CEM43°C thermal dose thresholds for MRI

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History of clinical practice

- Skin injury incidence < 0.0004% for all exams (0.2-3.0T)

  (IEC 60601-2-33)

- Safe for patients and workers

  “Sensations of warmth occur only rarely and are always temporary…The magnetic induction, however, occurs at the surface where heat dissipates more readily into the environment. The MRI system fans typically provide sufficient cooling from the increased temperature caused by RF absorption. It is therefore important that the fan is running during high energy sequences.”

  (Marshall et al., Can. J. Neurol. Sci. 2007; 34:11-17)

SAR limits for volume and local transmit coils

IEC 606601-2-33

	Whole body SAR	Partial body SAR	Head SAR	Local SAR (a)		
Body Region →	whole body	exposed body part	head	head	trunk	extremities
Operating Mode ↓	(W/kg)	(W/kg)	(W/kg)	(W/kg)	(W/kg)	(W/kg)
Normal	2	2 - 10 (b)	3.2	10 (c)	10	20
1st Level Controlled	4	4 - 10 (b)	3.2	20 (c)	20	40
2nd Level Controlled	>4	>(4 - 10) (b)	>3.2	>20 (c)	>20	>40
Short duration SAR	The SAR limit over any 10 s period shall not exceed two times the stated values					

Note: Averaging time of 6 minutes.

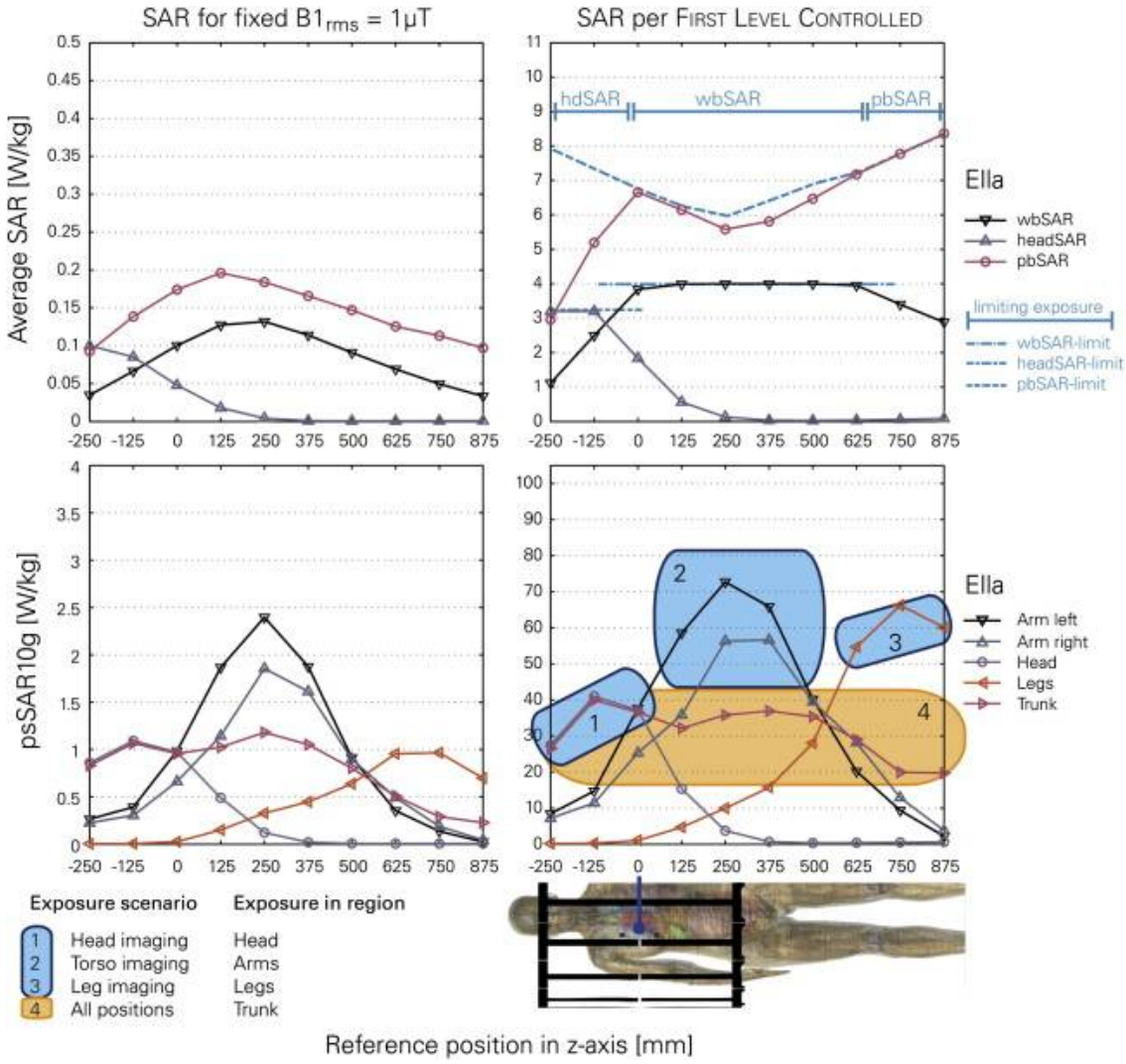
(a) Local SAR is determined over the mass of 10 g.

