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CEM43°C thermal dose thresholds: a potential guide for magnetic resonance radiofrequency exposure levels?

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Abstract

Objective—To define thresholds of safe local temperature increases for MR equipment that exposes patients to radiofrequency fields of high intensities for long duration. These MR systems induce heterogeneous energy absorption patterns inside the body and can create localised hotspots with a risk of overheating.

Methods—The MRI + EUREKA research consortium organised a "Thermal Workshop on RF Hotspots". The available literature on thresholds for thermal damage and the validity of the thermal dose (TD) model were discussed.

Results/Conclusions—The following global TD threshold guidelines for safe use of MR are proposed:

1. All persons: maximum local temperature of any tissue limited to 39 °C
2. Persons with compromised thermoregulation AND
    a. Uncontrolled conditions: maximum local temperature limited to 39 °C
    b. Controlled conditions: TD<2 CEM43°C
3. Persons with uncompromised thermoregulation AND

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a. Uncontrolled conditions: TD<2 CEM43°C

b. Controlled conditions: TD<9 CEM43°C

The following definitions are applied:

Controlled conditions	A medical doctor or a dedicated trained person can respond instantly to heat-induced physiological stress
Compromised thermoregulation	All persons with impaired systemic or reduced local thermoregulation

Keywords

MRI; Thermal dose; Thermal threshold; Radiofrequency; CEM43°C; Safe exposure

Introduction

Radiofrequency (RF) electromagnetic fields are used for a wide variety of medical purposes. In many applications, they can be associated with some degree of local tissue heating. The resulting temperature increase depends on the intensity and distribution of the electromagnetic field and the electromagnetic and thermal properties of the tissue, e.g. permittivity, electrical conductivity, thermal conductivity, heat capacity and local blood perfusion. For therapeutic applications, the objective is to create a substantial temperature increase (to 40–45 °C in hyperthermia [1, 2] or 75–90 °C in thermal ablation [3–7]). However for diagnostic purposes, such as magnetic resonance (MR) imaging, the primary concern is to limit any temperature increase to levels with a minimal risk of thermal injury.

Owing to its high image contrast, its use of non-ionising electromagnetic fields and its relatively low health risk for patients and workers [8], MR imaging has become the gold standard diagnostic tool for soft tissue imaging and its use has accelerated over recent decades. Historically, the MR environment has a track record of being safe for patients and workers [8]. Stringent application of safety standards has kept the number of RF-related incidents low: for example skin injury incidence is below 0.0004 % for all examinations (0.2–3.0 T) [9]. However, as the pursuit to continuously improve contrast and resolution of the MR image intensifies, patients and workers are being exposed to RF electromagnetic fields of higher intensities over longer exposure times. Modern MR systems (1.5–7 T) use RF fields with a frequency of 64–300 MHz. At these frequencies, the field distribution inside the human body is highly complex and strongly dependent on tissue anatomy as well as shape, posture and position of the body.

The current edition of the MR safety standard IEC 60601-2-33 defines exposure limits for the absorbed power averaged over the exposed body region for the patient and the worker. The limit for the absorbed power, expressed as specific absorption rate (SAR), applies to the whole body, whereas partial body or local SAR is averaged over any 10 g of body tissue. Following this standard, the MR system uses the patient's weight to estimate the whole body or partial body SAR. However, there is currently no reliable method to relate these values to true local SAR. Numerical simulations of the SAR distribution during MRI have repeatedly shown hotspots inside the patient's body that significantly exceed the exposure limits for local SAR during normal operation mode of the MR system [10, 11]. This situation is even worse for multi-transmit coils [12]. The latest generation of MR systems has the potential to induce local temperature increases which may cause temporary or permanent tissue damage. A global reduction of the RF power, to prevent excessive heating, may lead to a significant deterioration of the imaging quality, impairing the applicability of the latest MR technology as a diagnostic tool. To maintain maximum performance, MR manufacturers consider it of great importance to establish guidance on levels of temperature and time intervals that pose

minimal or no risks to the patient in terms of thermal toxicity from MR imaging. The transient nature of heating (time-dependent temperature changes) and the different heat sensitivity of various tissues must be considered. The most obvious approach to establish these “safe” temperature–time intervals is to perform a comprehensive literature review on reported thermal tissue damage. Interpretation of results from such a diverse field of publications requires standardisation of the relationship between thermal exposure and thermal damage. The cumulative equivalent minutes at 43 °C (CEM43°C) model, as introduced by Sapareto and Dewey [13], is a simple concept that translates all different temperature–time histories to a single number representing a “thermal isoeffect dose”. The same dose concept can be used to quantify thermal exposure during MRI.

The MRI + EUREKA consortium was established to develop a new basis for assessing the RF safety of MR systems. A workshop organised by the IT’IS Foundation and the MRI + EUREKA research consortium under the title “Thermal Workshop on RF Hotspots” was held in March 2011, in Zurich, Switzerland, to define the threshold of safe local temperature increases for diagnostic MR applications. The workshop convened 31 experts (listed in the Electronic Supplementary Material) from the USA, the Netherlands, Greece, Denmark, Germany and Switzerland, who intensively discussed the needs of the regulators and the MR industry; strengths and deficiencies of international safety guidelines and standards; capabilities and limitations of modelling/measurement techniques in assessment of thermal exposure during MRI; thermoregulatory responses; tissue damage models; and effects of local heating on cell biology.

The MRI + EUREKA study reported here examines existing literature on thermal damage and aims to achieve two objectives: (1) to determine global limits of thermal isoeffect dose for MR exposure and (2) to discuss the feasibility of relaxing these values for the most exposed tissues such as skin, muscle, fat and bone.

Material and methods

Tissue thermal damage data

Data on time–temperature thresholds for thermal damage of healthy tissue were compiled in extensive reviews on thermal tissue damage published by Dewhirst et al. [14] and Yarmolenko et al. [15]. In these reviews the authors selected all papers identified in the literature until December 2010 that supplied adequate thermal dosimetry to identify thresholds for thermal damage to normal tissue. Detailed data of these two publications were made available for this study.

CEM43°C thermal dose isoeffect model

The extent of thermal damage to tissue depends on tissue sensitivity, temperature and exposure time. In vitro studies showed that the rate of cell death is exponential with respect to temperature over a limited temperature range (40–55 °C) [16, 17]. While sensitivity to heat is different across species as well as across different tissues and organs, a breakpoint in the rate of cell death was detected in cell culture around 43 °C and generalised as a part of the calculation of thermal dose. Extensive discussion on the kinetics of cell death by hyperthermia is available in the literature [16–18]. Temperature and exposure time are both highly variable across publications, requiring standardisation through the use of thermal dose as a common unit. In 1984 Sapareto and Dewey [13] proposed the cumulative equivalent minutes at 43 °C as a model to calculate a thermal isoeffect dose. Using this method any time–temperature history is converted to an equivalent number of minutes of heating at 43 °C, using the following formula:

$$\mathrm{CEM43^\circ C}=\sum_{i=1}^{n} t_i \cdot R^{(43-T_i)} \quad (1)$$

where CEM43°C is the cumulative number of equivalent minutes at 43 °C, t_i is the i-th time interval, R is related to the temperature dependence of the rate of cell death ($R(T<43$ °C)=1/4, $R(T>43$ °C)=1/2) and T is the average temperature during time interval t_i. The resulting CEM43°C value represents the effect of the entire history of heat exposure on cell death. Several factors are known to affect the rate of cell killing among these, thermotolerance being the best known [17].

