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REVIEW

Biological Effects of Electromagnetic Fields and Recently Updated Safety Guidelines for Strong Static Magnetic Fields

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Humans are exposed daily to artificial and naturally occurring magnetic fields that originate from many different sources. We review recent studies that examine the biological effects of and medical applications involving electromagnetic fields, review the properties of static and pulsed electromagnetic fields that affect biological systems, describe the use of a pulsed electromagnetic field in combination with an anticancer agent as an example of a medical application that incorporates an electromagnetic field, and discuss the recently updated safety guidelines for static electromagnetic fields. The most notable modifications to the 2009 International Commission on Non-Ionizing Radiation Protection guidelines are the increased exposure limits, especially for those who work with or near electromagnetic fields (occupational exposure limits). The recommended increases in exposure were determined using recent scientific evidence obtained from animal and human studies. Several studies since the 1994 publication of the guidelines have examined the effects on humans after exposure to high static electromagnetic fields (up to 9.4 tesla), but additional research is needed to ascertain further the safety of strong electromagnetic fields.

Keywords: ***ICNIRP guidelines, safety survey, static and time-varying electromagnetic fields***

Introduction

Humans are daily exposed to many artificial and naturally occurring electromagnetic field (EMF) sources. Many studies have addressed the potentially adverse effects induced by EMFs,[1–3] but other reports have demonstrated their beneficial and/or therapeutic aspects.[3–5] We review recent studies that examined the biological effects and medical applications of EMFs and discuss the recently updated safety guidelines related to static magnetic field (SMF) exposure.

Part I: Mechanisms of Biological Effects Caused by Magnetic Fields

Figure 1 illustrates the physical and biological effects caused by static and time-varying EMFs.[6,7] Five major properties related to SMFs can affect biological organisms: 1) motions within an inhomogeneous field that induce an electric current, the so-called ''motion-induced currents'' also known as ''eddy currents by displacement''; 2) Lorentz force; 3) magnetic force; 4) magnetic torque; and 5) radical pair effect. The biological effects caused by time-varying fields are much simpler than those of SMFs and include nerve stimulation caused by eddy currents and thermal effects observed at higher frequencies.

Effects caused by motion

Currents are induced by time-varying magnetic fields and by motions in SMFs.[6,8–10] In particular, movement along a field gradient or rotational motions in a uniform field or in a field gradient generate changes in the flux linkage, which induce an electric current, whereas a linear motion within a uniform static field does not.[6] For linear movement in a gradient field, the magnitude of the induced

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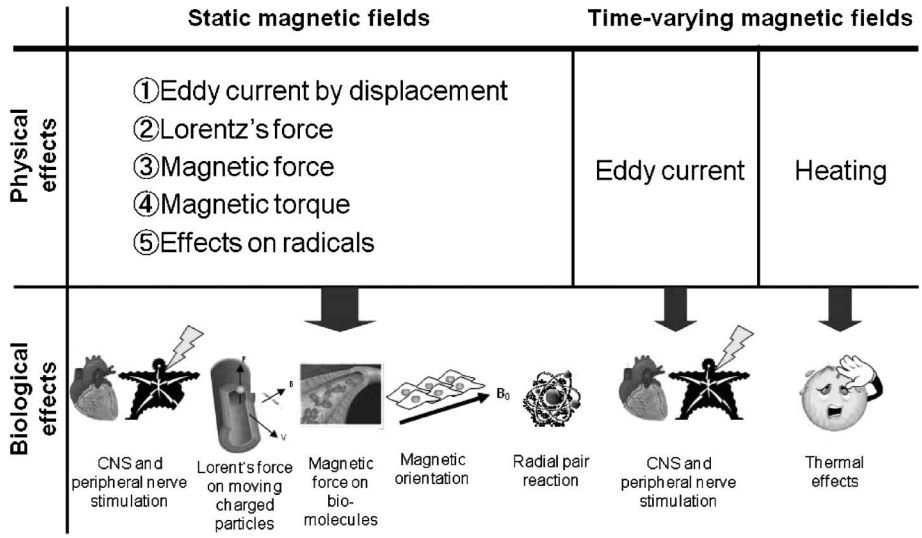