(b) The limit scales dynamically with the ratio "exposed patient mass / patient mass":

NORMAL OPERATING MODE: Partial body SAR = 10 W/kg – (8 W/kg * exposed patient mass / patient mass)
FIRST LEVEL CONTROLLED OPERATING MODE: Partial body SAR = 10 W/kg – (6 W/kg * exposed patient mass / patient mass)

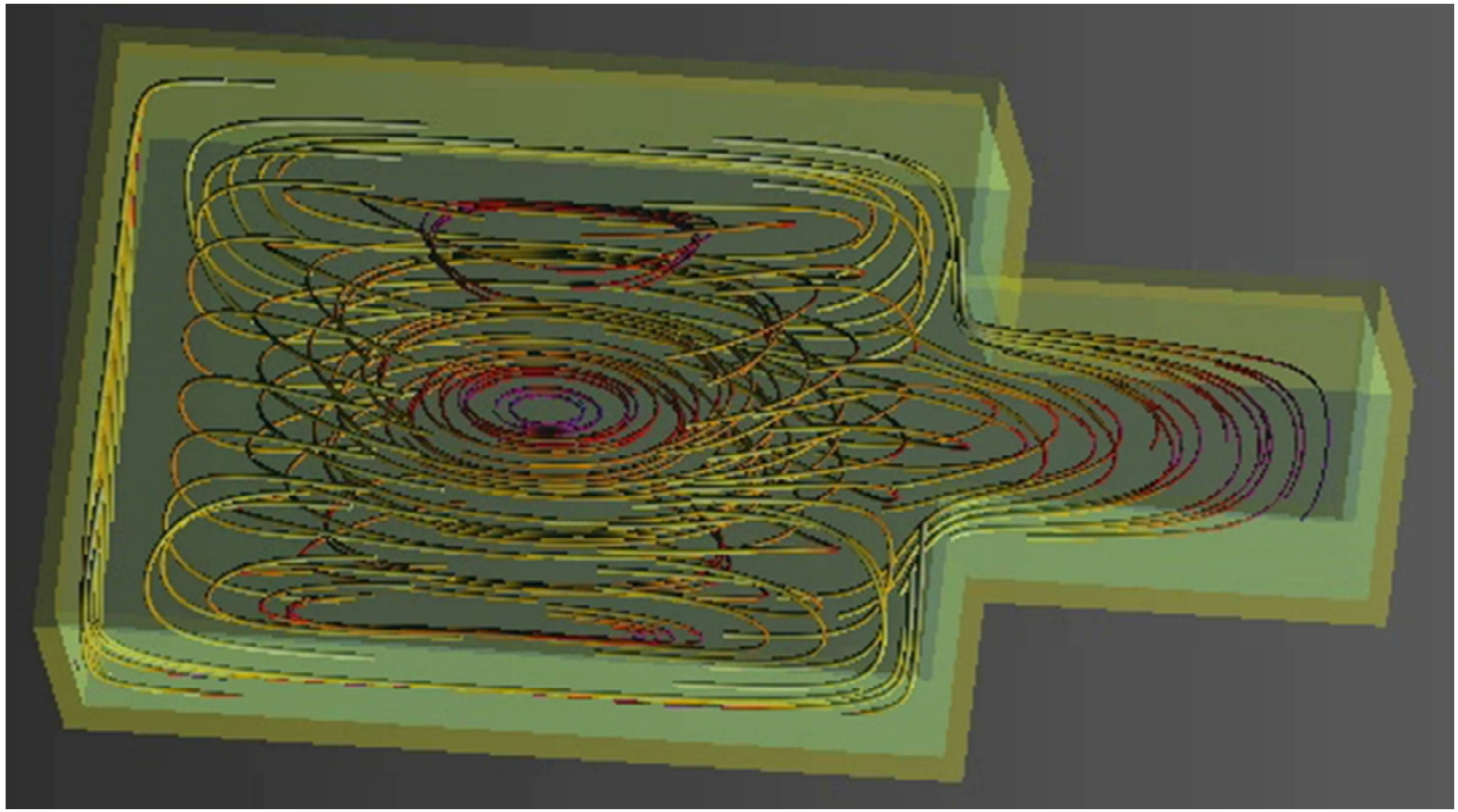
(c) In cases where the orbit is in the field of a small local RF transmit coil, care should be taken to ensure that the temperature rise is limited to 1 °C.

