) prepared an update of the Scientific Steering Committee's Opinion and concluded in its Opinion on "*Possible effects of Electromagnetic Fields (EMF), Radio Frequency Fields (RF) and Microwave Radiation on human health", of 30 October 2001, that the information that had become available since the SSC Opinion of June 1999 did not justify revision of the exposure limits recommended by the Council[7].* The Opinions delivered by the SCENIHR in March 2007[8], January 2009[9], July 2009[10] and January 2015[11] confirmed the earlier conclusion of the CSTEE and again highlighted the need for additional data and research on this issue and recommended that specific research areas should be addressed.

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[1] (OJ. L 199/59, 30.07.1999)

[2] http://www.icnirp.de/

[3] http://ec.europa.eu/health/electromagnetic_fields/role_eu_ms/index_en.htm

[4] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0040&from=en

[5] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:179:0001:0021:EN:PDF

[6] http://europa.eu.int/comm/food/fs/sc/ssc/index_en.html

[7] The main frequencies in the ELF frequency range are 50 Hz in Europe and 60 Hz in North America. The RF and lower microwave frequencies are of particular interest for broadcasting, mobile telephony. The 2.45 GHz frequency is mainly used in domestic and industrial microwave ovens

[8] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_007.pdf

[9] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf

[10] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_024.pdf

[11] https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf

The Commission relies on the SCHEER to periodically review new information that may influence the assessment of risks to human health in this area and to provide regular updates on the scientific evidence base to the Commission.

Since June 2014, the cut-off date for the previous review by the SCENIHR, a sufficient number of new scientific publications have appeared to warrant a new analysis of the scientific evidence on possible effects on human health of exposure to EMF.

In addition, ICNIRP has released new guidelines for the protection of humans exposed to radiofrequency electromagnetic fields in March 2020. While the 1998 guidelines already provide protection regarding EMF exposure in all frequency bands for existing technologies, and all bands currently envisaged for 5G, the new guidelines provide additional guidance on a set of issues relevant to the latest developments in 5G technology and cover the range 100 kHz to 300 GHz[12].

The full guidelines are published in the scientific journal Health Physics and are accessible at the website of ICNIRP[13].

Consequently, the SCHEER is being asked to examine this new scientific evidence and to address in particular the questions listed in the Terms of Reference.

1.2 Terms of reference

The scientific committee SCHEER is consulted on the need of a (technical) revision of the Council Recommendation 1999/519/EC annexes and of the annexes of Directive 2013/35/EU in view of the latest scientific evidence available, in particular the ICNIRP guidelines updated in 2020[14] with regard to radio frequency (100 kHz to 300 GHz).

Opinion I

To advise on the need of a (technical) revision of the Council Recommendation 1999/519/EC annexes and of the annexes of Directive 2013/35/EU in view of the latest scientific evidence available, in particular that of the ICNIRP-guidelines updated in 2020, with regard to radio frequency 100 kHz to 300 GHz.

Opinion II

To update the SCENIHR Opinion of 2015 in the light of the latest scientific evidence with regard to frequencies between 1 Hz and 100 kHz.

1.3 Deadline

Preliminary Opinion I: July 2022

Preliminary Opinion II: July 2023

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[12] https://www.icnirp.org/en/publications/article/rf-guidelines-2020.html;https://www.icnirp.org/en/rf-faq/index.html

[13] https://www.icnirp.org/en/publications /index.html

[14] https://www.icnirp.org/cms/upload/publications/ICNIRPrfgdl2020.pdf

2 OPINION

2.1 Exposure

The exposure of the general population in Europe remains below the exposure limits recommended in Council Recommendation 1999/519/EC.

2.2 Interaction mechanisms

There are no systematic reviews and meta-analysis available for melatonin hypothesis, radical pair mechanisms, oxidative stress or epigenetic effects. There is weak weight of evidence regarding the involvement of interaction mechanisms (oxidative stress, genetic/epigenetic effects) on health risks from ELF-MF observed in epidemiological and *in vivo* studies.

More research is needed, making use of standardised exposure conditions and optimised *in vitro* cell lines, with the possibility to extrapolate to *in vivo* models where the metabolic processes play an important role for the interpretation of the biological responses relevant in terms of human health.

2.3 Health effects from ELF-EMF

No systematic reviews or meta-analyses on ELF-EMF exposure and self-reported symptoms could be identified since 2015 to make an assessment in the current Opinion. It is noted that in the SCENIHR Opinion (2015) it was concluded there was no convincing evidence for a causal relationship between ELF-MF exposure and self-reported symptoms.

Published systematic reviews on leukaemia and ELF-EMF exposure, based, mainly on case-control studies, revealed that ELF-MF exposure showed consistent, but moderate risk estimates, but there was too little evidence to establish a dose-response curve. With respect to childhood leukaemia, there is weak to moderate weight of evidence from epidemiological studies (the primary line of evidence). However, the animal models used in the majority of studies were not appropriate for studying childhood leukaemia, therefore, there is weak weight of evidence from this line of evidence. Moreover, there is weak weight of evidence from interaction mechanisms on the induction of neoplasias by ELF-MF exposure. Consequently, overall, there is weak weight of evidence concerning the association of ELF-MF exposure with childhood leukaemia.

Overall, there is moderate evidence on the association between occupational exposure to ELF-EMF and ALS, weak evidence for the association of occupational ELF-EMF exposure with Alzheimer’s disease, and dementia, but only uncertain to weak evidence for residential exposure and these neurodegenerative diseases. No significant association can be established between EMF exposure and Parkinson's or multiple sclerosis disease.

No systematic reviews or meta-analyses could be identified on exposure to ELF-EMF and neurophysiological outcomes. Therefore, it is still not possible to draw a definite conclusion on potential effects.

The available systematic reviews and meta-analyses have not shown an association between ELF-EMF exposure and reproductive or pregnancy outcomes.

2.4 Health effects from IF-EMF

The weight of evidence on the health effects of IF-EMF exposure is uncertain due to contradictory information from different lines of evidence. No conclusive results can be reached based on human studies, either.

2.5 Environmental effects from LF-EMF

There may exist differences in the exposure conditions for human, plants, and animals, because the latter (plants and animals) may get closer to sources of ELF-EMFs, such as power lines, or submarine power cables. Moreover, animals and plants possess receptors and structures not existing in humans, which could give rise to species-specific biological effects.

3 MINORITY OPINIONS

None

4 METHODOLOGY

4.1 Data/Evidence

The SCHEER, on request of Commission services, provides scientific opinions on questions concerning health, environmental and emerging risks. The scientific assessments carried out should always be based on scientifically accepted approaches, and be transparent with regard to the data, methods and assumptions that are used in the risk assessment process. They should identify uncertainties and use harmonised terminology, where possible, based on internationally accepted terms. In its scientific work, the SCHEER relies on the Memorandum on Weight of Evidence (WoE) and uncertainties (SCHEER, 2018), *i.e.*, the search for relevant information and data for the SCHEER comprises of identifying, collecting and selecting possible sources of evidence in order to perform a risk assessment and/or to answer the specific questions being asked. For each line of evidence, the criteria of validity, reliability and relevance need to be applied and the overall quality must be assessed. In the integration of the different lines of evidence, the strength of the overall evidence depends on the consistency and the quality of the results. The weighing of the total evidence is then presented in a standardized format that classifies results of analysis for human and environmental risks in terms of:

- Strong weight of evidence: Coherent evidence from a primary line of evidence (human, animal, environment) and one or more other lines of evidence (in particular mode/mechanistic studies) in the absence of conflicting evidence from one of the other lines of evidence (no important data gaps).
- Moderate weight of evidence: good evidence from a primary line of evidence but evidence from several other lines is missing (important data gaps).
- Weak weight of evidence: weak evidence from the primary lines of evidence (severe data gaps).
- Uncertain weight of evidence: due to conflicting information from different lines of evidence that cannot be explained in scientific terms.
- Weighing of evidence not possible: No suitable evidence available.

The initial literature search was performed in PubMed with the following search string:

> ("electric"[All Fields] OR "magnetic"[All Fields] OR "electromagnetic"[All Fields])
>
> AND
>
> (("extremely low frequency"[All Fields] OR "extremely low frequencies"[All Fields] OR "ELF"[All Fields] OR "50 Hz"[All Fields]) OR ("intermediate frequency"[All Fields] OR "intermediate frequencies"[All Fields]) OR ("low frequency"[All Fields] OR "low frequencies"[All Fields]))
>
> AND
>
> (("health effects"[All Fields] OR "biological effects"[All Fields]) OR ("leukaemia"[All Fields] OR "leukemia"[MeSH Terms] OR "cancer"[All Fields] OR cancer[MeSH Terms]) OR ("neurodegenerative"[All Fields] OR "Parkinson's"[All Fields] OR "Alzheimer's"[All Fields] OR "dementia"[All Fields]) OR ("brain"[All Fields] OR "cognitive function"[All Fields] OR "EEG"[All Fields]) OR ("behavior"[All Fields] OR "developmental effects"[All Fields] OR "pregnancy"[All Fields]) OR ("hormones"[All Fields]))

for publication dates between June 1, 2015, and July 31, 2023, i.e., since the publication of the SCENIHR report. This literature search resulted in about 3510 articles.

Filtering these articles for meta-analyses, systematic reviews and reviews resulted in 284 articles, of which a large number was about existing or emerging medical applications in the clinical practice (mainly, non-invasive stimulation of the central or peripheral nerve system with magnetic or electric fields, high-voltage short-duration electric pulses or pulsed electromagnetic fields (PEMF)) and were excluded, i.e., they were not considered by the SCHEER.

It was decided to address the Terms of Reference (ToR) of the current Opinion using mainly meta-analyses and systematic reviews, since they can efficiently handle the heterogeneity of individual studies resulting in an improved reliability of the level of evidence. When there was a lack of meta-analyses and/or systematic reviews on a biological/health effect, other reviews, like narrative reviews, were used. It was necessary for these reviews to have been performed with a methodology similar to the WoE approach of SCHEER (SCHEER, 2018). On the contrary, when a review, even characterised as systematic, suffered from methodological problems, it was not considered for risk assessment. The most common methodological problems were: (i) bias in the selection of reviewed literature (i.e., no clear search strategy or inclusion criteria were described); (ii) lack of quality assessment of the studies (e.g., no evaluation of exposure setup/control, statistical power, biological plausibility, etc.); (iii) overall conclusions drawn from all reviewed studies without differentiating the exposure frequency range, e.g., ELF (powerlines) and RF (smartphones).