Fig. 1. Well established properties of static and time-varying electromagnetic fields that can affect biological systems

current and associated electric field increase with the velocity of the movement and amplitude of the gradient.[6] Patients, volunteers, and magnetic resonance (MR) staff have reported many different temporally sensational effects, including vertigo, nausea, and magnetophosphenes, when they moved quickly under an EMF.[8–10]

Lorentz force

Lorentz force is defined as the vector product of the charge velocity and magnetic flux density and is perpendicular to the direction of the electric charge flow.[3,11] For humans, concerns have been raised regarding the magnetically induced potential associated with blood flow,[12] but SMFs (up to 9.4 tesla) have not been shown to affect other cardiovascular functions adversely.[13]

Magnetic force

Magnetic force is caused by a spatially inhomogeneous magnetic field.[3,11] Materials tend to move along the direction of the steepest field gradient when exposed to an inhomogeneous field. The magnetic force that acts on the material is proportional to the magnetic flux density (B), the gradient of the magnetic flux density B (grad B), and the magnetic susceptibility (χ) of the material as: $F = (\chi B(\text{grad } B))/\mu_0$, where μ_0 is the magnetic permeability in a vacuum. This well known ''missile'' or ''projectile'' effect can occur when, for example, a ferromagnetic object is not secured in a room containing an MR imaging instrument.[14]

Magnetic torque

In a spatially homogenous magnetic field, materials tend to rotate in a stable direction, which is determined by the anisotropy of a material's magnetic susceptibility.[3,11] The torque acting on the material is: $T = -1/2\mu_0 \cdot B^2 \Delta\chi \sin 2\theta$, where B and μ_0 are defined above, $\Delta\chi$ is the anisotropy of the material's magnetic susceptibility, and θ is the angle between the direction of the magnetic field and the long axis of the material. The torque orients certain diamagnetic materials, such as fibrin and collagen, and some cells, such as osteoblasts and Schwann cells.[15,16]

Radical pair effect

The influence of a magnetic field is observed when a radical pair of electrons recombines, a well known mechanism by which SMFs interact with biological systems.[17–19] The radical pair is usually in the singlet state with the spin of one of the unpaired electrons anti-parallel to that of the other and is influenced by the magnetic field, which can affect the rate and extent of radical pair conversion to the triplet state (parallel spins) but not the spin-correlated radical pair recombination.

Time-varying field effects

The coupling of low frequency magnetic fields and the absorption of energy from the EMF is a basic mechanism by which time-varying electric and magnetic fields directly interact with living matter.[2,7] The physical interaction of a time-varying magnetic field with the human body induces electric fields and circulating electric currents within the body. The magnitudes of the induced field strength and current density are proportional to the radius of the loop, electrical conductivity of the tissue, and rate of change in the magnitude of the magnetic flux density.[7] Such currents may stimulate nerves. MR imaging gradient coils generate time-varying magnetic fields, and MR imaging operating conditions are set so that the intensity of

the induced current is less than that required for nerve stimulation. Although nerve stimulation by a time-varying EMF is an undesirable side effect of MR imaging, magnetic stimulation (MS) is used for diagnosis and treatment of diseases and functional mapping of the brain. During transcranial MS, a pulsed magnetic field (PMF) generated by a coil attached to the scalp is applied to the brain. The applied PMF typically has an intensity of one tesla and pulse duration in the sub-millisecond range. Single- or double-pulse stimulation is normally used for diagnosis and functional mapping of the brain.[20,21] For neurological and psychological diseases, transcranial MS is repetitively applied to increase treatment efficacy.[22,23]

Exposure to an EMF at a frequency greater than ~100 kHz can cause considerable energy absorption and temperature increase. In general, exposure to a uniform (plane-wave) EMF produces a highly non-uniform deposition of energy within the body that must be assessed by dosimetric measurement and computer calculation. The specific absorption rate (SAR) should be minimized so that blood flow and other bodily mechanisms of heat transfer can dissipate the heat. The magnitude of SARs is a critical problem, particularly in high field MR imaging systems.