Local thermal load



(Murbach et al., Prog. Biophys. Mol. Biol. 2011; 107:428-433)

Thermal load distribution



Thermal load distribution

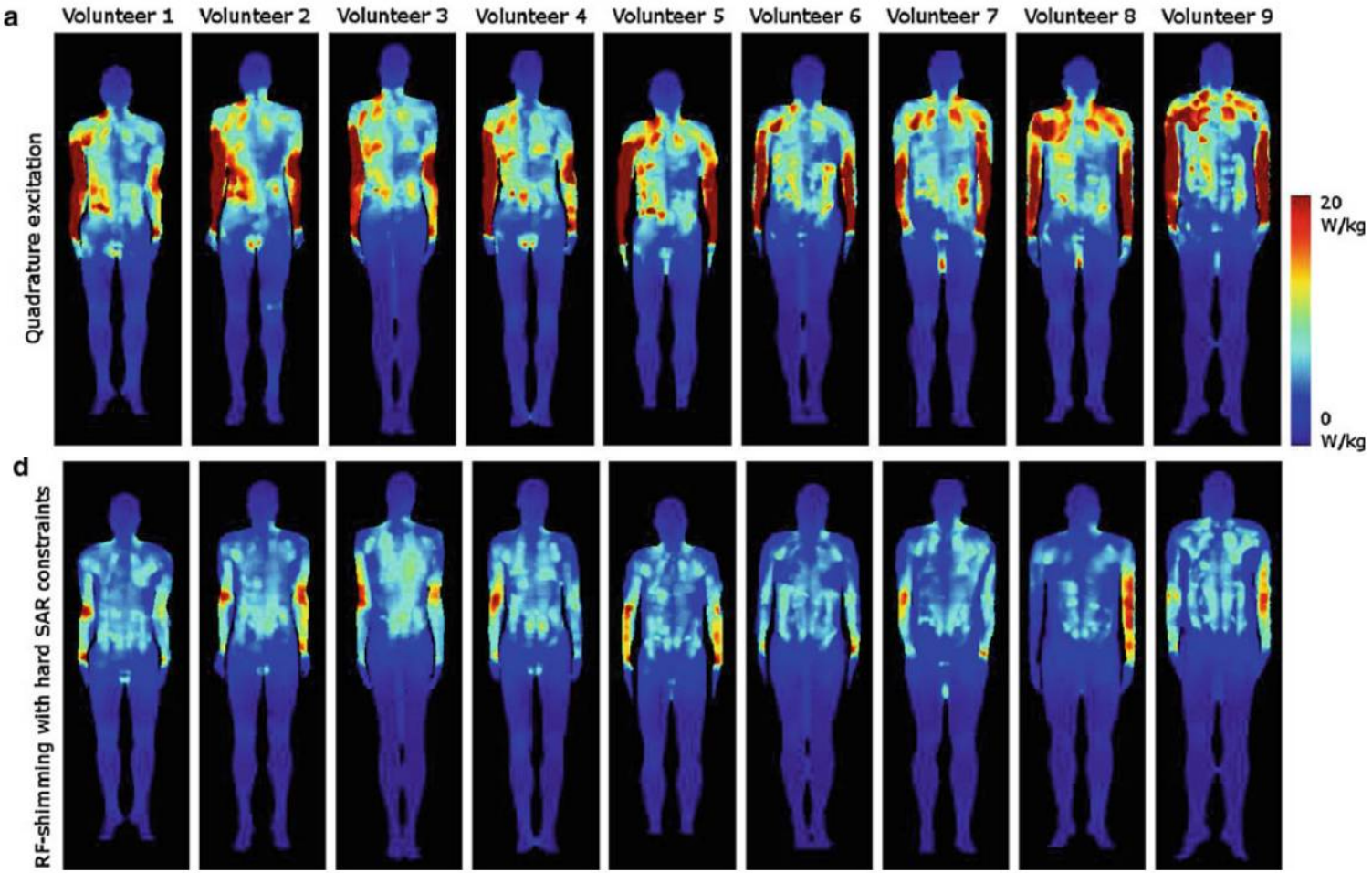


Fig. 3 Maximum-intensity-projections of SAR distributions: **a** quadrature excitation, **b**, **c** RF shimming without SAR constraints, and **d** with SAR constraints. All values were normalized to 2 μT