Data analysis

Thermal dose (CEM43°C) was calculated on the basis of thermal histories from all available data (as reviewed elsewhere [14, 15]). Subsequently, the data (per organ or specific tissue) were plotted in graphs with the x-axis representing the reported temperature at which the original exposure was performed and the y-axis (log scale) representing the thermal dose expressed as CEM43°C. As a standard reference, the graph includes two lines relating an exposure time of 30 or 60 min at the indicated temperature to the related CEM43°C minutes. The exposures of 30 and 60 min were selected as being close to typical durations that a patient is exposed to RF fields during MR imaging, although heating is not expected to be either spatially or temporally constant during the entire imaging session. As an additional discriminating factor, markers indicate whether thermal damage was found. These graphs provide a comprehensive overview of available data and point to possible thresholds for thermal damage in MR imaging. To obtain an overview of the thermal sensitivity for different tissue types, three graphs were constructed to illustrate the highest CEM43°C reported for (1) no damage found, (2) the lowest CEM43°C at which damage is reported for humans or large animals, and (3) the lowest CEM43°C at which damage is reported for all species, including rodents.

Results

The first review by Dewhirst et al. [14] covered 109 papers that had been published until 2002. The second review by Yarmolenko et al. [15] is an update of the first review for papers published between 2002 and 2010. For the second review Yarmolenko et al. applied a strict protocol on the quality of the reported data when selecting the papers for inclusion in their study. Of the initial 463 papers identified, only 152 provided sufficient and accurate information on the thermal exposure (time–temperature history at the site of tissue damage) to pass their criteria. The reasons for excluding papers from their analysis are described extensively by Yarmolenko et al. [15]. Collectively, the reviews gathered data for 11 species and reported the threshold thermal doses for damage on 31 different normal tissues after local heat exposure (Table 1). Graphs plotting thermal damage as a function of the CEM43°C thermal dose were produced for all organs and specific tissue types. Figure 1 shows the results for rectum and small intestine. It illustrates the principle of using the CEM43°C thermal dose model for rectal tissue: damage is greater at higher thermal doses (obtained by heating at a constant exposure time of 30 min at different temperatures, Fig. 1a). Figure 1b shows for small intestine that the CEM43°C thermal dose leading to 50 % crypt stem cell survival in mouse or to 50 % “gut death” in hamsters is basically constant (higher temperature is compensated by shorter exposure times). These findings demonstrate the great variability in sensitivity to heat both across organs and across species: at the thermal dose of 1,000 CEM43°C, no thermal damage was noted in the rabbit rectum, whereas significant damage was reported in pig rectum at this dose (Fig. 1a).

Muscle and fat tissues represent the largest fraction of human body mass/volume and most likely peak heating will occur in these tissues. Ichinoseki-Sekine et al. [19] investigated the effect of microwave heating in human skeletal muscle (vastus lateralis) in 11 healthy adult men. For a thermal dose ranging from 5 to 21 CEM43°C, no signs of thermal damage were observed in either blood creatine kinase activity or in the qualitatively analysed (by pathologists) histological biopsy specimens taken 24 h after the heating. Acute but minor damage was seen in the range of 41–80 CEM43°C, with significant and permanent damage above 80 CEM43°C [14]. In pigs, damage to fat tissue was noted around 90 CEM43°C, though the damage was not detected in another study at 100 CEM43°C (Fig. 2).

While thermal damage of muscle and fat may cause discomfort, damage to more complex and/or critical organs may be of greater concern, as such damage could result in permanent dysfunction. Data on thermal thresholds for damage to the eye are available in great detail (Fig. 3). Of the various parts of the rabbit eye, the lens is most sensitive, with damage reported for a thermal dose of 2.4 CEM43°C. With the exception of the lens, retina and cornea, the other tissues of the eye were insensitive to thermal doses below 10 CEM43°C (rabbit, dog). Figure 4 shows similar results for brain tissue, where the threshold for thermal damage is also in the range of 10 CEM43°C. In general, blood–brain barrier (BBB) effects were reported at lower thermal doses following whole body hyperthermia than after local heating.

Figures 5, 6 and 7 provide a visual representation of all data available on thermal sensitivity for all the different tissue types and species, aggregated at three different levels. Figure 5 provides the highest CEM43°C for all tissues and all species reported with “no damage found”. Clearly skin tissue is the least sensitive to thermal damage with reported thresholds for thermal damage varying from 240 CEM43°C for mouse to above 600 CEM43°C for human skin. Human skeletal muscle tissue [19] could be heated at a maximal thermal dose of 21 CEM43°C with no thermal damage noted. Figure 6 provides the lowest CEM43°C reported for tissue damage for all tissues but only for larger animals and humans. Overall, Fig. 6 shows that tissue damage was only detected at thermal doses of about 10 CEM43°C, with great variability across species and across organs/tissue for any one species. Figure 7 is an extension of Fig. 6 and shows the lowest CEM43°C reported for tissue damage for all tissues and all species, i.e. including rodents. In general thermal thresholds for rodents appear to be lower than for humans or large animals. In Fig. 7, the lens of the rabbit eye has the lowest threshold for thermal damage at 2.4 CEM43°C.

Discussion

Recent activities

Thermal hazards and their time-dependent thresholds were discussed at the international workshop “Thermal Aspects of Radio Frequency Exposure” that was held in Gaithersburg, Maryland, USA on 11–12 January 2010[1] [15, 20–24]. Although the emphasis of this workshop was slightly different, i.e. to establish improved public exposure limits for RF energy, the underlying goal to identify safe thermal dose thresholds to replace the various established SAR criteria was similar. Foster and Morrissey [25] summarised the major topics discussed at the workshop. They divided thermal hazards from excessive RF exposure into hazards associated with whole body effects and those that are restricted to local effects only. Whole body effects concern adverse physiological effects resulting in behavioural disruption associated with an increase of the core temperature by 1 °C or more and are well

[1]This workshop was co-sponsored by the Mobile Manufacturers Forum, the GSM Association, and the US Food and Drug Administration. A selection of the presentations are published in the Special Issue entitled “Thermal Aspects of Radio Frequency Exposure on Human Health”; *Int. J. Hyperthermia*; 4, 2011. Guest Editor: Joseph Morrissey.

covered by the current exposure guidelines. Foster and Morrissey [25] also indicated that the basis to limit thermal hazards for local regions is poorly supported by scientific data, and that the Maryland workshop was successful in providing better understanding and more data on this topic. For example Bergeron [25] reported that healthy, well-hydrated children of 8 years or older have thermoregulation capacity similar to that of young adults (20–30 years).