Electromagnetic Field Dosimetry

Figure 2 diagrams the assessment of biological effects of EMF exposure. The magnitudes of the fields in different body parts and tissues must be considered to understand these effects. Dose must be defined as an appropriate function of the electric and magnetic fields and is essential for characterizing biological effects. However, no technique exists for direct measurement of EMFs within the human body; rather, fields are estimated using numerical simulations. Several research groups around the world have developed and distributed numerical models of the human body designed for EMF dosimetry.[24] A web-based database of the electric properties of biological tissues at arbitrary frequencies is also available (http://niremf.ifac.cnr.it/tissprop/).[25] Choice of computational method depends on the frequency of the EMF. Low frequency EMFs, such as MR imaging gradient fields, can be analyzed using the impedance method or the finite element method, whereas high frequency EMFs, such as radiofrequency fields, can be analyzed using the finite-difference time-domain method or the finite element method. Software for these calculations, such as Photo-series (Photon, Kyoto, Japan), is commercially available.

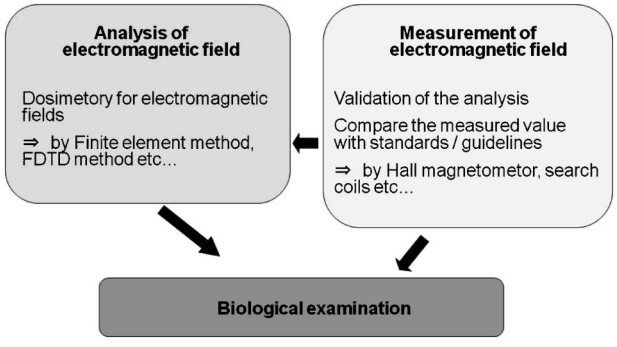

Fig. 2. Procedure(s) for evaluating the biological effects caused by electromagnetic fields

Recent Medical Applications that use Electromagnetic Fields

Many studies have found that EMFs adversely affect humans,[1–3] and others have demonstrated their potentially beneficial and therapeutic aspects.[3–5] Beneficial effects have been reported for both static[26,27] and time-varying magnetic fields.[5]

Magnetic stimulation (MS) uses a PMF to induce an electric field in tissues by electromagnetic induction and is a technique that does not require invasive surgery or external electrodes.[28,29] MS has been widely applied to neurological research, such as in studies that map the cerebral cortex[30,31] and cognitive science studies,[32,33] and was recently used clinically for neurological disorders.[22,23] Our group has demonstrated the enhanced killing efficiency of imatinib mesylate (IM, Gleevec®, Novartis, East Hanover, NJ, USA) in human breakpoint cluster region-abelson (*BCR/ABL*) (+) leukemia cells when the cells were subsequently exposed to MS.[34] *BCR/ABL* is a chimeric gene, generated by the Philadelphia (Ph) chromosome translocation, t(9;22)(q34;q11),[35] and IM was developed as a potent and specific inhibitor of the *BCR/ABL* tyrosine kinase.[36,37] Figure 3 shows the system used to expose cells to MS; the stimulus conditions tested were 25 pulses/s and 0.1T (1000 pulses/day), 0.25T (1000 or 6000 pulses/day), or 0.5T (1000 pulses/day). Using the finite method,[38] we calculated the magnetic flux as 0.11 to 0.18T and eddy current as 26.8 to 38.1 A/m^2 as in the culture medium for 0.25T (Fig. 4). We cultured TCC-S cells, which are human chronic myelogenous leukemia-derived *BCR/ABL* (+) cells,[38] in the presence of 100 nM IM and then exposed them to MS for one, 12, 24, 36, 48, and 56 hours after drug treatment. The combined effects of MS and IM depended on the stimulus intensity and pulse dose (Table 1, Fig. 5). Electrical stimulation is well known to cause changes in the local pH and/or temperature, which