(Homann et al., Magn. Reson. Mater. Phy. 2012; 25:193–204)

Formulation

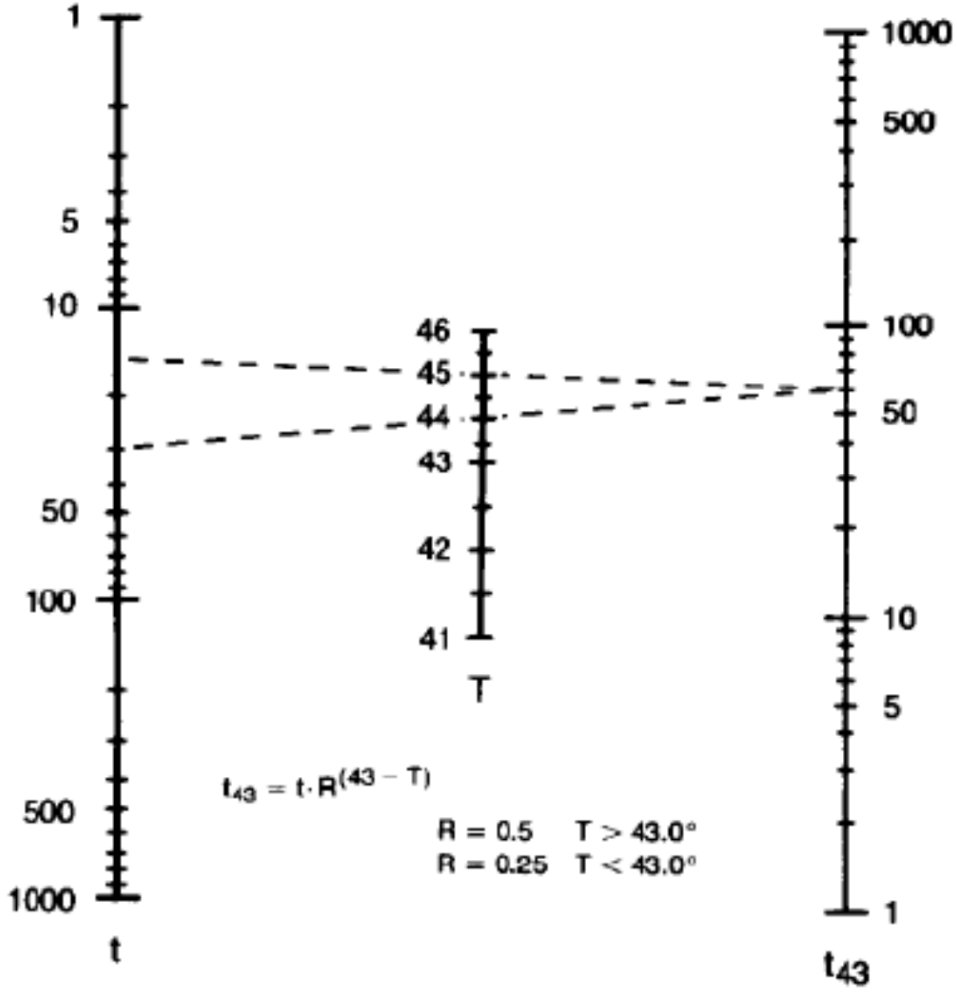
$$CEM_{43} = \sum_{i=1}^{N} [R_{CEM}]^{(43-T_i)} t_i = \int_0^{\tau} [R_{CEM}]^{(43-T)} \mathrm{d}t$$

$R_{CEM} = 0.5$ for temperatures above 43 °C
0.25 for temperatures below the breakpoint
(Chinese hamster ovary (CHO) cell experiments)

R_{CEM} =0.428 for temperature above 43.5 °C
0.233 for temperature below the breakpoint
(Human cells *in vitro*)

(Pearce, Int. J. Hyperthermia 2013; 29:262–280)

Visualization



(Miller and Ziskin, 1989)

Notes on the CEM43 model (1)

The model originates from the work of Svanté Arrhenius

$$R_{CEM} = e^{\frac{-E_a}{RT_1(T_1+1)}}$$

where E_a is the activation energy

Notes on the CEM43 model (1)

Table II. Collected representative Arrhenius kinetic coefficients for heating processes.