Single research papers that fulfilled the required quality criteria were only used in exceptional cases (e.g., wide coverage of the general population), as for biological/health effects, mainly to strengthen the WoE in risk assessment (SCHEER, 2018).

4.2 Background

4.2.1 SCENIHR (2015) Opinion

4.2.1.1 Introduction

The SCENIHR Opinion of 2015 on "Potential health effects of exposure to electromagnetic fields (EMF)" investigated the whole frequency spectrum from static fields to 300 GHz. Here we repeat and update the main findings of the frequency range from 1 Hz to 100 kHz.

4.2.1.2 Intermediate Frequency

The exposure in the Intermediate Frequency (IF) band (300 Hz - 100 kHz) was mainly associated with the use of induction hobs and plasma balls, which can be considered as decorative or play items. SCENIHR had identified a few new studies on health effects from IF exposures in general, but no epidemiological studies. Some *in vivo* studies reported the absence of effects on reproduction and development of IF fields up to 0.2 mT in the frequency range of 20-60 kHz.

4.2.1.3 Low Frequency

The most representative exposure to Extremely Low Frequency (ELF) fields (0.1 Hz – 300 Hz) is related to electric power production, distribution and use (50/60 Hz).

Neoplastic diseases

The SCENIHR Opinion concluded that a possible association between long-term exposure to ELF magnetic fields (MF) and an increased risk of childhood leukaemia remained valid. A positive association had been observed in multiple studies in different settings at different exposure windows. Little progress has been made in explaining the findings, either in terms of a plausible mechanism for a causal relationship with the magnetic field at these frequencies or by identifying alternative explanations. Animal and *in vitro* studies did not provide further insight into how MF could contribute to an increased risk of childhood leukaemia. Although data generated *in vitro* suggests that ELF-MF may induce both genotoxic and other biological effects at flux densities of 100 μT and higher, the underlying mechanisms are not established and the biological relevance for a connection between ELF-MF exposure and childhood leukaemia is unclear.

Nervous system effects and neurobehavioral disorders

The studies considered by the SCENIHR, did not provide sufficient support for the conclusion that ELF-MF exposure increases the risk for Alzheimer's disease.

The approaches to investigate possible effects of exposure on the power spectra of the waking EEG were quite heterogeneous with regard to applied fields, duration of exposure, number of considered leads, and statistical methods. Therefore, these studies were not useful for drawing meaningful conclusions. The same was true for the results concerning behavioural outcomes and cortical excitability.

Animal studies have continued to investigate the effect of MF on neurobiology using various models and exposure conditions. They reported that exposure to ELF magnetic fields had no effect on activity or locomotion. There was some evidence from animal studies that exposure to ELF-MF might affect the performance of spatial memory tasks (both deficits and improvements have been reported) and generate subtle increases in behavioural anxiety and stress. Several of the animal studies had investigated potential molecular and cellular mechanisms, and despite several studies continued to report candidate mechanisms, particularly, regarding effects on reactive oxygen species (ROS), no mechanism could be firmly identified operating at exposure levels found in the everyday environment.

The few available *in vitro* studies did not provide any support for drawing conclusions on the possible effects of ELF on the nervous system and neurobehavioral disorders.

Symptoms

The studies considered by SCENIHR showed discordant results. Observational studies suffered from weaknesses and did not provide convincing evidence of an effect of ELF exposure on symptoms in the general population. Most experimental evidence also pointed to the absence of any causal effect.

Reproductive effects

The SCENIHR concluded that the examined studies did not show an effect of ELF fields on the reproductive function in humans.

Developmental effects

The SCENIHR noted that data had been recently published that showed an association between ELF fields and childhood obesity and asthma. However, SCENIHR concluded that it would be necessary to further reproduce these results in order to evaluate their significance for risk assessment.

4.2.2 ANSES (2019) Opinion

In 2019 ANSES published its report on "Health effects linked to exposure to low-frequency electromagnetic fields" (ANSES, 2019).

Exposure

As far as knowledge of exposure is concerned, the ANSES noted a lack of available information. Therefore, they relied on published studies in occupational settings, and on original work aiming at characterizing exposure of individuals in residential environments. However, according to the ANSES, the electromagnetic environment is changing, for example with the development of renewable energies and the decentralisation of electricity production closer to consumers, thus modifying the spatial distribution of electromagnetic field sources. At present, the changes in the population's exposure to low-frequency electromagnetic fields that could result from these changes in the power generation and distribution system have not been documented.

Moreover, a study performed by the Institut national de recherche et de sécurité (INRS) and the Caisses d'assurance retraite et de santé au travail (CARSAT) had shown that some workers may be exposed to very high field levels, potentially exceeding the limit values defined in European Directive 2013/35/EU. It was also noted in the ANSES report that when a pregnant woman is exposed to a magnetic field intensity corresponding to the maximum exposure limit values for workers, the electric current density induced in the foetus, in certain exposure scenarios, may be higher than the exposure limit values recommended for the general public in the Council Recommendation 1999/519/EC.

Biological and health effects

The ANSES reported biological effects (oxidative stress, genotoxic effects, effects on cellular physiology) that occur at exposure levels around the action trigger values defined in the European Directive 2013/35/EU.

According to ANSES, a number of epidemiological studies highlighted a link between occupational exposure to low-frequency electromagnetic fields and the occurrence of certain health effects (neurodegenerative diseases and central nervous system tumours). The ANSES, therefore, recommended assessing the relevance of the scientific basis for the exposure limit values.

Recommendations

Given the persistent uncertainties surrounding the link between exposure to magnetic fields and childhood leukaemia, the ANSES recommended that research be continued on the most exposed populations (for example by studies looking at homes located near transformers), and by improving exposure assessment in epidemiological studies (for example by combining field measurements and modelling).

In the workplace, given the uncertainties associated with recent data suggesting an association between exposure to low frequencies and the appearance of brain tumours or neurodegenerative diseases (such as Alzheimer's disease and ALS) a causal link cannot be established. The ANSES, therefore, recommended encouraging epidemiological research into these health effects in the workplace.

5 ASSESSMENT

5.1 Exposure

Given the scarcity of systematic reviews on the exposure of population to the emerging applications of low-frequency fields, in some cases below, research articles with a robust methodology were selected to demonstrate the exposure level of the general public under specific conditions.

5.1.1 Intermediate frequency (IF) fields

5.1.1.1 Household appliances

Aerts *et al.* (2017) conducted a survey of the IF fields in 42 residences in three European countries (Belgium, Slovenia, and the United Kingdom (UK)). Typical field levels in the properties were assessed by measurements in the middle of the most-frequented rooms (living room, kitchen, and bedroom), as reported by residents. The IF fields emitted from a wide range of household appliances were also investigated through measurements as a function of distance performed on 279 appliances, operating under real-life circumstances. The appliances were classified into 65 categories, of which power tools and compact fluorescent lamps were the largest. Four more categories consisted of more than ten appliances, and 32 categories contained only one. Three categories (i.e., fridges, laundry machines, and microwave ovens) were split in two because part of the appliances used inverter technology, causing distinct IF emissions. At a certain distance (>1 m) from any electric appliance, IF field levels in residences were found to be generally low, with average wideband field strengths between 1 kHz and 100 kHz of approximately 1 V/m and below 0.05 A/m (i.e., the measurement probes' noise floor). At a distance of 20 cm (or closer), however, IF field emissions from certain appliances (especially induction cookers, CRT displays, LCDs, compact and other fluorescent lights, some power tools, and some microwave ovens with inverter technology) can become relevant, i.e., with a total IF electric field (EF) or MF exposure above 5% of the ICNIRP (2010) reference levels, using the appropriate summation rules. Overall, fundamental frequencies of IF emitting appliances varied between 6 kHz (refrigerator with inverter technology) and 293 kHz (laundry machine with inverter technology), with most somewhere between 20 kHz and 60 kHz. Often, the fundamental frequencies were accompanied by harmonics (up to 400 kHz for strong emitters such as induction cookers). The maximum peak field strengths recorded at 20 cm were 41.5 V/m and 2.7 A/m (3.4 μT), both from induction cookers.

Kitajima *et al.* (2022) measured the magnetic fields generated by more than 70 induction cookers in a real household environment. The average value of the magnetic field measured in the survey was 0.23 μT (standard deviation: 0.13) at a horizontal distance of 30 cm at the height of the cooking table.

5.1.1.2 Wireless Power Transfer

Inductive Wireless Power Transfer (WPT) charging for Electric Vehicles (EV) is a technology that is expected to become widely used (Mahesh *et al.*, 2021).

Miwa *et al.* (2019) numerically calculated the exposure of the cabin passengers in an EV charging with a WPT inductive system at 85 kHz and 3.7 kW transmitted power. They found that the exposure depended strongly on the material of the vehicle frame, which can be made of iron, aluminium, and carbon fibre reinforced plastic (CFRP). The computational results revealed that when the body of the vehicle is composed of CFRP, the magnetic field strength leaking into the vehicle is higher than that with other materials. The maximum calculated internal electric field was 0.525 V/m for the vehicle frame made of CFRP.

Haussmann *et al.* (2022) also investigated the exposure scenario of a person standing next to the EV (a model of an electric taxi) being wirelessly charged at 85 kHz and 20 kW transmitted power. The maximum calculated internal electric field strength in the person standing outside the EV can reach a value of 1.59 V/m, when the primary coil of the system is shifted toward the person by 20 cm. In a similar scenario with a person standing behind the EV being charged at 85 kHz and 10 kW transmitted power, Wang *et al.* (2019) had calculated a maximum internal electric field strength of 0.673 V/m (obtained at the toe of the numerical phantom).

Liorni *et al.* (2020) assessed the exposure to electric vehicle inductive power transfer (IPT) systems both experimentally and numerically. Their work was performed within the framework of the European Project EMPIR-16ENG08 MICEV. It assessed the exposure of the general public to IPT stray magnetic fields for two different exposure scenarios: (1) for an IPT model system derived from the SAE J2954 standard operating at 85 kHz for a light electric vehicle coupled with the model of a realistic car-body model; and (2) for an IPT model system with a maximum rated power of 50 kW at 27.8 kHz for a real minibus that was reproduced with some simplifications in two different 3D finite element method (FEM) simulation tools. An ad hoc measurement survey was carried out at the minibus charging station to validate the simulations of the real bus station for both aligned and misaligned IPT coils. As highlighted in this study, the vehicle-body serves as an efficient screen to reduce the magnetic field by at least three orders of magnitude close to the coils. The exposure of three Virtual Population (ViP) human anatomical phantoms (one adult, one child, and a newborn) was assessed. The three phantoms were placed in different postures and locations for both exposure scenarios. The basic restriction limits, established by the ICNIRP (2010) guidelines, were never exceeded within the vehicles; however, the basic restrictions were exceeded when an adult crouched outside the minibus, i.e., near the coils, or when a newborn was placed in the same location, by 12% and 38%, respectively. Borderline values were observed in the light car.