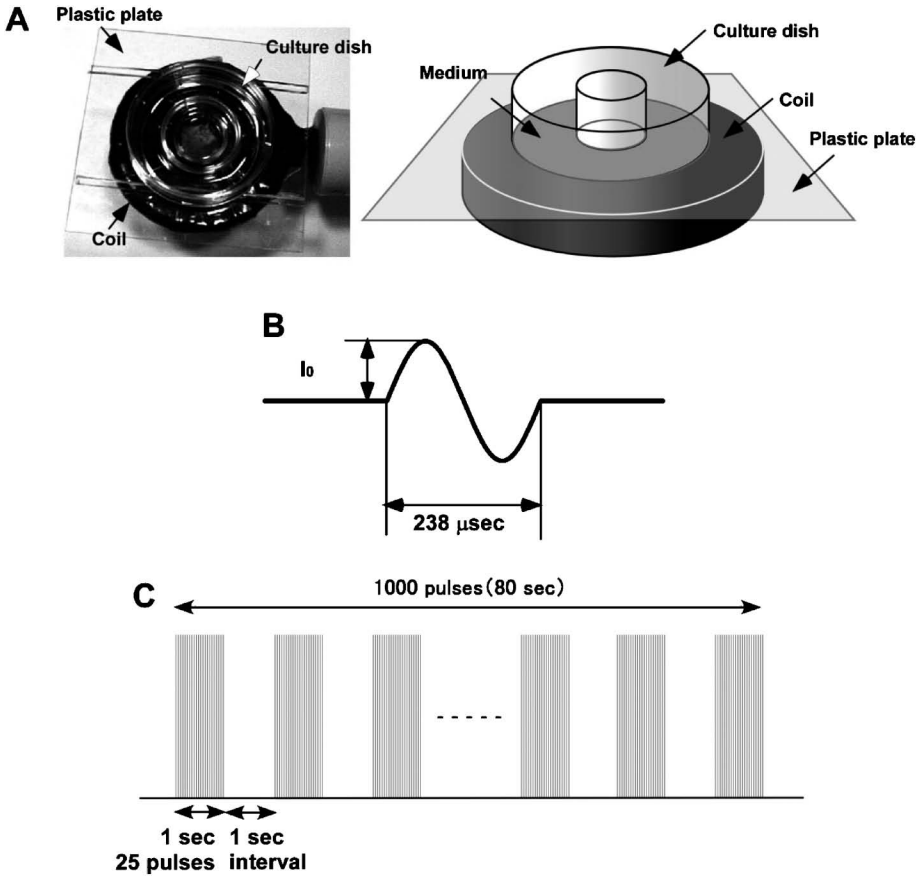

Fig. 3. Exposure system for magnetic stimulation and stimulus conditions.[32] **(A)** Exposure system for the cultured cells. A circular coil (inner diameter = 15 mm, outer diameter = 75 mm) was used. A plastic plate was placed over the coil to prevent thermal effects caused by coil heating. The dish was placed on the plate and 5 mm above the coil for magnetic stimulation (MS). **(B)** The coil-current waveform. I_0 is the peak intensity of the waveform. The stimulator delivered biphasic cosine current pulses of 238 μs duration. **(C)** The stimulation pattern used per day. ©2006IEEE

can lead to cell death.[37,38] However, the eddy currents generated in our study induced change in neither pH nor temperature (2.66×10^{-10}°C/pulse).[37] We also tested the effects of IM and MS on IM-resistant *BCR/ABL* (+) cells to examine what cellular mechanisms were involved.[38] Cell death occurred when MS (0.25T, 25 pulses/s, and 1000 pulses/day) was applied to IM-resistant *BCR/ABL* (+) cells after IM treatment as it had for IM-sensitive [*BCR/ABL* (+)] cells. The combined treatment caused functional changes, i.e., the loss of the mitochondrial membrane potential, an increase in cytosolic cytochrome c, and activation of the apoptosis-related proteins Poly ADP ribose polymerase and caspase-9. Apparently, changes in mitochondrial function are important triggers for the mitochondrial apoptosis-signaling pathway. To determine if MS can noticeably polarize cell membranes, Ye and colleagues calculated transmembrane potentials for an ''internal cell organelle'' induced by a time-varying magnetic field.[39] They examined factors that could impact the polarization of the organelle, including magnetic field frequency, presence of the outer cytoplasmic membrane, and electrical and geometrical parameters of the cytoplasmic and organelle membranes. They demonstrated that organelle polarization was largely dependent on magnetic field frequency and not significantly affected by the low frequencies (2 to 200 kHz) used for transcranial MS.[39] However, others have reported that exposure of cells to EMFs affects several important physiological processes related to the mitochondrial membrane potential, such as ATP synthesis,[40,41] metabolic activities,[42,43] and Ca^{2+} flux.[44] Therefore, MS may induce changes in mitochondrial functions under certain stress conditions, such as the drug treatment used in our study.