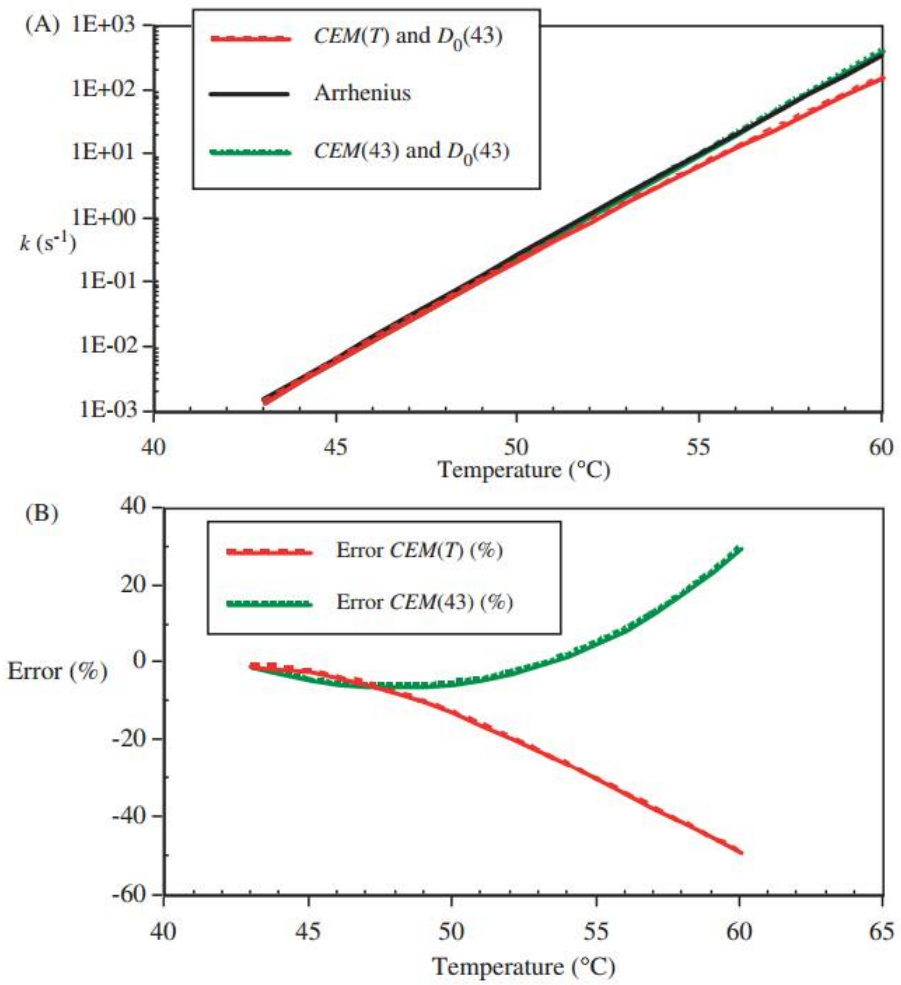
Process	Arrhenius process parameters			Notes
	A (s^{-1})	E_a ($J\,mol^{-1}$)	R_{CEM} 44 C	
Cell death				
Sapareto [20]	9.386×10^{101}	6.344×10^{5}	0.467	Asynch. CHO cells, $T > 43\,°C$
Beckham [80]	6.9×10^{116}	7.3×10^{5}	0.417	Without Hsp70 production
	3.7×10^{157}	9.8×10^{5}	0.309	With Hsp70 production
He [14]	2.53×10^{24}	1.684×10^{5}	0.818	Hu. BPH; EthD-1
	1.79×10^{23}	1.613×10^{5}	0.825	BPH; apoptosis and necrosis
Bhowmick [72]	1.66×10^{91}	5.68×10^{5}	0.506	AT-1 cells <50 °C, 3 h culture
	173.5	1.97×10^{4}	0.977	AT-1 cells >50 °C, 3 h culture
Borrelli [81]	2.984×10^{80}	5.064×10^{5}	0.545	BHK cells
He [62]	4.362×10^{43}	2.875×10^{5}	0.708	SN12 cells, suspended
	3.153×10^{47}	3.149×10^{5}	0.685	SN12 cells, attached
Arrhenius [29]	$**2.02 \times 10^{60}$	3.82×10^{5}	0.635	*B. typhosus*
Arrhenius [29]	$**9.40 \times 10^{29}$	2.02×10^{5}	0.786	*B. paratyphosus* in phenol
Shah [82]	3.495×10^{31}	2.295×10^{5}		HepG2 cells, suspended
Shah [82]	5.396×10^{36}	2.486×10^{5}		HepG2 cells, attached
Erythrocytes				
Lepock [83]	7.6×10^{66}	4.55×10^{5}	0.579	Haemolysis
Arrhenius [29]	$**5.72 \times 10^{40}$	2.66×10^{5}	0.729	Haemolysis
Przybylska [84]	$*1.08 \times 10^{44}$	2.908×10^{5}	0.705	Haemol. normal
	$*3.7 \times 10^{43}$	2.88×10^{5}	0.708	Down's syndrome
Skin burns				
Henriques [4]	3.1×10^{98}	6.28×10^{5}		NOT recommended
Diller [11]	8.82×10^{94}	6.03×10^{5}	0.485	$T \leq 53\,°C$ (same data)
	1.297×10^{31}	2.04×10^{5}		$T > 53\,°C$
Weaver [9]	2.19×10^{124}	7.82×10^{5}	0.391	$T \leq 50\,°C$
	1.82×10^{51}	3.27×10^{5}		$T > 50\,°C$
Brown [66]	1.98×10^{106}	6.67×10^{5}	0.449	Microvascular disruption
Collagen				
Pearce [41]	1.61×10^{45}	3.06×10^{5}		Birefringence loss, rat skin