A large collection of publications on thermal damage to normal tissue was analysed in two reviews [14, 15]. The present analysis on risks of thermal damage from MR radiofrequency exposure levels is based on the data from these two reviews. An important next step in assessing critical levels of thermal exposure is to aggregate all the available information in an understandable way and translate it into practical application. We have attempted to do so here by summarising the data on thermal damage in various tissues in three different categories (Figs. 5, 6 and 7):

- End point ‘highest CEM43°C value reported for no damage observed’ (Fig. 5).

  CEM43°C values for no damage vary between 0.2 min for rectum tissue of dogs [26] to above 600 min for human (mild hyperaemia only) and pig skin [27]. Although these data can not be conclusive for the threshold at which thermal damage will occur, the majority of the reported data indicate that in general a thermal dose of 10 to 20 CEM43°C is needed to induce thermal damage.

- End point ‘lowest CEM43°C value for tissue damage reported for humans and large animals’ (Fig. 6).

  The lowest CEM43°C values for thermal tissue damage are all found in dog tissue: brain [28], blood brain barrier [14] and liver [29] with a CEM43°C value of 7.5, 9.9 and 9.9 min, respectively.

- End point ‘lowest CEM43°C value for tissue damage reported for all species’ (humans, large animals and rodents; Fig. 7).

  The lowest thermal dose that results in tissue damage across all examined species is 2.4 CEM43°C. This number comes from thermal damage to the eye lens as measured for rabbits [30]. The next lowest CEM43°C value (3.4 min) is found for the mouse testis [31].

Physiological and functional aspects

Aside from the direct cytotoxic effect of local heating, it is also important to consider specific physiological or functional conditions that may render patients more vulnerable to adverse side effects that are histologically or pathologically undetectable.

Particular attention is required with thermal thresholds for the fetus because of its higher vulnerability to temperature elevation. In the most recent and extensive review on teratogenic effects of heat, Ziskin and Morrissey [22] reported that the fetus is entirely dependent upon the maternal temperature and circulation to avoid hyperthermia. Hand et al. [32] reported that 80 % of heat loss by the fetus to the mother is achieved through heat transfer from fetal to maternal blood in the placenta. The remaining heat loss is across the fetal skin/amniotic fluid and amniotic fluid/uterine wall boundaries. According to Asakura [33] a temperature difference of approximately 0.5 °C between fetus and mother is required for sufficient conductive cooling. As a general rule, maternal core body temperature increase of about 2 °C for extended periods of time, approximately 2.5 °C above normal for 0.5–1 h, or at least 4 °C above normal for 15 min can result in heat-induced abnormalities in the developing mammalian fetus [22]. The absolute thermal threshold is dependent upon the animal model, the specific developmental stage of the fetus at exposure, and the malformation studied. Miller et al. [34] reported a similar value for the threshold

temperature elevation for hyperthermia-induced teratogenic effects, i.e. 1.5–2.5 °C above core body temperature for exposures of long duration. While identification of thermal thresholds loses precision at higher temperature exposures, Miller et al. [34] mention that a threshold thermal dose could exist at 5 min or more at a temperature elevation of 4 °C above core temperature. Extrapolating results from animal models to humans is difficult because of the differences in normal body temperatures and heat sensitivity between species. Nevertheless Ziskin and Morrissey [22] conclude that an elevation of approximately 2 °C for at least 24 h (due to fever or other sources) is needed to correlate with an increase in developmental abnormalities.

Heynick and Merritt [35] reported that RF fields at low intensities (i.e. not causing temperature increases) are not associated with teratogenicity. They also reported that the first trimester is considered the most sensitive period for teratogenesis in humans. Using these data Ziskin reported at the Zurich Workshop that the thermal threshold for teratogenicity, reproduction and developmental effects in animals is around a CEM43°C of 1–2 min.

Homeostasis

Temperature detection and regulation are of vital importance to any homeothermic organism. These sensory processes are not only needed to control and maintain internal temperature homeostasis but also serve as a warning system to inform us when our environment is too hot or too cold in order to prevent tissue damage. The most important mechanisms in humans that counteract temperature increase due to a thermal load are transportation of heat to the body surface using the cardiovascular system and loss of heat through sweating [36].

When considering the impact of the impaired thermoregulation, one must keep in mind that the RF exposure associated with MR has a limited effect on core temperature of the patient with an undisturbed thermoregulation [37–39]. In addition Hirata et al. [39] calculated that a whole-body-averaged SAR well above current guidelines is required to induce a body temperature increase of 1 °C, i.e. an SAR_{wb} of 9 W/kg for a 3-year-old child and 6 W/kg for an adult. In contrast, Bakker et al. [40] reported that a localised temperature increase of 1 °C may occur at a minimum SAR level of 2.2 W/kg (10 g spatial-averaged SAR). More recently Murbach et al. [10] reported that performing MR in first level operating mode (e.g. 4 W/kg whole-body averaged exposure) afforded peak spatial 10 g averaged SAR (psSAR10g) values as large as 60 W/kg in the trunk and 104 W/kg in the extremities in adults. At the Zurich workshop Murbach reported that such psSAR10g values in a healthy volunteer may result in a local temperature increase of 4 °C in thermally isolated skin tissue. In the case of compromised thermoregulation he predicted that the local temperature could increase by 7–15 °C for similar psSAR10g values.

In summary, persons with impaired or (temporarily) reduced systemic thermoregulation (elderly, young children or patients with fever) or reduced local thermoregulation, often combined with an inability to sense heat (scar, oedematous tissue, nerve diseases, including diabetic neuropathies and paraplegia) represent patient groups who need specific attention when exposed to heat. In this respect it is also important to note that in deep regional hyperthermia an excessively high temperature for deeply located tissue is often reported/sensed as pressure, pain or other feelings of discomfort [41]. To avoid thermal damage, local effects must be considered in addition to whole body effects.