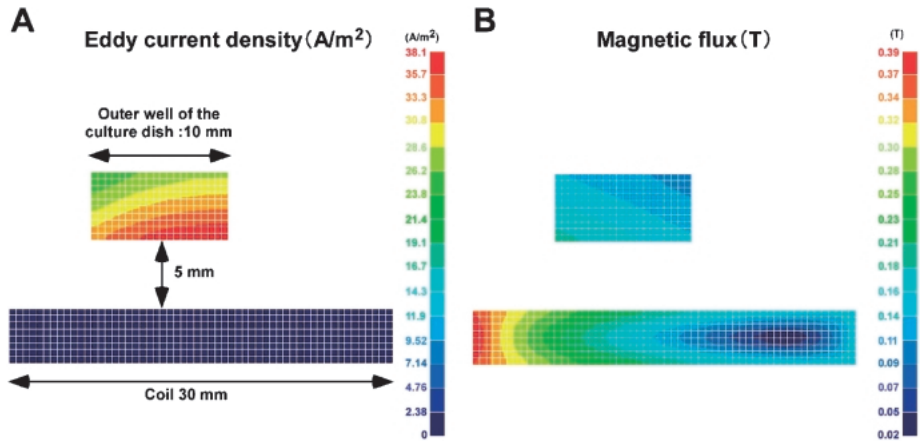

Fig. 4. Calculated distributions of the magnetic flux and the eddy current during magnetic stimulation (0.25T) of the system described in Fig. 4.[32] **(A)** Eddy current density, **(B)** magnetic flux. The calculated magnetic flux was 0.11 to 0.18T and eddy current, 26.8 to 38.1 A/m², within the culture medium. © 2006IEEE

Table 1. Effects of magnetic stimulation (MS; 0.25T) with or without imatinib mesylate (IM) pretreatment on the viability of *BCR/ABL* (+) leukemia-derived TCC-S cells 72 hours after drug treatment. Viable cells were detected using the water soluble tetrazolium salts (WST–8)–based assay. The IC_{50} of IM for TCC-S cells was 0.2 μM. RPMS: repetitive magnetic stimulation. $^{**}P<0.01$ vs. control (untreated cells). Each value is expressed as the mean ± standard error (SE). N = 4.[32] ©2006IEEE

	Control	0.25T 1000 pulses	0.25T 3000 pulses	0.25T 6000 pulses
TCC-S + RPMS	100.0 ± 7.9	74.4 ± 14.1	89.9 ± 8.1	73.7 ± 12.9
TCC-S + RPMS Imatinib 100 nM	55.4 ± 4.9	46.4 ± 5.1	46.9 ± 4.6	31.7 ± 2.6**

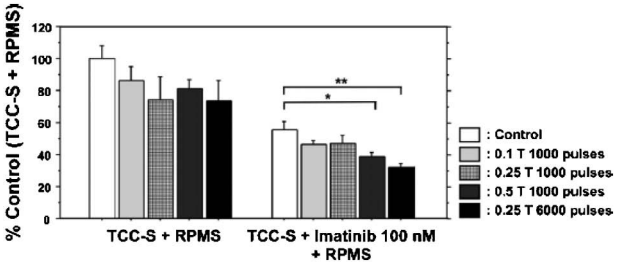

Fig. 5. Effects of magnetic stimulation on the viability of *BCR/ABL* (+) leukemia-derived TCC-S cells 72 hours after treatment with imatinib mesylate (IM). Viable cells were detected with the water soluble tetrazolium salts (WST–8)—based assay.[32] The IC_{50} of IM alone for TCC-S cells was 0.2 μM. RPMS: repetitive magnetic stimulation. $^{*}P<0.05$, $^{**}P<0.01$ vs. control (untreated cells). Each value is expressed as the mean ± standard error (SE). N = 4. ©2006IEEE

Notably, treatment with MS alone has only a slight cytotoxic effect on cancer cells and normal human lymphocytes used in our study[38] (Fig. 6). Radeva and Berg also reported a difference between normal human lymphocytes and cancer cells HL-60 in lethality caused by low frequency EMFs.[45] Finally, Aldinucci and colleagues demonstrated that magnetic fields decrease the levels of interleukin-2 and Ca^{2+} in Jurkat cells but did not affect concentrations of interleukin-1β, -2, and -6, interferon, and tumor necrosis factor α in normal human lymphocytes.[46] These reports indicate differences between normal and cancer cells in sensitivity to magnetic fields.

In conclusion, the results of the aforementioned studies indicate that including MS during cancer treatment may improve efficacy.