5.1.1.3 Electric vehicles charging

The increased number of electric vehicles (EV) drives the need for more EV charging stations in the urban (even domestic) environment. Standard or fast chargers exposes their users to the low-frequency EMF they generate. Bae and Park (2023) measured the electromagnetic field exposure of six EV chargers, which they evaluated against the ICNIRP (2010) guidelines. Higher electromagnetic fields were measured with standard chargers than with fast chargers. For the fast charger in the charging state, the magnetic field increased with the charging current. Electromagnetic field exposures for all six chargers did not exceed the limits set in the guidelines.

5.1.1.4 Powerline communication

In recent years, with the development and availability of novel technological solutions, smart building and smart city concepts have started to be widely implemented. In a smart building environment, home appliances, heating or air conditioning can be controlled or operated remotely, and unexpected events can be monitored (with appropriate sensors) and dealt with (with the corresponding actuators) in almost real time. One of the possible technologies suitable for smart buildings is Powerline Communication (PLC). PLC systems carry data along the conductors that are used to transmit or distribute electric power to buildings and consumers. PLC can be compared to wireless solutions in terms of the cost of building a communication infrastructure, because power lines are already built and are available everywhere (Mlýnek *et al*., 2021). In Europe the band 3–148.5 kHz has been allocated to narrowband PLC and has been used for smart utility meters. In a recent report ANSES (2023, p.24) concludes: "Thus, although there is currently very little data on the potential health effects of exposure to electromagnetic fields in the frequency bands relating to PLC (approximately 50-150 kHz), given the very low levels of exposure measured and the conclusions of previous expert reports it is highly unlikely that exposure to the electromagnetic fields emitted by both radio and other (PLC) communicating meters could cause short- or long-term health effects.". Moreover, literature shows that it is the broadband PLC frequency range, above 1.8 MHz, that concentrates most of the interest for smart applications (Monadizadeh *et al.*, 2021).

5.1.2 Combined exposure

The MRI electromagnetic (EM) environment is one in which combined exposure to EMF of various frequency ranges takes place. In the SCENIHR (2015) Opinion research on the potential health effects of the MRI, in particular among workers and paediatric patients, was marked as of high priority. However, not much work has been performed in this area since then. The new research on MRI exposure (which is a complex EM environment including the gradient coil fields in the low frequency range) concerns either the static magnetic field or the RF-EMF of the MRI (Frankel *et al.*, 2018).

5.1.3 Low frequency (LF) fields

A narrative review of studies concerning LF (50 Hz–100 kHz) EMF exposure assessment in Europe was published (Gajšek *et al.*, 2016) shortly after the publication of the latest SCENIHR Opinion. The authors concluded that the average exposure to LF-MF of the general public in European countries was very low, between 0.01 and 0.1 μT. They calculated that approximately 0.5% of the general public was exposed for longer periods to levels above 0.2 μT from the fixed outdoor ELF-EMFs sources. In public areas of urban environments, the MF ranged from 0.05 to 0.2 μT, but higher values would occur directly beneath high-voltage power lines, at the wall of transformer buildings, and at the boundary fences of substations, in which case the maximum field could reach up to 20–80 μT. Elevated ELF exposure (up to a few μT) was measured in apartments very close to built-in power transformers, as well. The major contribution to the exposure to magnetic fields originates from household electric devices that are used commonly by the general public, but the duration of such exposure is extremely limited. In terms of lifelong cumulative exposure, approximately one third of the total exposure experienced by an individual could be attributed to the use of personal appliances, although the study that produced this result is very old by now and had identified electric alarm clocks, electromechanical digital alarm clocks, and electric blankets as the main sources of exposure (the first two of these EMF sources are almost obsolete). One of the exceptions is electric underfloor heating, which can lead to the exposure of all inhabitants of a house over 24 hours in the day. The same ranges of exposure levels to ELF-EMF were reported in an overview of more recent studies (after 2015) that was published by Bonato *et al*. (2023).

5.1.4 Guidelines concerning exposure

A harmonised standard is a European standard developed by a recognised European Standards Organisation (CEN, CENELEC or ETSI) at the request of the European Commission. A harmonised standard is recognised by the European Commission, by publication of its reference to the official journal of the European union, as giving presumption of conformity to essential requirements of EU regulation. In the case of low frequency EMF, the regulation includes Directive 2013/35/EU on the minimum health and safety requirements regarding the exposure of workers to the risks arising from electromagnetic fields, Directive 2014/35/EU[15] (Low Voltage Directive, LVD) on placing electrical equipment designed for use within certain voltage limits on the market, and Directive 2014/53/EU[16] (Radio Equipment Directive, RED) on placing radio equipment on the market.

Exposure limits for the general public in the low frequency range are set in the Council Recommendation (CR) of 12 July 1999 and are based on the ICNIRP (1998) guidelines. ICNIRP updated its exposure guidelines in the low frequency range for the general public in 2010 and is currently working to revise them further. It should be noted that the main changes in the low frequency range between the previous exposure guidelines (ICNIRP, 1998), recommended in the technical annexes of the CR, and the current guidelines (ICNIRP, 2010) are:

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[15] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0035

[16] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0053

- While in 1998 dosimetric considerations were based on simple geometrical models, the latest guidelines have used data from computational simulations based on anatomically detailed human body models. Moreover, the physical quantities used to limit exposure have changed, setting restrictions to induced electric field (V/m) instead of induced current density (A/m^2) inside the tissues.
- The latest basic restrictions, as well as the dosimetric models used, have resulted in reference levels in ICNIRP (2010) that deviated in some frequency ranges from the ones in ICNIRP (1998). For example, the reference level for the magnetic flux density at 50 Hz was raised from 100 to 200 µT, whereas the electric field reference levels are, with some exceptions, basically unchanged.

5.2 Interaction mechanisms

Trying to determine if there is any causal relationship between ELF magnetic field and increased health risks has led many research scientists to examine the potential mechanisms by which such fields might affect human health.

The stimulation of excitable tissues has a well-understood biophysical basis and is an indisputably demonstrated effect. Several hypotheses for other mechanisms have been proposed and are discussed below.

5.2.1 Tissue stimulation

As a result of the time-varying fields exposure with frequencies up to 10 MHz, the stimulation of excitable tissues is the unequivocally demonstrated established acute effect. Upon exposure to these fields, electric fields and current are generated inside the body and can interfere with the body's electric fields and current flows due to the biological functions. If the induced internal fields reach a certain threshold level, the direct stimulation of nerve and muscle tissue occurs, with muscle cells generally less sensitive than nerve tissue (Reilly, 1998).

The peripheral nerve stimulation (PNS) is a well-known and documented phenomenon associated also with gradient switching in MRI systems (ICNIRP 2010, 2014). The phenomenon of PNS originates from the interaction of the electric fields with the nerve fibres in the human body (Budinger *et al.*, 1991; Cohen *et al.*, 1990). As a consequence of the application of an electric potential gradient to a nerve fibre, the nerve membrane will be charged electrically (depolarisation or hyperpolarisation). If a strong depolarisation occurs, a non-physiological action potential will start that will give rise to muscle contraction and sensory perceptions. If the applied potential is increased beyond this initial perception threshold, adverse effects can be generated such as pain, stimulation of the central nervous system with possible consequent seizures, and cardiac nerve stimulation with possible consequent arrhythmia. In So *et al*. (2004), authors estimated the minimum threshold for peripheral nerve stimulation of between about 4–6 V/m, based on the assumption that stimulation took place in the skin or subcutaneous fat.

The most robustly established effect of electric fields below the threshold for direct nerve or muscle excitation is the induction of magnetophosphenes. It consists of a visual experience of flickering lights upon exposure to a sufficiently strong MF; they occur in the absence of a visual stimulus and are thought to result from the interaction of the induced electric field with electrically excitable cells in the retina. The minimum threshold flux density is around 5 mT at 20 Hz, rising at higher and lower frequencies (ICNIRP 2010, 2014]. On the basis of computed data, the macroscopic retinal threshold current density for phosphenes at 20 Hz can be estimated as 10 mA/m^2 (-20% to + 30%, depending on the anatomical model (Laakso and Hirata, 2012).

These recognised effects can be avoided by meeting appropriate basic restrictions on electric fields induced in the body.

5.2.2 Melatonin hypothesis

The melatonin hypothesis has emerged and states that exposure to ELF fields might decrease melatonin production and may promote the development of cancer in humans. Melatonin is one of the major markers of the circadian system whose disruption has emerged as a pathophysiological mechanism underlying cancer and cancer-treatment related symptoms (Amidi and Wu, 2022). For many decades, data from *in vivo* and human studies testing this hypothesis has been published in scientific literature but no systematic reviews or meta-analyses are available.

In the review paper by Touitou *et al*. (2012), 42 *in vivo* studies on different animal species and 34 human studies were compiled and analysed. The ELF exposure was from one week to several months at magnetic flux densities from few μT up to few mT. The results were contradictory, with some modification of melatonin secretion (25 studies) and absence of effect (17 studies) in the *in vivo* studies. When human studies were considered, a decrease in melatonin secretion was found in 11 studies, while 23 studies reported absence of effect. A similar controversy was also highlighted in the review by Halgamuge (2013).

The impact of ELF-MF on melatonin levels in rat models and in human subjects was recently analysed by Bouché and McConway (2019). The authors used both parametric and non-parametric approaches to analyse a total of 62 studies retrieved from review papers available in the literature. The results showed that rat and human studies are consistent with one another, but only when the MF strength covers the same range with $B \leq 50$ μT. Moreover, exposure longer than 22 days appears to decrease melatonin levels only when MF is below the one of the static geomagnetic fields (about 30 μT). Authors concluded that the result of their analysis could reconcile the studies reporting effects on melatonin levels and the ones not reporting an effect, and asked for further research.

Ohayon *et al.* (2019), in their review of the studies on the effects of EMF on melatonin secretion and sleep architecture concluded that results were still inconclusive and often contradictory. They also mentioned that several factors other than EMF, such as age, might had a greater influence in modifying melatonin secretion but had rarely been adequately controlled in the reviewed studies.