Thermal thresholds for brain tissue

Regarding the effect of heat on the brain, it is hard to discriminate between an adverse effect and a normal physiological response to heat stress. As reported by Yarmolenko et al. [15], damage to the nervous system can be assessed in many ways, with each tissue having a different sensitivity to heat stress and overall results being difficult to interpret in terms of their impact on brain functioning. Changes in BBB permeability, metabolism, cerebral blood flow, neural activity and other measures have been reported to occur at very low (0.1 CEM43°C) thermal exposure. In general the effects seemed to be higher for longer, lower temperature exposure than for shorter, higher temperature exposures [15]. The majority of the studies did not assess long-term damage, and used whole body hyperthermia to heat the animal. Kiyatkin and Sharma [42] reported that the albumin-positive cells and albumin leakage in neuropil appeared in the brain within the range of physiological hyperthermia (38.5–39.5 °C), suggesting that increased BBB permeability is not solely pathological, but also a normal physiological phenomenon occurring during various conditions associated with hyperthermia. Such hyperthermia effects, for example, occur during copulatory behaviour and heroin self-administration [43]. It is therefore difficult to delineate the role of temperature or thermal dose in the observed physiological effects with respect to the normal response of the nervous system to systemic thermal loads. This is further supported by two additional publications that were not included in the Yarmolenko et al. [15] and Dewhirst et al. [14] reviews. Versteegh [44] subjected sheep to whole body hyperthermia for 3 h at 42 °C, i.e. a CEM43°C value of 45 min. He found no indication of oedema and measured a maximal increase in intracranial pressure of 20 mmHg. Van Rhoon et al. [45] subjected dogs to whole body hyperthermia for 2 h at 41.8 °C, i.e. a CEM43°C of 23 min, and also found neither oedema nor a change in intracranial pressure. Hence, clear thresholds for pathological damage from heating are at present difficult to determine because of significant variability in available data across species, combined with a paucity of such data in humans.

Transforming threshold into guidelines

When transforming the thermal thresholds in Figs. 5, 6 and 7 into guidelines on thermal dose that pose minimal risk to the patient in terms of thermal toxicity from the MR imaging, the model used to translate the many different temperature–time histories into a single thermal dose parameter is of pivotal importance. Since, the thermal dose model to calculate CEM43°C is an empirical one, the soundness of the selected values must be evaluated carefully, as explicitly indicated by Dewhirst et al. and Dewey [14, 16]. In general the validity of the CEM43°C model is unclear when the data are extrapolated to very low or high temperatures. Discussions are ongoing with regard to the correct R value (0.25 at temperatures below 43° C and 0.5 at temperatures of at least 43 °C) and on how to incorporate thermotolerance effects for long heating times, step-down heating, repeated exposures, or sensitising effects of physical or chemical agents like drugs, etc. Clearly, the accuracy of the determined threshold is critically dependent on the accuracy of the obtained temperature data from all experiments.

The thermal thresholds reported in all studies thus far have been obtained for tissue under normal physiological conditions. In a clinical situation many possible physiological conditions may impair tissues chronically (scar, oedema) or temporarily (pressure spot causing cessation of perfusion), resulting in a higher sensitivity to heat. Main and Lovell [46] measured the interface pressure between seven different types of stretchers (also used in MR) and the skin of patients lying on them. They found mean values that exceeded 20 mmHg and 40 mmHg in the thoracic and sacral areas of the spine, respectively. Suzuki et al. [47] investigated the impact of ischaemic skin due to mechanical pressure on thermal sensitivity. They found for Wistar rats that at approximately 28 mmHg and approximately 49 mmHg interface pressure on the skin the exposure time at 50 °C to induce deep dermal

burn reduced to 3 min (384 CEM43°C) and 2 min (256 CEM43°C), respectively, from 10 min (1,280 CEM43°C) without compression.

An interesting point for discussion is whether guidelines on thermal threshold should be generic for all tissues or more tissue-specific allowing relaxation of the guidelines for tissues for which it has been demonstrated that thermal damage occurs at higher CEM43°C values. The latter is of special interest as the highest local temperature rise during MR imaging of the human body is typically observed in superficial tissues (skin, muscle, fat) and in bone through thermal conduction [10]. Table 2 summarises the reported different thermal dose threshold for known reversible and irreversible effects in skin, muscle, fat and bone. In light of the long history of safe use of MR imaging, it should be further studied whether for specific tissue the gap between no effect to reversible and next irreversible effects allows for relaxation of the thermal threshold guidelines for instance for muscle.

In their first review Dewhirst et al. [14] reported significant acute and chronic damage to the skin above 41 CEM43°C, followed by complete necrosis above 288 CEM43°C. The latest data on humans [48, 49] as reported elsewhere [15] are consistent with these thresholds. Werner et al. [49] reported, in addition to acute and significant skin erythema, that the sensitivity of the skin to heat and pressure stimuli was also altered in a reversible manner at 112 CEM43°C. Full recovery was noted within 4 h after exposure.

For muscle tissue, acute but minor thermal damage is reported to occur from 41 CEM43°C with the damage (haemorrhage and necrosis) becoming significant and chronic above 80 CEM43°C [14]. In the update of their review [15], the authors reported that the majority of the published data were still consistent with these values.

Subcutaneous adipose tissue (SAT) and fat are not discussed separately in either of the two reviews [14, 15], probably because they are usually included in studies of thermal damage to the skin or muscle. Nevertheless, fat is a tissue with limited blood perfusion and, consequently, more susceptible to heating. In a recent study Franco et al. [50] reported on the thermal sensitivity of human subcutaneous adipose tissue. They found delayed adipocyte cellular death occurring 9 days after exposure to 15 min at 43–45 °C (15– 60 CEM43°C); the delay in tissue damage appearance was also noted elsewhere [51].

Thermal damage in bone tissue was mainly studied out of interest in high-speed drilling and medical devices implantation. Yarmolenko et al. [15] used the experimental data that Eriksson and Albrektsson [52] had obtained with the use of a titanium thermal chamber implanted in rabbit tibia to approximate the thermal damage threshold for bone at 16 CEM43°C.

Need to identify means to include CEM43°C tools in MR

The current practice in MR imaging safety, for compliance with well-established limits to prevent adverse health effects from electromagnetic fields induced whole-body heating, is to monitor the deposited energy and whole-body exposure (averaged over different time intervals). However, the possibility for tissue damage from locally enhanced heating, i.e. creation of “hotspots”, generates a need for improved guidelines to be introduced. Local SAR values and temperature increases can only be estimated from simulations performed on anatomical models, but it is not yet clear to what degree these models need to be patient-specific. Basing the guidelines on thermal dose thresholds expressed in CEM43°C would allow one to consider exposure duration, the transient nature of heating and tissue sensitivity. Furthermore, a realtime safety supervision based on the previously executed scanning and the upcoming sequence would be highly valuable. This is only feasible if SAR and temperature modelling tools are developed and made available in the MR system.

Whether such predictive modelling can be done instantaneously for each patient or in a more generic fashion with local refinements for patient-specific anatomy is the subject of currently ongoing studies [10, 53, 54].

Conclusions and suggested guidelines

Considering the available data on thermal thresholds for thermal damage, the related discussion on validity of the thermal dose model and other uncertainties, the participants of the "Thermal Workshop on RF Hotspots", March 2011, Zurich, Switzerland, agreed that the following temperature–time exposure values provide suitable thermal threshold guidelines for safe use of MR during standard examinations, i.e. posing "no or minimal risk" of adverse thermal effects.