*The value for A has been estimated from Wright's line, Equation (17a).
**The value for A has been estimated from the He-Bischof line, Equation (17b).
Asynch: Asynchronous; Hu: Human; BPH: Benign Prostatic Hyperplasia; Haemol: Haemolysis.

(Pearce, Int. J. Hyperthermia 2013; 29:262–280)

Notes on the CEM43 model (2)

Figure 11. Comparison of the predicted rates of loss in CHO cell clonogenicity by the CEM and Arrhenius approximations. A) Rate of loss of clonogenicity, k, calculated from the Arrhenius relation (solid line), by using temperature-dependent $R_{CEM}(T)$ and $D_0(43) = 697.7$ s (- - -), and by $R_{CEM}(43) = 0.477$ and $D_0(43) = 697.7$ s (- • - • -). B) The errors in the two CEM approximations (%) referred to the Arrhenius rate (%); temperature-dependent $R_{CEM}(T)$ (- - -) and $R_{CEM} = 0.477$ (- • - • -).



(Pearce, Int. J. Hyperthermia 2013; 29:262–280)

Reviews

- Data until 2010

  Dewhirst et al., Int. J. Hyperthermia 2003; 19:267–294
  Yarmolenko et al., Int. J. Hyperthermia 2011; 26:1–26

- Data for 11 species and threshold thermal doses for damage on 31 different normal tissues after local heat exposure