5.2.3 Effects on ion channels and calcium homeostasis

Voltage-gated ion channels and calcium homeostasis have been frequently hypothesised to be a possible target of ELF magnetic field. These hypotheses have been both substantiated and rejected by numerous studies in literature.

The systematic review by Bertagna *et al.* (2021) analysed the effects of EMF of both ELF and RF exposure on neuronal ion channels. The author's main question was related to the influence on ion channel conductance and expression in the central nervous system. They collected original research papers published in the years 2005-2020. A total of 13 out of the 24 papers included in the analysis deal with ELF-EMFs at 50 Hz, delivered at several magnetic flux density. Several neuronal cell models were used in the included papers, and in the majority of them, acute (up to 2 h) or subchronic (≤48 h) exposure were investigated with magnetic flux density not exceeding 1 mT. Mainly, the effects of calcium channels were studied, and the results indicated that chronic exposure induced an increase in the intracellular calcium levels along with increases in the gene and protein expression of transmembrane calcium channels. Authors concluded that VGCCs (Voltage-Gated Calcium Channels) are an important transducer of the effects of ELF EMF in neurons where they exert a central role in the regulation of many physiological processes including modulation of neurotransmitter release and intersynaptic short- and long-term communication, neuronal plasticity and neurite outgrowth.

The SCHEER noted that inclusion criteria were that (1) the paper covered original laboratory research; (2) the model of the study was neurons, neuron-like cells, or neural tissue; and (3) the paper was relevant based on its title and abstract. The quality of the single papers was not considered in terms of ELF exposure.

A rigorous systematic review and meta-analysis of *in vitro* studies measuring the actual calcium release, uptake, fluctuations or homeostasis without the use of pharmacological inhibitors was published by Golbach *et al.* (2016). All inclusion criteria and methods of analysis were specified a priori in a protocol described in the publication itself.

At the end of the selection process, 42 papers, for a total of 148 experiments, were included in the analysis. All the studies were carried out on mammalian cells either immortalised cell lines (72 experiments) or primary *ex vivo* cell cultures (76 experiments). The magnetic flux densities ranged from 40 nT to 22 mT, and the duration of exposure ranged from a couple of minutes to many days. In the majority of the experiments, the cells were exposed to 50 or 60 Hz under acute exposures, in a few experiments, a specifically calculated calcium resonance frequency was applied.

The overall analysis revealed: 1) a statistically significant effect of LF MF exposure on the frequency of the calcium oscillations; 2) a statistically significant small increase in intracellular calcium levels caused by LF MF; 3) heterogeneous effects associated with the exposure frequency, magnetic flux density and duration in the subgroups analysis in the case of intracellular calcium levels.

The authors mentioned that some of the studies included might introduce a great risk of bias as a result of uncontrolled or not reported exposure conditions, temperature ranges and ambient fields.

The authors concluded that LF MF exposure might affect calcium homeostasis in mammalian cells *in vitro*, but the analysis is weakened by risk of bias and high heterogeneity.

In the review paper recently published by Panagopoulos *et al*. (2021), a biophysical mechanism has been suggested for which an irregular gating of electrosensitive ion channels or VGICs (Voltage-Gated Ion Channels) at the level of cell membrane are caused by polarised and coherent EMF at environmentally relevant intensities. Authors also suggested a sequence of events that might be activated by the electrochemical imbalance and could lead to ROS hyperproduction and DNA damage. They stated that such mechanism was due to the electric field and not to magnetic field and would apply to both ELF fields and ELF modulated radiofrequency (RF) fields. The SCHEER agrees with the authors that the proposed hypothetical mechanism needs further research in order to be substantiated.

5.2.4 Cryptochrome – radical pair mechanism

The radical pair mechanism (RPM) is a favoured hypothesis in which ELF-MF can affect specific types of chemical reactions, generally increasing concentrations of reactive free radicals in low fields and decreasing them in high fields (WHO, 2007). The plausibility of this mechanism has been studied in several investigations, with focus on cryptochrome (CRY), a blue-light sensing protein implicated in animal magnetoreception. These investigations include *in vitro* experiments on cellular responses to MF exposure, animal studies of magnetoreception, biochemical investigations of cryptochromes, and theoretical studies of cryptochrome-based radical pair formation. CRY are ubiquitous proteins in the animal kingdom, where they assume the regulation of circadian biorhythms and possibly magnetic compass sensing. The radical pair they host is the only known biological process to be sensitive to MF in the μT range (Maeda *et al.*, 2012), and furthermore the disruption of biorhythms regulated by CRY has been demonstrated to be correlated with breast cancer (Ball *et al*., 2016).

There are no systematic reviews and meta-analyses which address the evidence of the RPM.

The possibility that carcinogenic effects result from biological detection of weak ELF MF by magnetically sensitive radical reactions in CRY has been discussed in a narrative review paper by Juutilainen *et al.* (2018). They reviewed the understanding of the RPM in magnetoreception and its links to cancer-relevant biological processes, as well as experimental evidence for effects of ELF MF that may be relevant for carcinogenesis such as DNA damage responses, reactive oxygen species formation and genomic instability. They proposed a hypothesis for explaining the link between environmental MFs and childhood leukaemia which is based on the role of CRYs in magnetoreception and findings indicating that the circadian regulation system (including CRYs) is coupled to DNA damage responses and defence against ROS. Authors discussed the strengths and weaknesses of the proposed hypotheses at great length in the paper and concluded that cancer-relevant biological processes can be influenced by ≥100 μT, 50–60 Hz MF. Although the experimental findings at fields ≥100 μT do not directly explain the epidemiological association between childhood leukaemia and ≥0.4 μT ELF MF, the radical pair chemistry of CRYs appears to be the most plausible working hypothesis to guide further research.

5.2.5 Genetic and epigenetic effects

As the energy level produced by exposure to ELF-EMF is not sufficient to entail direct breakage of cell chemical bonds as for DNA, several authors (Wang and Zhang, 2017; Lai, 2019) consider that the genetic and epigenetic effects on biological systems are probably indirect and secondary, depending on several interacting factors e.g. frequency, intensity, exposure duration, number of exposure episodes, tested animal tissues/cell lines, etc., overall leading to an array of compensatory responses with the possibility of genetic homeostasis break down.

Concentrations of free radicals, such as ROS, can modulate cell signalling (Finkel, 2011), leading to biologically significant changes, including epigenetic ones (Afanas'ev, 2014). ROS could be involved in ELF-MF-induced epigenetic changes (Wang and Zhang, 2017; Consales *et al*., 2018). ELF-MFs may interact with membrane targets, such as transmembrane ion channels, including those involved in calcium metabolism regulation (Golbach *et al*., 2016). Calcium signalling also plays a role in gene expression and is relevant for epigenetic regulation (Puri, 2020).

More recently, the review paper by Giorgi and Del Re (2021) reported on the association between the exposure to ELF-MFs and epigenetic alterations in various cell types. Fifteen experimental studies evaluated the effects of ELF-MF exposure on epigenetic marks, however, these studies were very heterogeneous in duration (from 1 h to 60 days), mode of the exposure (continuous or intermittent) and physical characteristics of ELF-MF. Indeed, the magnetic field direction (changing continuously in rotating MF, RMF, with respect to sinusoidal and pulsed fields), its rise (rapid in pulsed EMF, PEMF, and smooth in sinusoidal alternating fields), the frequency itself and the intensity values are all parameters that might lead to different effects (IARC, 2002).

Despite the small number of publications included in this review, there was evidence indicating that ELF-MF exposure can be associated with epigenetic changes, including DNA methylation, modifications of histones and microRNA expression. Most of the studies (13 out of 15 studies) observed that ELF-MF exposure can induce an alteration of epigenetic marks. They found that the exposure promoted cell differentiation and Induced Pluripotent Stem Cell (iPSC) generation. It was already known that electromagnetic fields can contribute to reprogramming of human skin fibroblasts and can affect biological processes such as embryogenesis, regeneration, and cell fate conversion: the novelty of the reviewed studies was the finding that ELF-MFs affect these processes through epigenetic alterations. Some effects have been observed in differentiated cells, but it is unclear whether these effects are transient or not and which are the potential long-term consequences for cell biological functionality. Also, most of the results were obtained using *in vitro* systems consisting of monolayer cultures of neoplastic cells lines which lack the complexity of *in vivo* conditions.

In conclusion, SCHEER agrees that the molecular mechanisms through which ELF-MFs interact with organic molecules leading to epigenetic dysregulation are still unknown and that more research on epigenetic effects and their underlying mechanisms is needed in the future.

5.2.6 Oxidative stress

Experimental evidence from several studies has been accumulated showing that ELF MF exposure may affect biomarkers of oxidative stress, but there are no systematic reviews or meta-analyses available in the literature.

An informative narrative review was co-authored by Schuermann and Mevissen (2021), which presents details on information sources. This review includes a compilation of studies published in the last 10 years, and reports on key experimental findings on oxidative stress markers deriving from *in vivo* (animals, 13 studies) and *in vitro* (cells, 47 studies) experiments. The results are discussed in the context of molecular mechanisms that can be relevant for human health. The authors grouped the studies for the impact on nervous system, on reproduction, and on blood and immune system. The observations were made on several *in vivo* and *in vitro* models exposed to several exposure times and field strengths within the range of regulatory recommendation. A correlation with functional analysis is included to look for temporary or persistent effects. They concluded on the increased oxidative stress due to ELF-MF, as reported from the majority of animal studies and from more than half of the cellular studies. They also pointed out that some studies were subjected to methodological uncertainties or weakness or were not very comprehensive regarding exposure time, dose, number and quantitative analysis of the endpoints analysed. The authors suggested there was a trend showing that ELF-MF could affect cellular oxidative balance, and that this did not necessarily lead to health effects since, under certain conditions, an adaptation mechanism after a recovery phase was found. The authors stated that standardised experimental conditions would be required to confirm their conclusions.

Similar conclusions on the increased oxidative stress due to ELF-MF, and on the need for more standardised studies, can also be found in the review papers by Lai (2019) and by Wang and Zhang *(*2017).

5.2.7 Apoptosis

In the meta-analysis by Mansourian *et al.* (2016), the *in vitro* studies, covering the effects of ELF MF exposure and apoptosis published in the period 2000-2010, were analysed. Overall, 8 studies fulfilled the inclusion criteria and were included in the analysis. The results indicated that ELF-MFs could significantly increase the apoptosis level *in vitro* in both cancer and normal cells. Such an increase occurred with a distinctive range of flux density and time which were consistent with window effect with the maximum <0.5 mT and in the range 72 h - 5 days. Authors concluded that the sample size was very small and thus makes it difficult to accurately determine the effects of ELF-MFs on spontaneous apoptosis from an analysis of this data.