1. All persons (including pregnant women, elderly, children, patients with fever, impaired thermoregulations and implants): maximum local temperature of any tissue limited to 39 °C (Rationale: no damage is reported below this temperature; also it is the margin above which teratogenic effects of heat may occur).
2. Persons with compromised thermoregulation AND
    a. Uncontrolled conditions: maximum local temperature of any tissue limited to 39 °C
    b. Controlled conditions: thermal dose <2 CEM43°C. (Rationale: local temperature effects below this level have not been observed in any species)
3. Persons with uncompromised thermoregulation AND
    a. Uncontrolled conditions: thermal dose <2 CEM43°C
    b. Controlled conditions: thermal dose <9 CEM43°C. (Rationale: lower range of detected toxic effects in higher species)

The following definitions are applied:

Controlled conditions	A medical doctor or a dedicated specifically trained person is available to respond instantly and adequately to heat-induced physiological stress and patient complaints during MR
Compromised thermoregulation	All persons with impaired systemic thermoregulation (elderly, young children or patients with fever) or reduced local thermoregulation due to scar, oedematous tissue, nerve diseases, including diabetic neuropathies and paraplegia

The set of thermal thresholds as proposed above can be considered as a refined interpretation of the data provided by Dewhirst et al. [14] and Yarmolenko et al. [15]. Although established by a different way of reasoning, they are in very good agreement with those mentioned in the consensus report of the American Institute of Ultrasound in Medicine (AIUM) on safety of diagnostic ultrasound [55], following the review of thermal injury to tissue from ultrasound exposure by O'Brien et al. [56]. The values reported by AIUM correspond to 1 CEM43°C for exposures longer than 5 s and 10 CEM43°C for shorter exposures and are reported as a 'conservative boundary'.

The thermal thresholds reported for human skin, muscle, fat and bone are all higher than the 9 CEM43°C as recommended for uncompromised persons and controlled conditions. As the highest local temperature rise during MR imaging of the human body is typically observed in these tissues, it should be studied whether the guideline for these tissues can be relaxed to less than 16 CEM43°C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Standard MRI can cause local heating by radiofrequency absorption.
- Monitoring thermal dose (in units of CEM43°C) can control risk during MRI.
- 9 CEM43°C seems an acceptable thermal dose threshold for most patients.
- For skin muscle fat and bone 16 CEM43°C is likely acceptable.

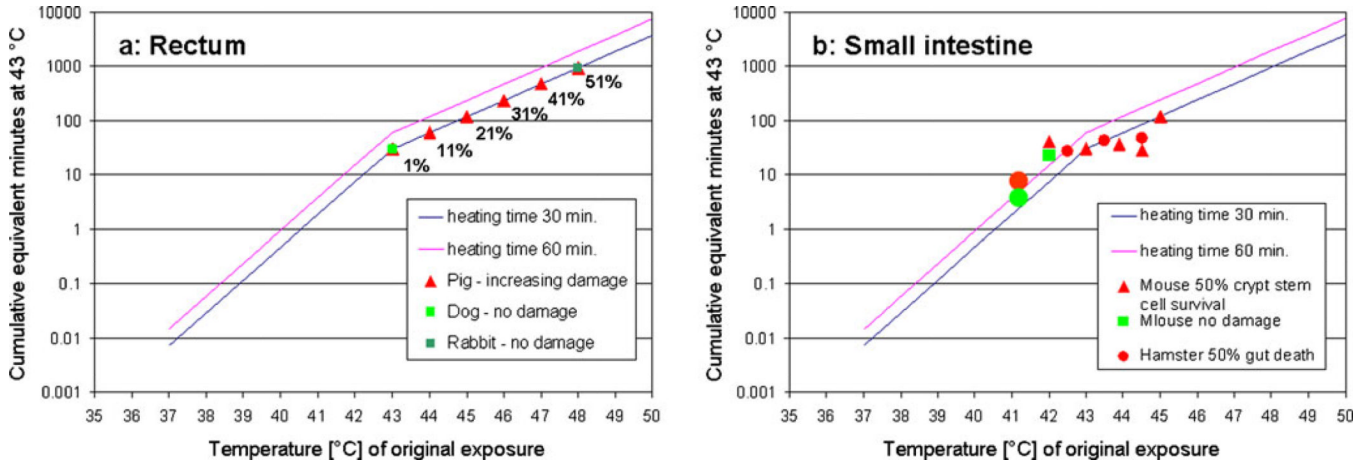

Fig. 1.

Graphs showing various levels of normal tissue damage for **a** rectum and **b** small intestine as a function of temperature of original exposure and the CEM43°C (equivalent exposure time in minutes at 43 °C). The CEM43°C model illustrates increasing tissue damage with increasing CEM43°C dose and constant tissue damage for the same CEM43°C dose (mouse 50 % crypt stem cell survival: higher temperature is compensated by shorter exposure). *Small symbols* data from [14]; *large symbols* in **b** only, from [15]. Rat (whole body hyperthermia) *green circle* 4.6 CEM43°C no effect; *red circle* 7 CEM43°C significant change

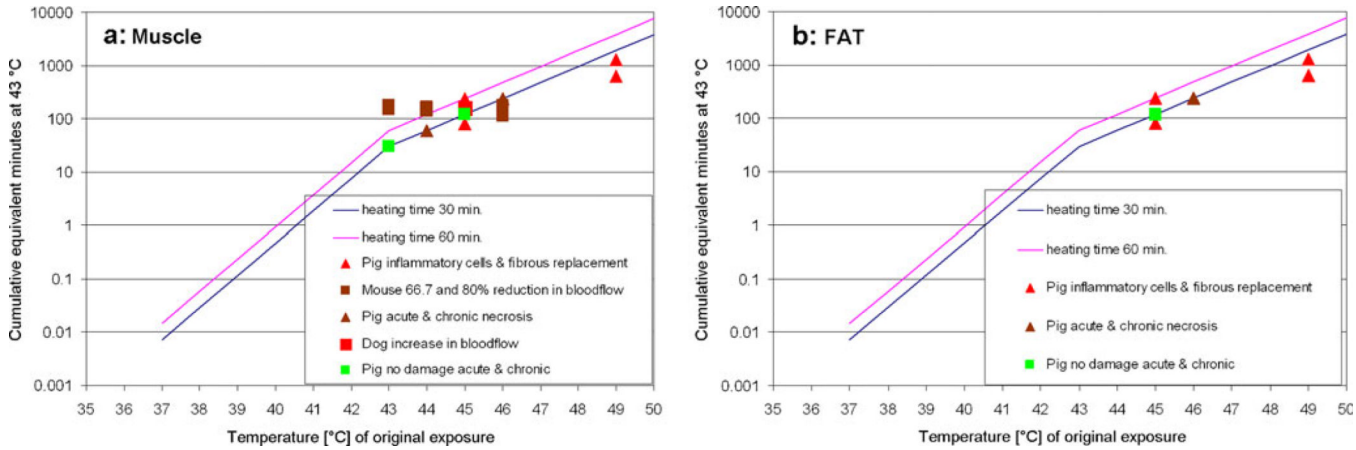

Fig. 2.