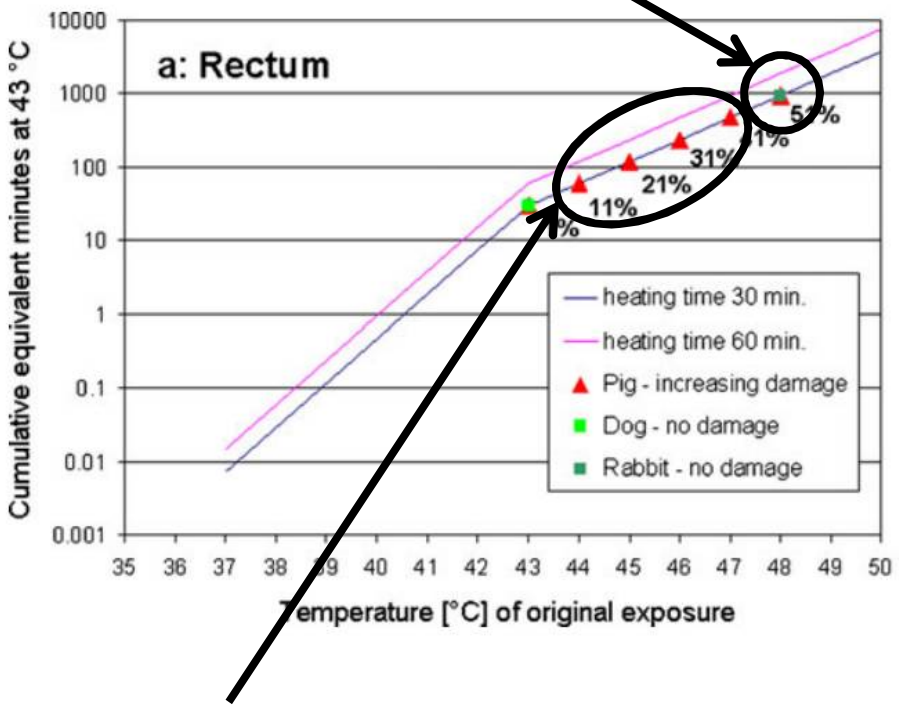
Reviews

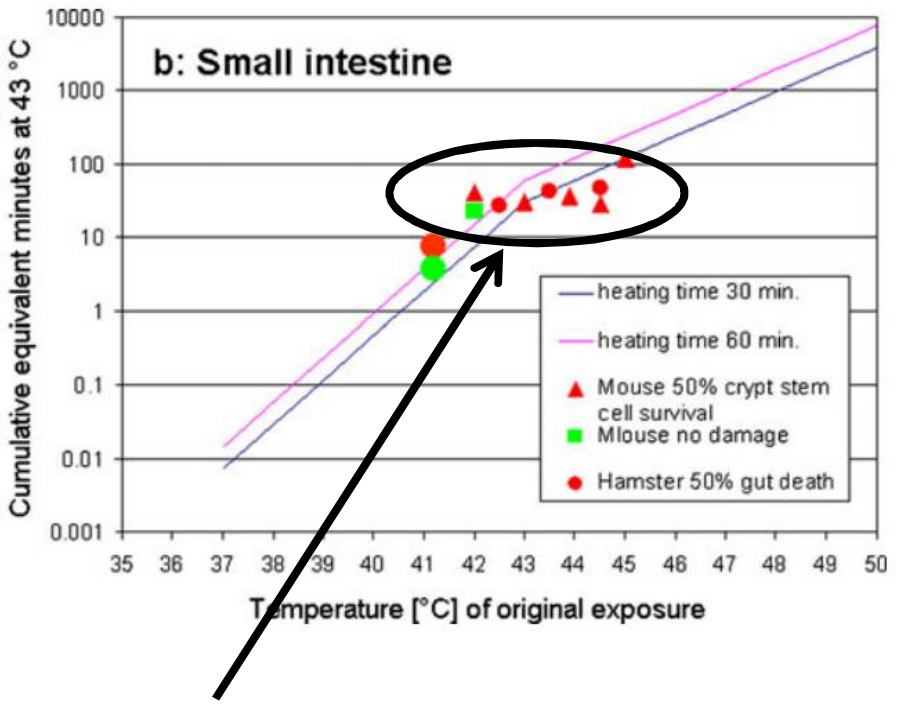
Table 1 Tissue types for which thermal thresholds for damage to normal tissue was assessed

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		
Thymus									X		
Urethra			X								