5.2.8 Conclusions on interaction mechanisms

The stimulation of excitable tissues has a well-understood biophysical basis and is an indisputably demonstrated effect of exposure to time-varying fields with frequencies up to 10 MHz.

Reviews dealing with other potential mechanisms by which ELF magnetic fields might affect human health have been considered here, namely melatonin hypothesis, radical pair mechanism-cryptochrome, effects on ion channels and calcium homeostasis, genetic and epigenetic effects, oxidative stress and apoptosis.

There are no systematic reviews or meta-analysis available for melatonin hypothesis, radical pair mechanisms and oxidative stress. The current scientific evidence based on narrative reviews highlights inconclusive and often contradictory results on melatonin hypothesis and radical pair mechanisms. There is a trend showing that ELF-MF could affect oxidative balance not necessarily leading to health effects.

ELF-MF exposure might affect calcium homeostasis in *in vitro* models, but the analysis is weakened by risk of bias and high heterogeneity, while there are controversial indications in the case of apoptosis, and the meta-analysis available suffers from small sample sizes.

There are no systematic reviews and meta-analysis available for epigenetic effects, either. However, there is evidence that ELF-MF exposure can be associated with epigenetic changes, including DNA methylation, modifications of histones and microRNA expression, although the molecular mechanism through which ELF-MFs interact with organic molecules leading to epigenetic dysregulation is still unknown. More research is needed, making use of standardised exposure conditions and optimised *in vitro* cell lines, with the possibility to extrapolate to *in vivo* models where the metabolic processes play an important role for the interpretation of the biological responses relevant in terms of human health.

In conclusion, there is weak evidence regarding the involvement of interaction mechanisms (oxidative stress, genetic/epigenetic effects) on health risks from ELF-MF observed in epidemiological and *in vivo* studies.

5.3 Health effects from ELF fields

5.3.1 Neoplastic diseases

The literature search resulted in sourcing information on the co-exposure of study subjects to ELF fields with other physical or chemical agents. The information sources that fulfilled the inclusion criteria were considered, but only for drawing conclusions on the potential risks of ELF fields exposure alone.

5.3.1.1 Epidemiological studies

Systematic and umbrella review papers, based on epidemiological studies, published since 2016 were evaluated.

Specifically, Schüz and Erdmann (2016) concluded that low EMF consistently showed a relatively small increase in risk of developing leukaemia, but several issues regarding bias and confounding among studies were raised. In particular, based on studies from South Korea, Germany and the UK, the authors concluded that there is evidence of an association between ELF-EMF exposure and childhood leukaemia incidence, with relative risks varying between 1.5 and 2.0 at daily average exposure levels exceeding 0.3/0.4 μT. Additionally, Kheifets *et al*., (2017) summarised a larger number of studies, with exposure categorised (based on either measured or estimated levels) into 3 or 4 bands. They reported a small, elevated risk above 0.3-0.4 μT of exposure. More recently, Onyije *et al.*, (2022) presented an umbrella review based mainly on case-control studies. The authors concluded that ELF-MF showed a moderate level of association with neoplastic diseases incidence (i.e., they observed consistent moderate relative risk estimates, RR>1.5), but they did not, however, complete a meta-analysis because of the small number of available studies (only 6) that reported results on EMF exposure.

Swanson *et al.* (2019) carried out a meta-analysis based on 41 studies examining the cumulative risk over time. Although the cumulative relative risk has indeed declined, it was not statistically significant. They further commented on their findings with higher risks observed in studies looking at higher exposures and in studies with better quality exposure assessment. Seomun *et al.* (2020) conducted a meta-analysis for the association between the ELF-MFs exposure level and childhood cancer based on 33 studies. They reported significant associations between exposure to ELF-MFs and childhood leukemia. Brabant *et al.* (2022) performed a systematic review and meta-analysis to clarify the relation between ELF-MF from several sources and childhood leukemia, taking into account the different measures used to assess magnetic field exposure: magnetic flux density measurements (<0.2 μT vs. >0.2 μT), distances between the child's home and power lines (>200 m vs. <200 m) and wire codings (low current configuration vs high current configuration). Their global meta-analysis indicated an association between childhood leukemia and ELF-MF driven mainly by studies conducted before 2000. Results indicated that the magnetic flux density threshold associated with childhood leukemia is higher than 0.4 μT. Amoon *et al.* (2022) performed a pooled, fixed-effects meta-analysis, combining raw individual-level data from four case-control studies on MF and childhood leukaemia that included 24,994 cases and 30,769 controls. They found no association between presence of leukaemia and exposure ≥0.4 μT compared with exposures <0.1 μT (odds ratio = 1.05, 95% CI: 0.59, 1.85). Similarly, no association was observed in the subset of acute lymphoblastic leukaemia. When the meta-analysis focused on the highest exposure category, i.e., ≥0.65 μT compared with exposures

<0.1 μT, the odds of having leukaemia increased to 1.45 (95% CI: 0.95–2.20); confirming that no significant association was evident.

The Health Council of the Netherlands performed a number of meta-analyses[17] (Health Council of the Netherlands, 2018a,b) including both studies in which field strength was measured, as well as studies in which field strength was calculated. The results showed that exposure to a magnetic field strength of typically more than 0.3 or 0.4 μT is frequently associated with a statistically significant increase in risk of neoplasias. However, the Health Council could not always find evidence of a statistically significant dose-response relationship. The available data (Health Council of the Netherlands, 2022a,b) showed that, for "most of the types of cancer under investigation, no indication of an increased risk was found. However, just as was the case for children, leukaemia may occur more frequently in adults who live close to overhead power lines".

In brief, some of the summary findings in each of the reviews considered here were based on only a small subset of original studies and one common conclusion was frequently reported that the findings were inconsistent, with potential explanations of this inconsistency due to bias and confounding, as well as self-recall for the retrospective case-control studies. Common recommendations were that larger studies should be developed. Nonetheless, there were findings of elevated risks, sometimes restricted to specific exposure ranges, but often the confidence intervals were wide, reflecting the considerable uncertainty, and there was frequently no apparent dose-response curve.

5.3.1.2 Animal studies

Systematic reviews or meta-analyses were not published since the last SCENIHR Opinion of 2015. As a result, the SCHEER broadened the inclusion criteria to allow for large single animal studies to inform the evidence base. Three (co-)carcinogenicity studies in rats conducted by the Ramazzini Institute (RI), Italy, were identified. Using 50 Hz ELF-MF alone or as promoter and co-carcinogen, the RI started in 2002 a large project with four different studies using 7,133 rats in total. The following three studies were published (Soffritti *et al.*, 2016a,b; Bua *et al.*, 2018) and commented accordingly (ICNIRP, 2020; SSM, 2018, 2019).

Soffritti *et al.* (2016a) (co-)exposed Sprague-Dawley rats from day 12 post-conception (pc) until death, 19 h/d to sinusoidal 50 Hz MF (and γ-radiation). The objective was to evaluate the applied 50 Hz MF as carcinogen-promoter. In a first study (study no. 1, reported in Bua *et al.*, 2018), groups of approximately 500 females and males each were exposed to 0, 2, 20, 100 or 1000 μT ELF-MF alone. The second study (study no. 2) consisted of three further groups of each about 100 female and male rats, which were similarly exposed to 0, 20 and 1000 μT, but received in addition 0.1 Gy of γ-radiation at 6 weeks of age. For both studies 501 females and 500 males of study no. 1 served as non-exposed controls. The authors reported results of the co-exposure groups of study 2 only. Body weight and survival were unaffected. The incidence of adenocarcinomas of the mammary gland was significantly increased in 20 μT+0.1 Gy-exposed males and in 1000 μT+0.1 Gy-exposed females. The stated "significant dose" (i.e. exposure) related increased incidence of mammary carcinomas in males ($p \leq 0.01$) and females ($p \leq 0.01$)" is not justified by the presented tabulated data. Furthermore, malignant schwannomas of the heart in both co-exposed groups and hemolymphoreticular neoplasias (HLRN) in the 1000 μT+0.1 Gy-exposed group were significantly increased. Reporting of this study appears to be selective. The observation period over the entire rats' life span of up to three years would justify the reporting of the tumour data of all animals and of all organ systems, but the complete tumour tabulation is missing.

In their third study (study no. 3) Soffritti *et al.* (2016b) "evaluated the potential co-carcinogenic effects of concurrent exposure to 1,000 μT S-50Hz MF plus formaldehyde administered at 50 ppm in drinking water with particular reference to haematological

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[17] The SCHEER has included the results of the meta-analyses reported by the Health Council of the Netherlands about powerlines and neurodegenerative as an additional line of evidence, since these meta-analyses have been performed following the methodology and fulfilling the quality criteria recommended by the SCHEER.

neoplasias". In the first group, 270 female and 250 male Sprague Dawley rats were exposed throughout their lives (from day 12 pc onwards) to 50 Hz 1 mT ELF-MF. Starting in week 6, group 2 (202 females and 200 males) received 50 mg/L of the carcinogen formaldehyde in their drinking water for 104 weeks, and group 3 (203 females and 200 males) was co-exposed (50 Hz 1mT ELF-MF lifelong, 50 mg/L formaldehyde for 104 weeks). The same 501 females and 500 males of study no. 1 served as non-exposed controls. During the first year, consumption of drinking water with formaldehyde was decreased for males only. In both sexes, no differences in body weight and survival were observed between the groups. No significantly different incidences of benign tumours were reported, whereas in males only the incidence of malignant tumours was significantly increased in the co-exposed group 2 compared to the other groups. In males C-cell carcinomas of the thyroid and hemolymphoreticular neoplasias (HLRN) were significantly increased in the co-exposed group compared to the non-exposed controls. In females, no significant concurrent increases of specific and total malignant tumour incidences were observed. Again, only selective tumour data were presented and limit the interpretation of the results.

Finally, Bua *et al.* (2018) published the overall cancer results of the ELF-MF exposure alone, i.e., largely study no. 1. In total, 4,129 Sprague-Dawley rats were exposed from day 12 pc until death, 19 h/d to sinusoidal 50 Hz MF. Groups of approximately 500 females and males each were continuously exposed to 0, 2, 20, and 100 µT. Further 250-270 female and male rats each were either exposed to continuous or intermittent (30 min on / 30 min off) 50 Hz 1 mT MF. The observation period over the entire rats' life span of up to three years did not result in significant differences of specific (adenocarcinomas of the mammary gland, malignant schwannomas of the heart, thyroid C-cell carcinomas, hemolymphoreticular neoplasias) and total malignant tumour incidences between the groups. Unfortunately, the complete tumour tabulation is also missing in this publication.