Graphs showing various levels of tissue damage for **a** muscle and **b** fat with respect to temperature during the thermal exposure and the CEM43°C (equivalent exposure time expressed in minutes at 43 °C). *Small symbols* data from [14]; *large symbols* in a only, from [15]. Human *orange circle* 26 CEM43°C threshold to induce thermal damage in the muscle

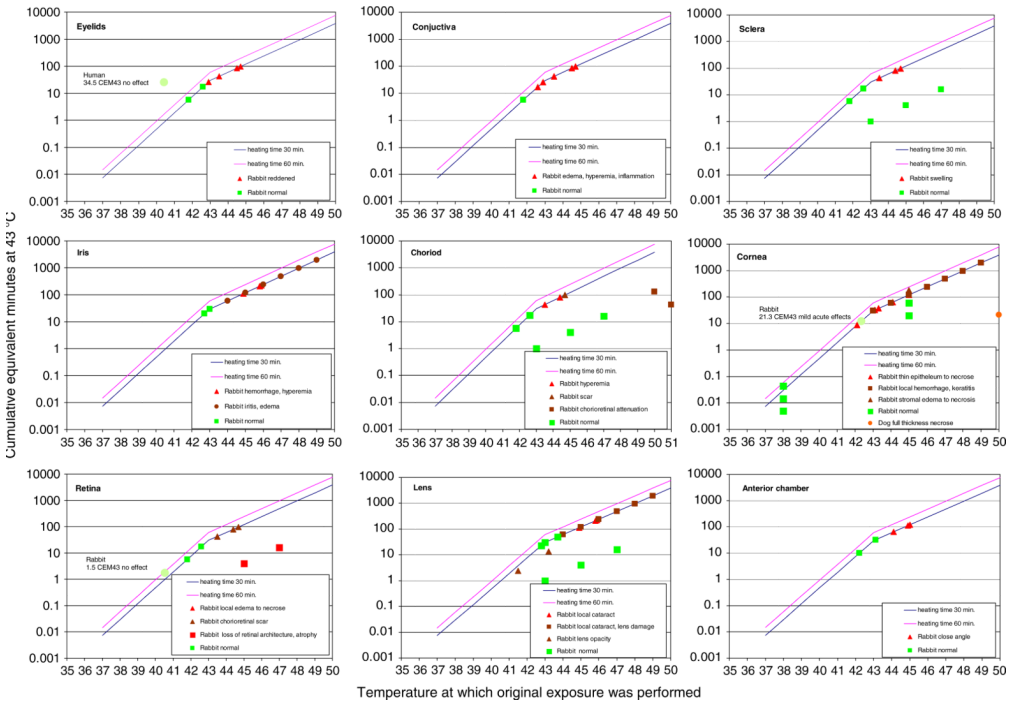

Fig. 3.

Thermal threshold as CEM43°C for normal tissue damage of multiple parts of the eye. Data from [14]; *inserts* are new data from [15]

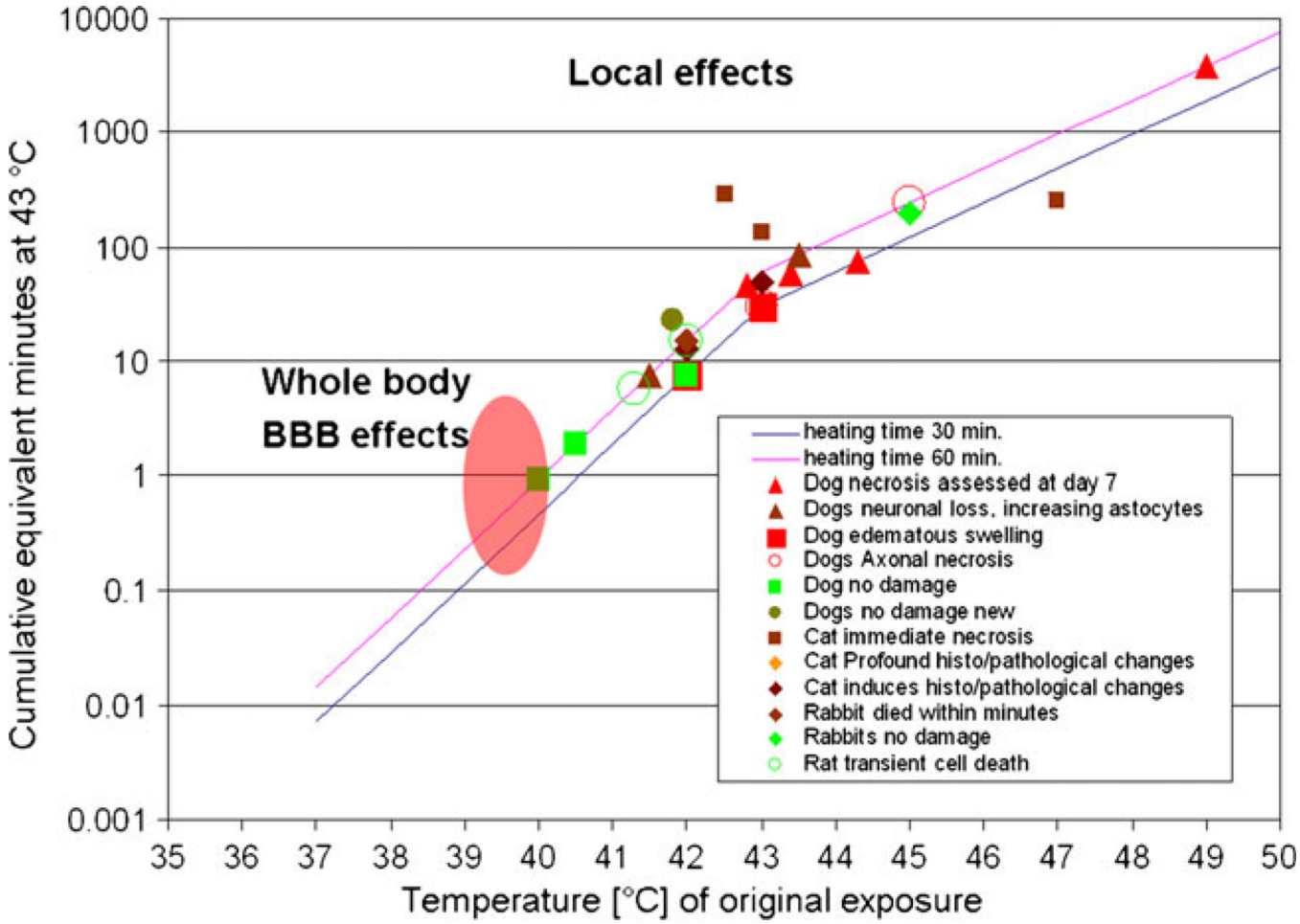

Fig. 4.