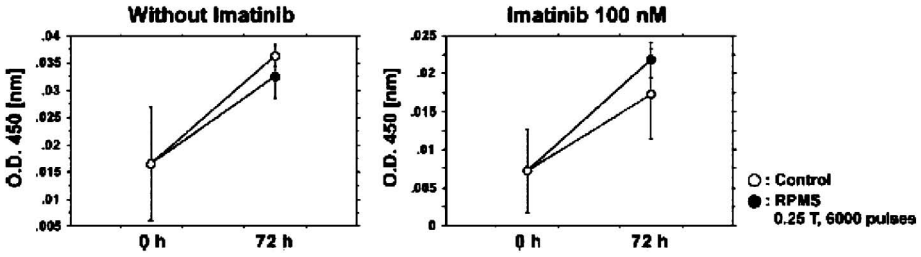

Fig. 6. Effects of magnetic stimulation on human normal lymphocytes (peripheral blood mononuclear cells) with and without pretreatment with imatinib mesylate (IM).[32] RPMS: repetitive magnetic stimulation. Viable cells were detected with the water soluble tetrazolium salts (WST-8)—based assay. Each value is expressed as the mean ± standard error (SE). N = 4. ©2006IEEE

Table 2. Comparison of the guidelines presented in the 1994 and 2009 International Commission on Non-Ionizing Radiation Protection (ICNIRP) reports for exposure to static electromagnetic fields.[7,53] Limits of exposure to static magnetic fields[a]

ICNIRP 1994[53] Magnetic flux density	Exposure characteristics	ICNIRP 2009[7] Magnetic flux density
Occupational[b]		
200mT	Whole working day (time-weighted average)	Time-weighted average removed in new guideline
2T (ceiling value)		2T (head and of trunk)[b]
5T (limbs)		8T (limbs)[c]
General public[d]		
40mT (continuous exposure)		400mT (any body part)

[a] The ICNIRP (2009) recommends that these limits be viewed operationally as spatial peak exposure limits.
[b] In ICNIRP 2009, exposure up to 8T can be justified for specific work applications if the environment is controlled and appropriate work practices are implemented to control movement-induced effects.
[c] Not enough information is available on which to base exposure limits beyond 8T.
[d] Because of potential indirect adverse effects, ICNIRP 2009 recognizes the need to implement practical policies to prevent inadvertent harmful exposure of persons with implanted electronic medical devices and implants containing ferromagnetic material and avoid dangers from flying objects, which can lead to much lower restriction levels, such as 0.5mT.
* The exposure limits to be set with regard to these nonbiological effects are not, however, the duty of ICNIRP.

Part II: Recently Updated Safety Guidelines for Static Magnetic Field Exposure

Accompanying the development of superconducting technology, the use of SMFs has become widespread in medical and engineering fields. MR imaging is the most widely used application of high SMFs that have tesla values between 0.15 and 3T (for clinical scanners) and between 3 and 10T (or higher) (for laboratory MR imaging instruments).[47] The main advantages of higher fields are better signal-to-noise ratios, which increase spatial resolution and decrease acquisition time, and increased frequency separation between the metabolite peaks of *in vivo* spectroscopy.[47] Because MR imaging instruments generate multiple electromagnetic fields, such as SMFs, PMFs (equivalent to intermediate frequencies), and radiofrequency fields, safety surveys related to MR imaging use are of great interest. A number of reports and guidelines have been published about SMFs and EMFs generated by MR imaging instruments,[48–52] but little is known about the effects of high SMFs.

Exposure guidelines published by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) are the most widely accepted

Table 3. Summary of studies recording the effects of high static magnetic fields (SMFs upper than 3T) on humans. ◯: Positive effects, △: Effects are positive under specific conditions, —: Negative effects