5.3.1.3 Conclusions on neoplastic diseases

The considered (co-)carcinogenicity studies did not provide evidence that exposure to ELF-MF alone could cause cancer. However, (improved) mouse models of childhood leukaemia, especially of acute lymphoblastic leukaemia, are now available (Isidro-Hernández *et al.*, 2022) and should be used in well-designed and controlled studies.

Regarding leukaemia and EMF exposure, a recent umbrella review of published systematic reviews (Onyije *et al.*, 2022), based, mainly, on case-control studies, revealed that ELF-MF exposure showed consistent, moderate risk estimates (i.e., ORs/RRs > 1.5). As reported, there are some inconsistencies in the findings, and the design of the studies included, i.e., retrospective case-control, may hide serious selection and recall bias. In a previous systematic review of studies (Kheifets *et al.*, 2017), including co-exposure of subjects to ELF and/or another physical agent, the authors identified and included in their review 33 key and 35 supplementary papers from ten countries. Authors found some indications of bias and reported that the studies' results were not clear and consistent. There was a small, elevated risk for ELF MF exposure to 0.3-0.4 µT but little evidence to establish a dose-response curve.

Concerning leukaemia and EMF exposure in human, published systematic reviews, based mainly on case-control studies, revealed that ELF-MF exposure showed consistent, but moderate risk estimates, but little evidence to establish a dose-response curve. It should also be noted that there are some inconsistencies in the findings of these studies, whereas the design of the previous studies, i.e., retrospective case-control, may hide serious selection and recall bias. With respect to childhood leukaemia there is weak to moderate weight of evidence from epidemiological studies (the primary line of evidence). However, the animal models used in the majority of studies were not appropriate for studying childhood leukaemia, therefore there is weak evidence from this line of evidence. Moreover, there is weak evidence from interaction mechanisms on the induction of neoplasias by ELF-MF exposure (see paragraph 5.2.8). Consequently, overall, there is weak evidence concerning the association of ELF-MF exposure with childhood leukaemia.

As far as other neoplastic diseases are concerned, the weight of evidence is uncertain, because of conflicting results from the lines of evidence (animal and human studies) examined.

5.3.2 Neurodegenerative diseases

5.3.2.1 Epidemiological studies

Regarding neurodegenerative diseases, six systematic and umbrella reviews were found in the literature that fulfilled our criteria and were examined. The majority of the reviews were concerned with occupational exposures. Specifically, Killin *et al.*, (2016) provided a systematic review related to dementia and concluded that there is at least moderate evidence implicating electric and magnetic fields. Gunnarsson and Bodin (2017) identified 10 original papers on associations between occupation exposure to EMF and Parkinson's disease. Exposure to EMF was addressed in two case-control studies and eight register/cohort studies. The weighted pooled RR was 1.07 (95% CI 0.97-1.19). Follow-up analyses were based on stratification by design with RR of 1.33 (95% CI 0.85-2.09) for studies with a case-control design and 1.02 (95% CI 0.90-1.16) for register and cohort studies. Stratification by quality gave RR of 1.31 (95% CI 0.97-1.78) for studies of class II and 1.05 (95% CI 0.97-1.14) for class III. Stratification by funding showed that studies with public funding had an RR of 0.99 (95% CI 0.82-1.18). A paper by Gunnarsson and Bodin (2019) which integrated and stratified meta-analyses on occupational exposure to EMFs, found 19 studies whose weighted pooled RR for occupational exposure to EMFs was 1.26 (95% CI 1.07–1.50) for ALS, 1.33 (95% CI 1.07–1.64) for Alzheimer’s disease and 1.02 (95% CI 0.83–1.26) for Parkinson’s disease. Occupational exposure to EMFs seemed to involve some 10% increase in risk for ALS and Alzheimer’s disease only. It should also be underlined that the authors concluded there was evidence of publication bias. Huss *et al*., (2018) completed a systematic review and meta-analysis and reported a slightly increased risk of ALS in those exposed to higher levels of ELF-MF compared to lower levels with a summary RR (sRR) of 1.14 (95% CI: 1.00–1.30) and for workers in electrical occupations (sRR 1.41, CI: 1.05–1.92), but with large heterogeneity between studies. The authors investigated the reasons for this heterogeneity, sub-dividing analyses depending on e.g. studies with full occupation histories vs those with limited information. The authors concluded that some of the heterogeneity was partially driven by imprecision in the exposure assessment. A meta-regression did not show evidence of an increased ALS risk with increasing exposure to ELF-EMF. Röösli and Jalilian (2018) *conducted* a meta-analysis to assess the association of residential exposure to ELF-MF with the risk of ALS. Based on five studies that have considered the risk of ALS in relation to overhead power lines, they found no statistically significant pooled relative risk for the most exposed population group. Jalilian *et al*. (2018) conducted a meta-analysis of workers exposed to ELF-MF and risk of Alzheimer’s Disease (AD). Based on 20 studies, they concluded that the pooled results pointed to an increased risk of AD (RR: 1.63; 95% CI: 1.35, 1.96). The risk estimate from case-control studies gave a combined effect of OR: 1.80 (95% CI: 1.40, 2.32), whereas from cohort studies the combined effect was RR: 1.42 (95% CI: 1.08, 1.87). The authors highlighted a moderate to high heterogeneity between studies and indication for publication bias.

Habash *et al.* (2019) published a scoping review on the potential health effects of exposure to ELF-EMF, including neurodegenerative diseases, in which they listed ten articles. The latter reported conflicting relationships between neurodegenerative effects and ELF-EMF exposure. Only two of the included studies (both on occupational exposure) found significant associations between ELF fields and Alzheimer’s disease.

The Health Council of the Netherlands (2022c,d)[18] has recently published a report on exposure to powerline EMF and neurodegenerative diseases in adults, namely amyotrophic

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[18] The SCHEER has included the results of the meta-analyses reported by the Health Council of the Netherlands about powerlines and neurodegenerative as an additional line of evidence, since these meta-analyses have been performed following the methodology and fulfilling the quality criteria recommended by the SCHEER.

lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease and multiple sclerosis (MS). This report had mainly focused on epidemiological studies, taking into account studies on exposure in both residential areas and the workplace. A distinction was made in the analyses depending on whether the comparator group was the general population (in a case-control design), described as occupational exposure in a general population, or an industrial population (in a cohort design).

The meta-analysis showed that people living at a distance of less than 50 metres from a high-voltage powerline do not have an increased risk of ALS. The risk estimate was calculated at 0.99 (95% CI: 0.65-1.52). The meta-analysis of the epidemiological studies investigating the results of occupational exposure in the general population (after determining a complete occupational history) resulted in a calculated risk estimate of 1.56 (95% CI: 0.83-2.93). This association is also demonstrated in the industrial population studies with a risk estimate of 1.55 (95% CI: 1.17-2.06).

Based on three studies that investigated the relationship between residential exposure to magnetic fields and the occurrence of Alzheimer's disease, a risk estimate of 1.11 (95% CI: 0.97-1.28) was calculated. For occupational exposure in the general population with complete determination of the occupational history, the risk estimate was 1.15 (95% CI: 1.01-1.30), and for industrial populations it was 1.24 (95% CI: 0.87-1.78). Heterogeneity is high for the studies on exposure of workers in industrial populations. Particularly in the older studies, the quality of diagnosis of Alzheimer's disease is uncertain.

The analysis of residential exposure resulted in a calculated risk of 1.08 (95% CI: 0.93-1.26) for Parkinson's disease. The meta-analyses reveal that neither of the occupational studies show an increased risk of the occurrence of Parkinson's disease in the event of exposure above the background level. For the studies of occupational exposure in the general population, the calculated risk estimate was 1.03 (95% CI: 0.95-1.11). The risk estimate for the studies in industrial populations was 0.97 (95% CI: 0.75-1.26). The heterogeneity in the risk estimates was high and some studies indicated an increased risk, while others indicated a reduced risk.

The scarce epidemiological data presented in the Health Council of the Netherlands (2022c,d) on Multiple Sclerosis (MS) and residential or occupational exposure to magnetic fields showed no associations.

5.3.2.2 Animal and in vitro studies

No systematic reviews of animal or *in vitro* studies were identified that were published after the SCENIHR (2015) Opinion.

The narrative review paper by Wyszkowska (2022) presents an overview of the results arising from the epidemiological, *in vitro*, and *in vivo* studies dealing with EMF (both radiofrequency and ELF) exposure and the occurrence of neurodegenerative diseases. The overall result was that studies investigating the possible effects of EMF exposure on neurodegenerative diseases are too diverse with regard to the applied field, the duration of exposure, and the statistical methods to draw any reasonable and satisfactory conclusion. The effects on ROS, lipid peroxidation, and antioxidant defence are among the proposed mechanisms, although none of them has been demonstrated. The difficulties with the identification and experimental validation of the EMF influence mechanism are due to the variability of biological responses and a lack of consistency in the findings.

The Health Council of the Netherlands (2022c,d) reported experimental studies found in the EMF Portal (www.emf-portal.org), which included three experimental studies that investigated the relationship between exposure to magnetic fields and ALS. Two were animal studies of a rare familial form of ALS. None of these studies showed statistically significant effects at exposures up to 1 mT (around 1000 times higher than residential exposures). One *in vitro* study was identified on ALS. The study, carried out on a well-characterised *in vitro* experimental model of ALS, demonstrated that long-term ELF exposure (50 Hz, 1 mT) did not show any effect.

In the report of the Health Council of the Netherlands (2022c,d), five studies with laboratory animals with Alzheimer's disease found that exposure to magnetic fields had health benefits in the form of improved cognitive ability. Two other studies found no adverse health effects in healthy laboratory animals. Exposure levels varied from 100 µT to 10 mT. Six studies were also reported on cellular models for Alzheimer's disease. Two found no effects of exposure to ELF magnetic fields, three found effects that may indicate pathological effects and one study found a potentially beneficial effect. The exposure levels ranged from 50 µT to 3.1 mT.

In the same report, two publications were listed on animal research on the relationship between exposure to magnetic fields and Parkinson's disease. Both investigated the effect of implantation of mesenchymal stem cells exposed in culture to 0.4-1 mT fields in experimental animals in which Parkinson's-like symptoms had been induced. A reduction of symptoms was reported in both studies. Five studies were reported on cellular models for Parkinson's disease. In two of those, no effects were found from exposure to magnetic fields and in three studies effects were found on oxidative stress, which may be related to adverse effects, at exposure levels 1 or 2 mT.