Thermal threshold of brain tissue damage after local heat exposure including a range for the thermal threshold in CEM43°C for an effect of the blood brain barrier (BBB) response after whole body hyperthermia (data from [14, 15])

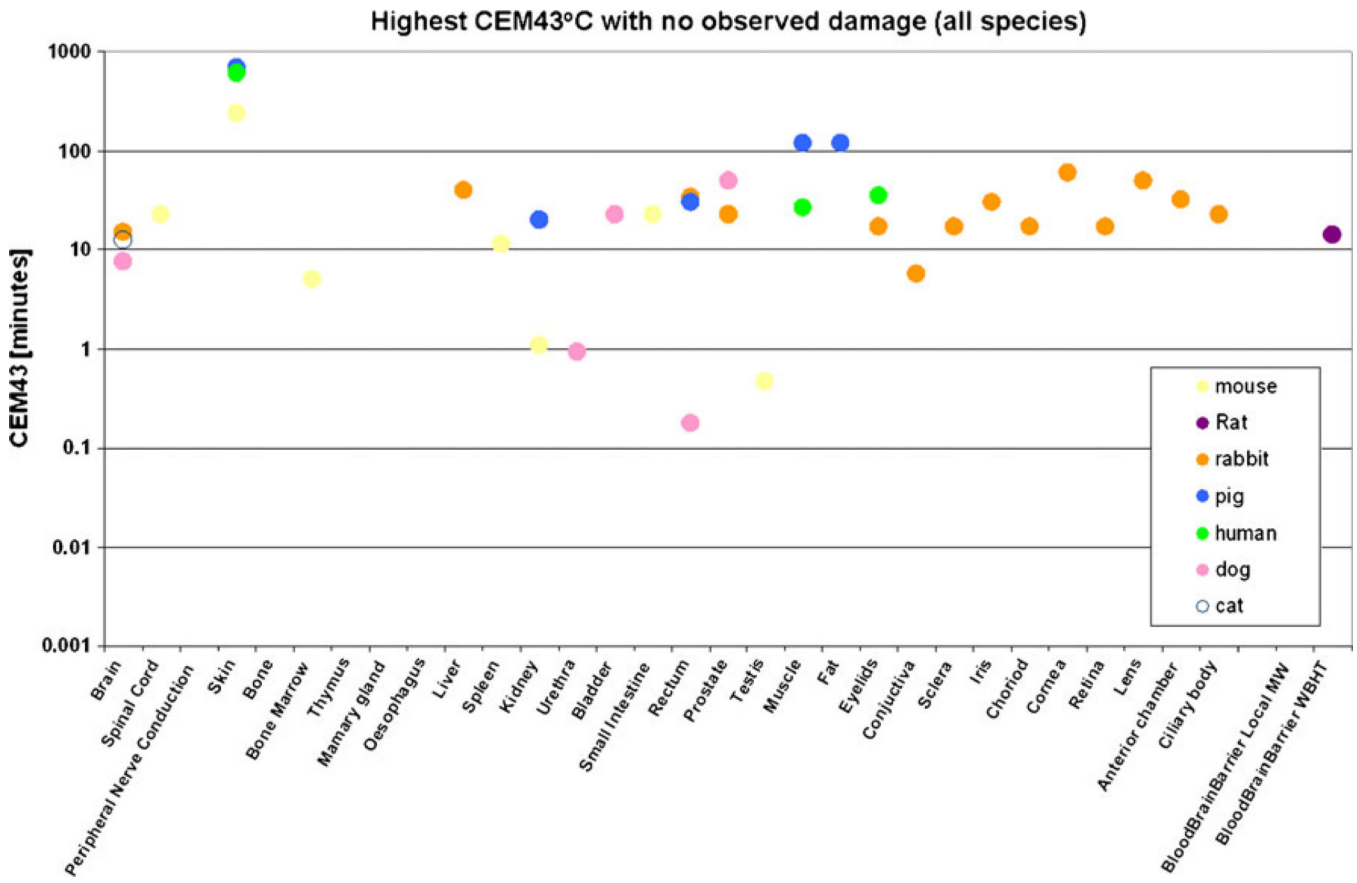

Fig. 5.

Highest CEM43°C for all tissues and all species for which “no damage” or “no effect” was reported