Authors	*Endpoint*	*Effects*	*Exposure*	*Results*
Evoked and spontaneous brain activity				
Volkow et al., 2000[58]	Brain glucose metabolism	△	4T 35 min	(↓) Metabolism decreased both in real and simulated MRI environments. SMF affected visual stimulation.
Sensory perception				
Schenck et al., 1992[8]	Sensory experiences during motion within the field	◯	1.5, 4T total exposure 135 h over one year	At 4T increased vertigo, nausea, metallic taste, magnetophosphenes.
Schlamann et al., 2009[59]	Motor threshold Cortical silence period (SP)	△	1.5T, 7T 63 min	(↑) SP was greatly prolonged immediately after exposing subjects to 1.5T or 7T fields. Motor threshold was also increased. After 15 min, the measurements were normal.
Cognitive functions				
Chakeres et al., 2003a[54]	Eleven different standardized neurocognitive tests and an auditory motor reaction time test	—	0.05, 8T ~1 h	No effects, except for a small negative effect on short-term memory.
Kangarlu et al., 1999[57]	Cognitive, language, and motor functions	—	8T 1 h	No effects. Some reports of vertigo and metallic taste in the mouth during movement.
Chakeres and de Vocht, 2005[9]	Vital signs Twelve different standardized neuropsychological tests and for auditory-motor reaction times	—	Up to 8T	No effects, except for slight increases in systolic blood pressure with increasing magnetic field strength.
Atkinson et al., 2007[13]	Vital signs Five different cognitive tests	—	9.4T (+105.92 MHz RF)	No effects, except for slight changes in performances of several tasks due to practice effects
Cardiac function, blood flow and pressure				
Kangarlu et al., 1999[57]	Body temperature, heart rate, respiratory rate, and blood pressure measurements; cognitive changes; and ECG	—	8T 1 h	No effect; ECG changes were within the normal range.
Chakeres et al., 2003b[55]	ECG and heart rate, respiratory rate, systolic and diastolic blood pressure, finger pulse oxygenation levels, core body temperature measurements	—	1.–8T 5 min	No clinically significant changes in vital signs. Systolic blood pressure increased upon exposure to 8T. ECG rhythm strip analyses showed no significant changes after exposure.
Weikl et al., 1989[60]	Electrocardiography (ECG)	—	0.54T 10 or 30 min	No arrhythmias, no changes in heart rate. Small reversible changes in ECGs caused by the Hall effect.
Body and skin temperature				
Chakeres et al., 2003b[55]	Core body temperature measurement	—	1.58T 5 min	No effect on core body temperature.

in the world. In 2009, the ICNIRP published new guidelines for SMFs[7] and produced an amended statement concerning magnetic resonance (MR) procedures.[52] As noted in the recent ICNIRP guidelines,[7,52] occupational exposure to SMFs during MR imaging procedures is a concern for all staffers who work inside imaging rooms, including medical professionals, researchers, cleaning staff, and the technicians who maintain MR imaging instruments. Table 2 shows the updated SMF exposure guidelines described in the ICNIRP 2009 report.[7] That report sets the SMF exposure limit for the

general public at 400 mT instead of 40 mT as suggested in the previous guidelines.[53] The maximum occupational exposure limits were increased to 2T for head and trunk and 8T for limbs. When the environment is controlled and appropriate work practices have been implemented to control for movement-induced effects, a maximum of 8T is also acceptable for head and trunk exposure.

The increased SMF exposure limits recommended in the new ICNIRP guidelines were determined using scientific evidence obtained from recent animal and human studies. Especially for human studies, the 2009 ICNIRP guidelines were derived from studies of higher SMF strength (up to 9.4T)[14,54–56] than considered for the previous guidelines.[56] Table 3 summarizes the conditions, biological functions observed, and results of studies of high SMF exposure that used SMFs greater than 3T and that were performed in humans. The only adverse effects observed were temporal sensations caused by subject motion in strong SMFs.[7] The effects on cardiac function have been a concern for humans exposed to strong SMFs, but significant changes in ECG or heart rate have not been observed, though small systolic blood pressure increases have been documented.[57]

World Health Organization (WHO) Fact Sheet 232[1] recommended additional research to identify gaps in knowledge concerning possible health effects of SMF exposure. Additional studies using humans were given a high priority because they are needed for MR imaging staffers who work near a magnet, such as in interventional MR imaging procedures, to clarify the effects of a gradient magnetic field on head and eye coordination, cognitive performance, and behavior. Additionally, high priority investigations are needed to delineate the mechanisms and intensity effects of field-induced vestibular dysfunction, such as vertigo, because it is likely that, in the future, medical staff will perform complicated tasks for extended periods within an SMF. Medium priority research concerning cognitive performance and behavior was also mentioned. Moreover, additional studies on cardiac function as well as the effects of magnetic fields on the cardiovascular system would be useful. Such studies may need to be performed with fields exceeding 3T to evaluate potential risks that are sometimes observed in the routine clinical environment. Although several studies have been published in accordance with WHO recommendations (Table 3), further research is needed to ensure the safety of SMFs.

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