5.3.2.3 Conclusions on neurodegenerative diseases

In conclusion, a significant association of occupational exposure to EMFs with ALS, Alzheimer's disease and dementia was observed, but the presence of publication bias, and the large heterogeneity in the respective meta-analyses, as well as the poor quality of diagnosis, particularly of Alzheimer's, and other neurodegenerative diseases, especially in the older studies, may degrade the observed associations.

No significant association can be established between EMF exposure and Parkinson's or multiple sclerosis disease.

Overall, there is moderate evidence (mainly from human studies) on the association between occupational exposure to ELF-EMF and ALS, weak evidence for the association of occupational ELF-EMF exposure with Alzheimer's disease, and dementia, but only uncertain to weak evidence for residential exposure and these neurodegenerative diseases.

5.3.3 Neurophysiological effects and cognition

5.3.3.1 Provocation studies

In a systematic literature review, Ohayon *et al.* (2019) investigated EMF effects on sleep. For the frequency range 30 – 300 Hz three studies were included. Two experimental studies published in 1999, which assessed sleep polysomnographically, observed disturbances of sleep following an all-night 50 Hz / 1 µT exposure and an intermittently applied 60 Hz / 28.3 µT exposure, respectively. A 60 Hz / 28.3 µT continuous exposure did not affect sleep parameters.

5.3.3.2 Animal and in vitro studies

Klimek & Rogolska (2021) systematise and summarise ELF-MF-mediated changes at different levels of organism organisation in a narrative review of 144 references, mainly from the last decade. In particular, the authors attempt to define acute and chronic stress effects following ELF-MF exposure (*in vivo* and *in vitro*) and to explain molecular mechanisms. Overall, the typical responses observed after stimulation with any stressor, including ELF-MF, can lead to detrimental or beneficial effects. However, the question remains where the threshold for ELF-MF exposure lies, above which the adaptive capabilities of the organism are exceeded. For future studies, the authors consider it essential to include "detailed characterization of internal electromagnetic fields in addition to other parameters of ELF-MF exposure."

Modolo *et al.* (2018) looked at studies on the neurophysiological effects of low-level electric fields (EF ≈ 1 V/m) on brain activity, which are induced for example by transcranial direct/alternating current stimulation (tDCS, tACS), at the *in vitro* and *in vivo* (animal and human) level, added by mechanistic insights gained from in silico models. In conclusion, this narrative review identified four crucial points to consider when studying behavioural effects or novel non-invasive therapies for neurological disorders: 1) systematic dosimetry of the EF delivered, 2) EF used *in vitro* should be close to the fields induced by tDCS/tACS, 3) combined *in vivo/in vitro* studies should be encouraged as an attempt to validate candidate interaction mechanisms, and 4) besides effects on neurons, potential low-level EF effects on astrocytes and microglia should also be studied.

5.3.4 Reproductive and Developmental effects

5.3.4.1 Epidemiological studies

Ghazanfarpour *et al.* (2021) performed a systematic review and meta-analysis of the effect of the whole electromagnetic spectrum (up to X-rays) on abortion, therefore, no conclusions can be drawn on the impact of ELF-EMF on abortion.

In their review on the influence of the built environment on adverse birth outcomes (mainly low birth weight and preterm birth), Woods *et al.* (2017) identified two studies, which both showed no significant associations of the effects on birth outcomes with residential distance from powerlines.

Zhou *et al.* (2022) performed a meta-analysis on the pregnancy outcomes from exposure to ELF-EMF. They included seven studies in their meta-analysis, all assessed for heterogeneity and quality, of which six were of high quality (score >8 out of 10). The total sample size of this meta-analysis was larger than 3 million women. The authors concluded that "no correlation had been found between maternal ELF-EMF exposure and miscarriage, stillbirth, neonatal birth defects and preterm delivery, while the effects on small gestational age and low birth weight were still uncertain". The included studies in the meta-analysis were almost all (see above) of good quality as assessed by a specific tool. Some methodological issues should be considered, before incorporating this meta-analysis in a line of evidence. It should be noted that only the exposure to low frequency EMF caused by power lines was examined. The inclusion of only cohort epidemiological studies enhances the findings of the meta-analysis as it eliminates selection and recall bias that may have occurred through retrospectively designed studies, but, due to the limited number of studies retrieved, as well as the nature of the exposure and the outcome, retrospective studies could be also useful to draw more robust results. Regarding the literature search strategy, it should be noted that the terms "miscarriage" and "fetal death", were not included, and, thus, some relevant studies may have been missed. Moreover, publication bias was not adequately checked, and the methodology used to analyse the individual studies' results could be benefited from an in-depth meta-regression approach, instead only of a sensitivity and subgroup analyses.

Darbandi *et al.* (2018) have performed a literature review that included human and animal studies on rabbits, mice, rats, and boars. However, this review is not relevant for risk assessment because of some methodological inadequacies (e.g., problematic search strategy, undefined selection criteria, absence of quality assessment of papers).

Ramezanifar *et al.* (2023) performed a systematic review of occupational exposure to various chemical and physical agents and its potential effects on reproduction. They identified one study (Suri *et al.,* 2020) on the levels of reproductive hormones among power plant workers, which found "no relationship between exposure to magnetic fields in power plants and reproductive hormone levels".

5.3.5 Immune system

No systematic reviews or meta-analyses were identified on the exposure to ELF-EMF and the immune system.

A review paper (Piszczek *et al.*, 2021) was recently published which reports on immunity and electromagnetic fields including low frequency fields. The authors focused on both *in vivo* and *in vitro* studies reporting on the effects on immune cell types involved in the innate and adaptive immunity. The general conclusion of the authors was that the large number of results obtained for various EMF parameters and experimental conditions did not allow for a simple comparison of findings across different laboratories. They also concluded that EMFs seem to be a promising tool for modulation of various immune cell signalling pathways and immune system responses. The review paper lacks the criteria for literature selection and characterisation of methodological quality of the individual included studies.

The potential use of low frequency EMF for immunomodulation has also been highlighted in the scoping review of Rosado *et al.* (2018).

5.3.6 IEI-EMF and symptoms

Leszczynski (2021) published a review of the scientific evidence on the individual sensitivity to EMF, in which he included both provocation and observational (survey) studies, although cross-sectional observational studies cannot provide evidence for causality between subjective or objective symptoms and exposure to EMF. Moreover, the criteria for literature selection and a description of the methodological approach for reviewing the eventually selected studies are lacking from the review. Leszczynski (2021) concludes that most of the studies did not find any causal link between EMF and electromagnetic hypersensitivity (EHS), at least as far as acute effects were concerned, since the studies "did not have capability to examine delayed EMF responses". The author identifies several methodological shortcomings of the hitherto studies and proposes the use of both subjective symptoms and objective biomarkers to research for causality, "because the scientific research data is of insufficient quality to be used as a proof of the lack of causality" (between EMF exposure and EHS).

5.3.7 Other effects

Bouché and McConway (2019) analysed possible relationships between ELF-MF and melatonin (MLT) levels in humans and rats, mainly by examining two review articles dating from 2010 and 2013.

In total, 28 human and 34 rat studies were analysed by the parametric Bayesian logistic regression approach and the non-parametric Support Vector analysis. The human studies are all from Halgamuge (2013). After removing duplicates and verifying the studies, 28 of the original 33 studies were included for the analysis, none of which had been published after 2006. Human studies mostly covered MF strengths from 0.1 to 50 μT which influence the MLT level after exposure durations of about 22 days. By contrast to the evaluated human studies, half of the rat studies have MFs above ca 50 μT and the correlation oft MLT to (exposure) duration is weaker.

Overall, the authors found that

- MF exposure duration is the most significant parameter in causing changes in the MLT levels both in humans and in rats,
- MFs of 0.5 to 100 μT do not dose-dependently change MLT levels, however weaker ELF-MFs (≤30 μT) show some window effect, and
- after matching MF strengths to ≤50 μT human and rat studies are consistent.

Therefore, Bouché and McConway (2019) suggest targeted research on rats using ELF-MFs from 20 nT to 20 μT.

Alkayyali *et al.* (2021) in a narrative review, reported changes in the function and morphology of the thyroid gland in rats exposed to ELF (50Hz) EMF between 50 and 500 μT. All research papers on the thyroid and this specific frequency range were from the same group (Rajkovic *et al.*), published between 2001 and 2006, and the findings have not been replicated independently by other groups since then.

In their narrative review, Tang *et al.* (2022) collected several papers that investigated the effect of magnetic fields of varying frequency and intensity on the circadian rhythms of both humans and animals. The endpoints examined ranged from gene expressions to behavioural effects. The authors reported that there remained inconsistencies in the study conclusions about the influence of magnetic fields on circadian rhythms.

5.4 Health effects from IF fields

Bodewein *et al.* (2019) systematically reviewed biological effects of electric, magnetic, and electromagnetic fields in the IF range. Fifty-six human, animal and *in vitro* studies (out of 819 potentially relevant articles) were included. Bodewein *et al.* (2019) did not address carcinogenesis in their systematic review.

Lee *et al.* (2022) systematically analysed experimental rodent studies published from January 1988 to August 2021. They reviewed 38 papers out of 239 initially identified research articles. Of these, 7 articles addressed general toxicity, 4 carcinogenesis, 16 developmental toxicity, and 11 miscellaneous effects. Frequencies tested were in the range of 7.5 kHz to 82 kHz, and the magnetic flux density 15 µT to 23.5 mT (mostly <<1 mT).

5.4.1 Neoplastic diseases

5.4.1.1 Animal studies

Overall, and according to Lee *et al*. (2022), IF exposures did not result in carcinogenic effects.

5.4.2 Reproductive Developmental effects

5.4.2.1 Animal studies

Of the above total 56 papers finally reviewed by Bodewein *et al.* (2019), 28 described animal studies, mainly using mice and rats but also invertebrates. An effect of IF-MF exposure on developmental parameters (increased and decreased development, malformation, increased mouse sperm motility) was reported in six out of 13 studies. Six further studies did not find effects on parameters of reproduction. The 13th paper showed an exposure-dependency between number of offspring in fruit flies and the field strength as well as DNA damage in the gonads of flies exposed to the highest EF of 400 kV/m.

Lee *et al*. (2022) summarised that the reported effects of IF-MF (20 kHz, 15 up to 200 µT) on early development (number of implantations, death, resorption, malformation, and body mass) are inconsistent and seem to be dependent on animal strain.