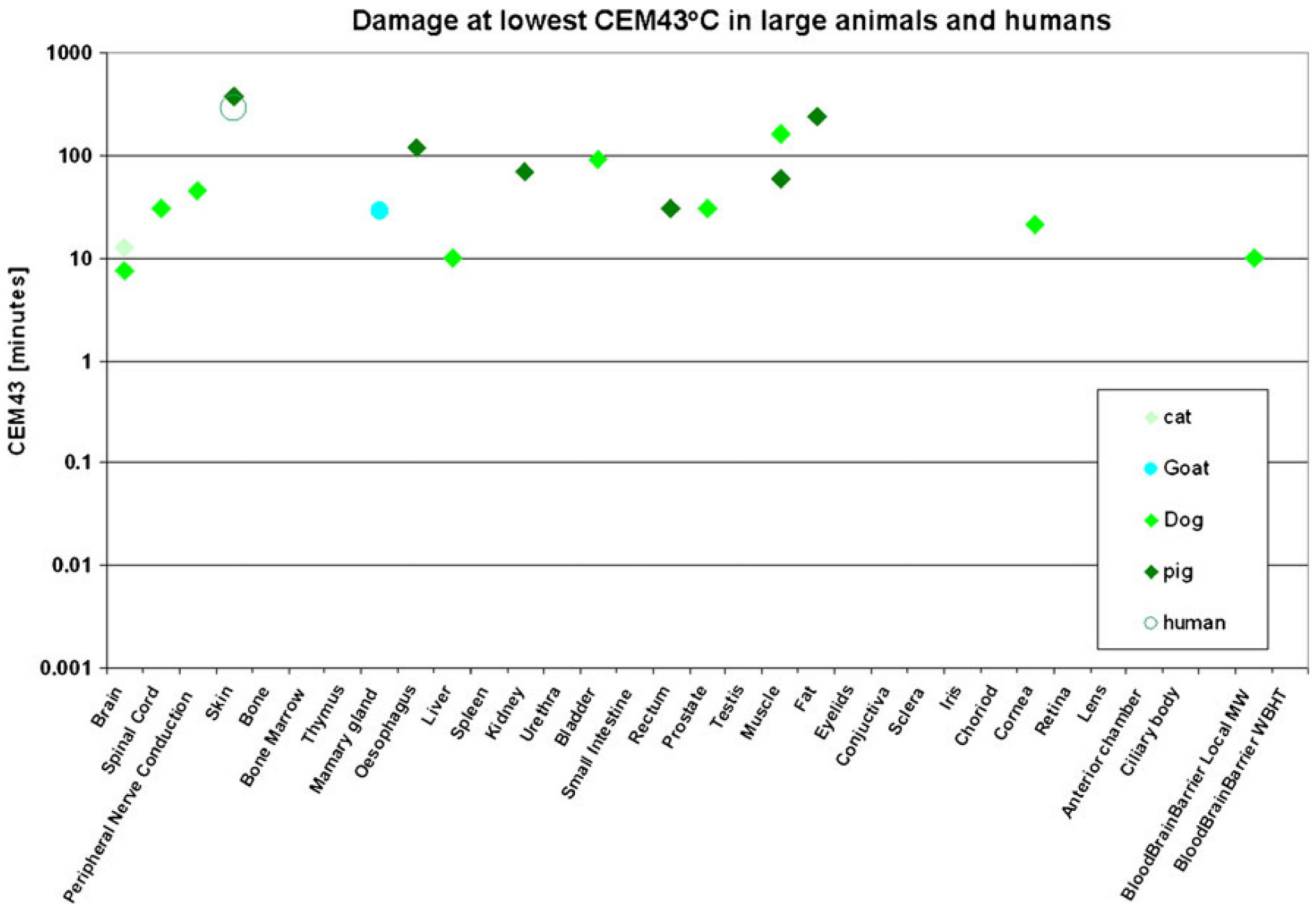

Fig. 6.
Lowest CEM43°C for tissue damage for all tissues reported in larger animals and humans only

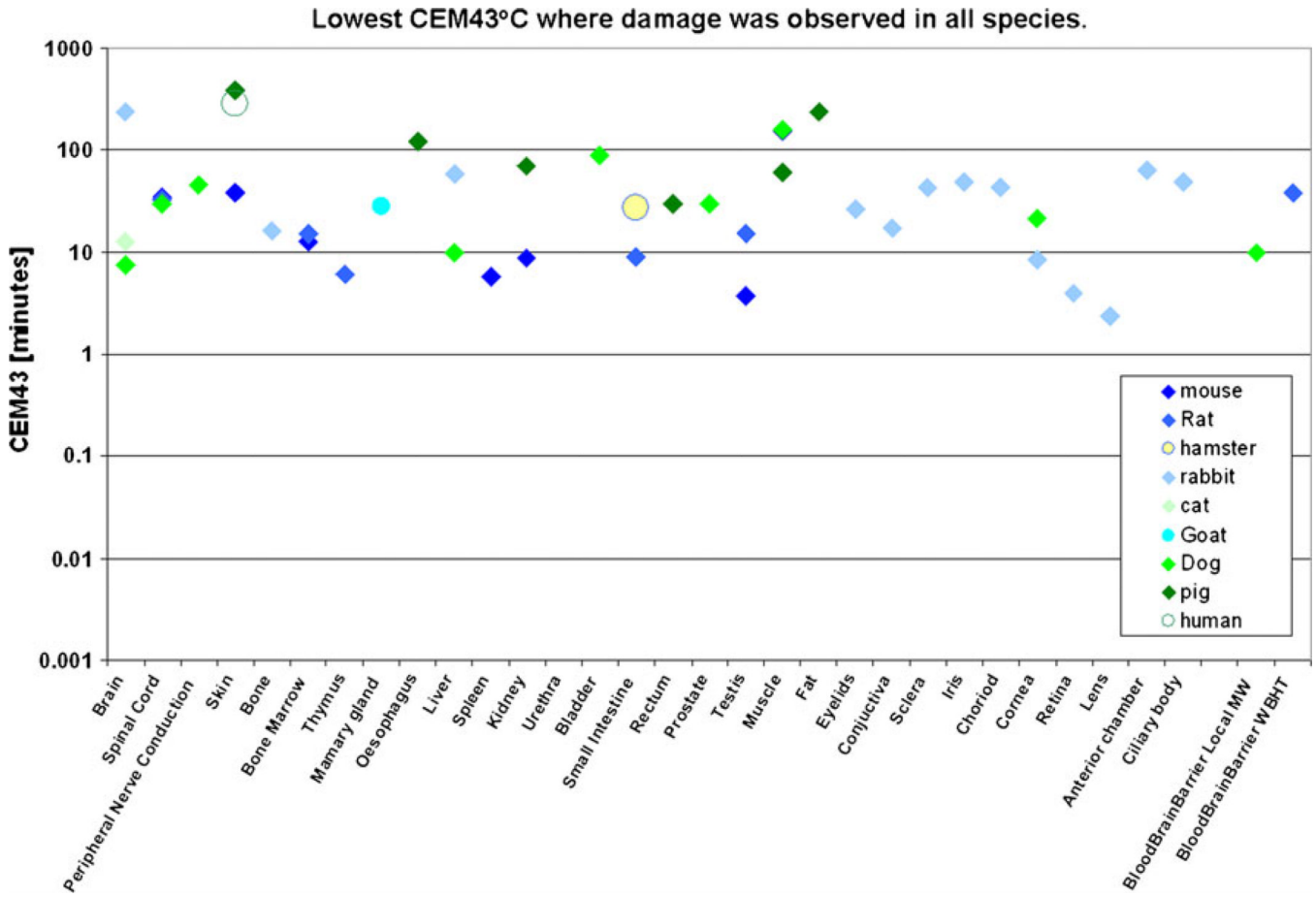

Fig. 7.
Lowest CEM43°C reported for tissue damage for all tissues and all species

Table 1

Tissue types for which thermal thresholds for damage to normal tissue was assessed

Tissue type	Human	Pig	Dog	Cat	Goat	Guinea pig	Monkey	Mouse	Rat	Hamster	Rabbit
Anterior chamber											X
Bladder			X						X		
Blood brain barrier			X						X		X
Bone	X								X		X
Bone marrow								X	X		
Brain		X	X	X			X		X		X
Choriod											X
Ciliary body											X
Conjuctiva											X
Cornea	X		X								X
Epidermis	X	X				X		X	X		
Eyelids											X
Fat		X									
Iris											X
Kidney		X	X					X			X
Lens											X
Liver		X	X								X
Mammary gland					X						
Muscle	X	X	X					X	X		X
Oesophagus		X									
Peripheral nerve conduction			X						X		
Prostate			X								X
Rectum		X	X								X
Retina											X
Sclera											X
Small Intestine		X	X					X	X	X	
Spinal cord			X					X	X		
Spleen								X			
Testis	X						X	X	X		

Tissue type	Human	Pig	Dog	Cat	Goat	Guinea pig	Monkey	Mouse	Rat	Hamster	Rabbit
Thymus									X		
Urethra			X								

Table 2

Differentiation in thermal dose for reversible and irreversible effects

Tissue	Thermal dose threshold	
	Reversible effects	Irreversible effects
Skin		>40
Muscle	>40	>80
Fat	15	
Bone		16