5.4.3 Neurological and neurobehavioural effects

5.4.3.1 Human studies

In the review of Bodewein *et al*. (2019), only three of the 56 studies were human experimental studies. Based on risk-of-bias criteria (following the OHAT approach) studies were placed into tiers, with the first tier indicating the highest level of study quality. The three human experimental studies, which represent tiers 1 (two studies) and 2 (one study), addressed different outcome parameters: human visual function, visual evoked potentials, and short-term memory and cognitive functions. Two of the studies observed no statistically significant differences between exposure and control conditions, while one study reported variable effects on short-term memory, which according to the authors, should be regarded as a preliminary result.

5.4.3.2 Animal studies

Bodewein *et al*. (2019) reviewed four studies describing contradictory effects on the brains of mice and rats. Another two studies investigated the effects of MF (2 nT to 250 µT) on animal behaviour. The (magnetic) orientation of amphipods to the earth's MF was significantly impaired by a 969 kHz MF at field strengths as low as 2 nT. In rats, a 250 µT MF had no effect on motor activity.

5.4.4 Cardiovascular effects

5.4.4.1 Animal studies

Two studies concerning effects on the cardiovascular system and haematological parameters showed contradictory results (Bodewein *et al*., 2019).

5.4.5 Other

5.4.5.1 Animal studies

Finally, six studies reviewed effects of MF and EMF exposure (0.1 μT to 2 mT) on various biological parameters (Bodewein *et al*.,2019). One group found an improved regeneration of the sciatic nerve at frequencies of 500 Hz and 1000 Hz, another saw an increased vascular calcification in predisposed rats. The remaining four studies did not find any effects of IF exposure. They tested a therapeutic approach on tumour growth or hormone levels or on various haematological, and (histo)pathological parameters.

Lee *et al.* (2022) stated that most studies in rats and mice have not reported any adverse effect after IF-MF exposure. However, two studies reported some adverse effects on white blood cells, interleukins, hormones, and the morphology of liver, spleen, ovary, and testes. Furthermore, few papers have described effects on the brain and behaviour such as an increased rate of nerve regeneration and lipid peroxidation in the cerebellum, a transient upregulation of genes related to memory function, and mild impairment of learning and memory performance, following exposure to IF-EMF.

Since the reported "effects of IF-EMFs were not independently reproduced and were not dependent on the degree of IF-EMF exposure" the authors conclude "that IF-EMF exposure within ICNIRP limits (ICNIRP reference levels: 27 μT for the general public and 100 μT for occupational exposure) did not produce any harmful effects on animals."

5.4.5.2 In vitro

Of the total 56 paper reviewed by Bodewein *et al*. (2019), 26 studies examined the *in vitro* effects. The majority of the studies were carried out in the frequency range 300 Hz–100 kHz and applied field strengths above the ICNIRP reference levels. The studies deal with human and animal cells, bacteria and yeasts exposed to EF or EMF or MF, with the latter having the highest number of publications. The most commonly studied endpoint was cell proliferation followed by genotoxicity, gene expression and other cellular processes and parameters.

The results suggest that genotoxic effects from MF < 100 kHz are unlikely, and most other endpoints give inconsistent results with some studies not reporting effects and other studies suggesting e.g., effects on cell proliferation and cell viability. It was speculated by the authors of the single studies that such modifications could be caused by a direct interaction of the MF with cell components or ions. However, it is also possible that other factors such as unintentional co-exposures, the type of cell model and the frequency of the field might be crucial for the observed effects. Overall, from the reviewed studies, the quality of evidence for adverse effects of MF in the IF-range is inadequate to draw a conclusion. Moreover, methodical flaws in the majority of studies lowered the credibility of the reported results.

5.4.6 Conclusions on health effects from IF fields

An overall weight of evidence assessment is not possible, even though there is some evidence from animal and *in vitro* studies, but not from human studies.

5.5 Effects from low frequency fields on fauna and flora

The effects of low frequency EMF on fauna and flora are indirectly related to human health since they concern the living environment. Therefore, although not explicitly mentioned in the previous SCENIHR Opinion (2015) or in the current mandate, they are briefly treated here.

A number of narrative reviews and individual studies have been published, but there remain very few systematic reviews. Their findings are briefly discussed in this section. A recent paper (Karipidis *et al.*, 2021) provided a systematic map of evidence on the impacts on animals and plants. Their search criteria identified more than 24,000 articles of which only 334 were relevant (237 fauna, 97 flora), and the vast majority of studies were experiments in the laboratory. They concluded on the existence of distinct evidence clusters for fauna on insect and bird reproduction, development and behaviour and for flora, germination and growth. They concluded that more specific systematic reviews are needed. A study from the Scientific Foresight unit of the European Parliament (STOA, 2021) summarises a literature review of the environmental impacts of 5G and also reiterates the need for more research. One comprehensive report on the effects of anthropogenic electric, magnetic, and electromagnetic fields in the frequency range from 0 to 100 MHz on flora and fauna was recently published by Pophof *et al.* (2023). This report summarises the works presented at an international workshop which was held in November 2019, in Munich. Biological effects on fauna and flora following IF exposure were not explicitly described in this meeting report.

Pophof *et al.* (2023) suggest that there may exist differences in the exposure conditions for human, plants, and animals. They give the example of flying animals (insects, birds, or bats) and high trees which may be closer to sources of ELF-EMFs, such as power lines, and may thus be exposed at intensity levels exceeding the limits adopted for humans. Furthermore, exposure close to submarine power cables may strongly differ from that in the air. Moreover, they highlight the fact that animals and plants possess receptors and structures not existing in humans, which could give rise to species-specific biological effects.

Two interaction mechanisms were identified for the induction of effects on fauna and flora by low frequency EMF. The first one is the induction of an electromotive force and, hence, currents in conductive tissues, which can ultimately lead to the activation of nerve cells. The second mechanism is based on electromagnetic induction and has been discussed for electrosensitive elasmobranchs and recently also postulated for pigeons; however, except for highly specialised electrosensitive species, the evidence on this mechanism is scant. The phenomenon of magnetoreception, i.e., the ability of many organisms to perceive the direction and intensity of the geomagnetic field and use it for orientation/navigation, is still under investigation and concerns mainly static magnetic fields. Some of the interaction mechanisms hypothesised include magnetic sensors based on magnetite or the radical pair mechanism that involves cryptochromes.

However, honeybees can also perceive ELF-EMF but with a lower sensitivity than shown for static fields. The results reviewed by Pophof *et al.* (2023) indicate that 'short-time exposure to magnetic fields, at levels that could be encountered in beehives placed under power lines or during foraging flights, could affect the ability of bees to forage and pollinate crops and to respond appropriately to environmental stimuli'. Moreover, two studies with honeybees reported results of field investigations (Lupi *et al.*, 2020; 2021) that have shown negative effects of electric and magnetic fields from power lines in combination with pesticides. Risk to pollinators was also studied in Vanbergen *et al.* (2019) who concluded that evidence of impacts is inconclusive, due to a lack of high-quality field studies. A recent paper by Molina-Montenegro *et al.* (2023) concluded "conclusive evidence of detrimental impacts of EMF on honeybee's pollination behaviour, leading to negative effects on plant community".

At the same time three review articles by Levitt *et al.* (2021a,b), as well as systematic reviews by Thill *et al.* (2023) on impacts on insects demonstrate the research activity within this area is very active, identifying and addressing a number of research gaps.

The exposure of marine species to anthropogenic ELF-EMF by substations and cables is increasing with the number offshore wind parks and the need for more submarine power cables carrying more power from coastal waters to the shore. Seabed species, which live closer to these submarine cables, are most likely to be exposed to higher intensities of anthropogenic ELF-EMF. In general, as Pophof *et al.* (2023) note, 'magnetic fields and induced electric fields apparently have physiological and behavioural effects on marine vertebrates and invertebrates, but the ecological consequences for species abundance and distribution remain largely unknown and need to be followed up, especially in the context of continuously increasing intensity and coverage of anthropogenic subsea ELF-EMF’.

In conclusion, this brief overview of some of the review articles and individual studies published since 2016 highlights the need for further research (and specifically) well-designed terrestrial and marine field studies.

6 RECOMMENDATIONS FOR FUTURE WORK

Regarding exposure to low-frequency fields, it is still unclear how the changes that have been taking place in the power grid architecture will impact population exposure. For example, in future power grids consumers will become “prosumers” (= producers + consumers) due to the decentralised and distributed power generation that will get closer to the residential environment. Moreover, emerging applications in public spaces (e.g., electric vehicle chargers) will change exposure characteristics of the general population. Therefore, real world studies (based on both measurements, e.g., though crowdsourcing, and simulations, e.g., environmental field calculations) are recommended to assess the exposure impact of the technological changes taking place in electrical power production, distribution and consumption.

Research in the IF spectrum remains very limited and there are very few studies regarding health outcomes. Consequently, systematic reviews and meta-analyses are scarce. In the absence of new epidemiological data, research in this frequency range remains a high priority.

In the case of ELF-EMF and their association with childhood leukaemia, further studies are recommended, using appropriate animal models for studying acute lymphoblastic leukaemia. Moreover, more *in vitro* hypothesis-driven studies are needed, which can elucidate the potential interaction mechanisms of ELF-EMF at the cellular level. With respect to all other neoplastic diseases, more epidemiological studies of adequate statistical power need to be conducted. Finally, it is important to perform further research on the quantification of the potential impact of ELF-EMF in the area of public health, also incorporating real world data.

In the case of ELF-EMF and their potential impacts on flora and fauna (both terrestrial and marine), it is recommended that further studies are undertaken.

With the advent of diagnostic techniques for neurodegenerative diseases and the introduction of validated biomarkers for them, more clinical and epidemiological studies are warranted, which could investigate any association between ELF-EMF exposure and these diseases, or even any underlying mechanisms that are involved.

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8 LIST OF ABBREVIATIONS AND ACRONYMS

ALS	Amyotrophic Lateral Sclerosis
CNS	Central Nervous System
CRY	Cryptochrome
EF	Electric Field
ELF	Extremely Low Frequency
EMF	Electromagnetic Field
EV	Electric Vehicle
IF	Intermediate Frequency
LF	Low Frequency
MF	Magnetic Field
MLT	Melatonin
PEMF	Pulsed Electromagnetic Field
PLC	Power-line Communication
PNS	Peripheral Nervous System
ROS	Reactive Oxygen Species
RPM	Radical Pair Mechanism
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
VGCCs	Voltage-Gated Calcium Channels
WPT	Wireless Power Transfer