Examples

Large interspecies variability





Increasing CEM43 dose → increasing damage

Constant CEM43 dose → constant damage

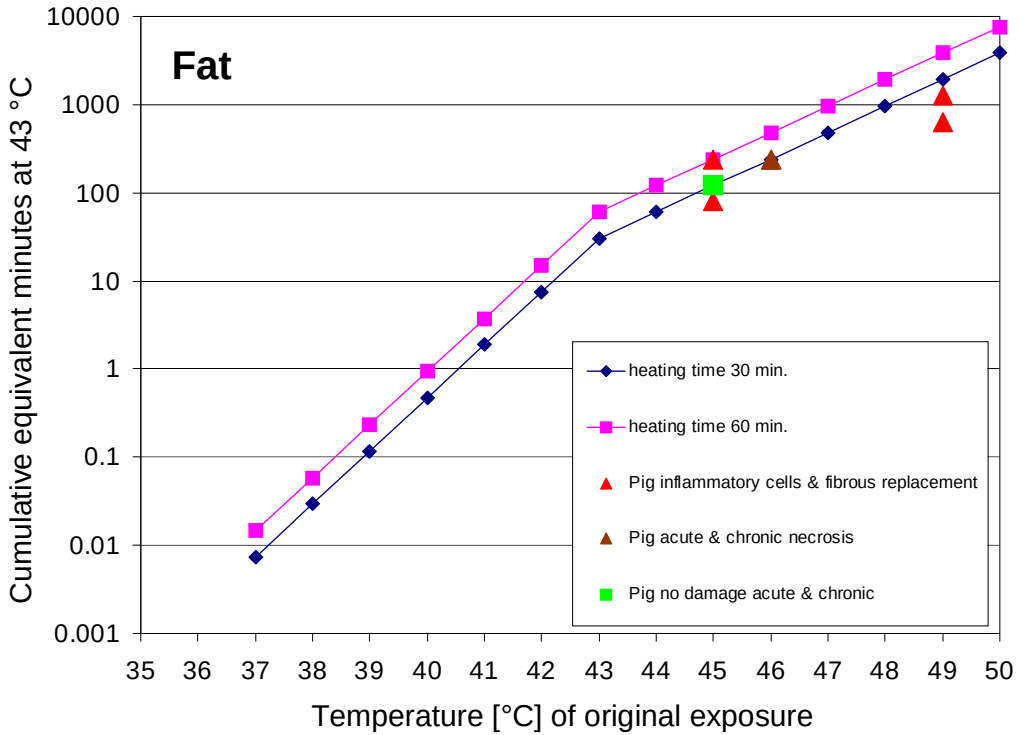
(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Skin

- In the first review significant acute and chronic damage to the skin was reported above 41 min CEM43, followed by complete necrosis above 288 min CEM43.
- The latest data on humans as reported elsewhere are consistent with these thresholds.
- In addition to acute and significant skin erythema, the sensitivity of the skin to heat and pressure stimuli was also altered in a reversible manner at 112 min CEM43. Full recovery was noted within 4 h after exposure.

(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

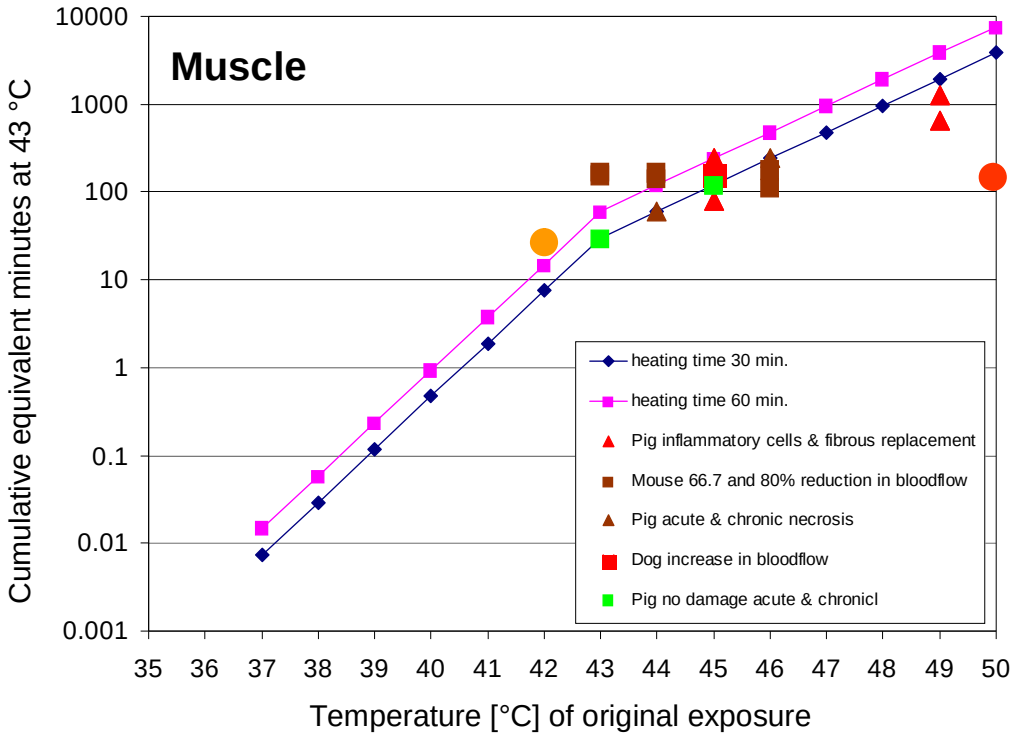
Fat



Franco et al (2010) reported on the thermal sensitivity of human SAT. They found delayed adipocyte cellular death occurring 9 days after exposure to 15 min at 43–45°C (15–60 min CEM43); the delay in tissue damage appearance was also noted elsewhere.

(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

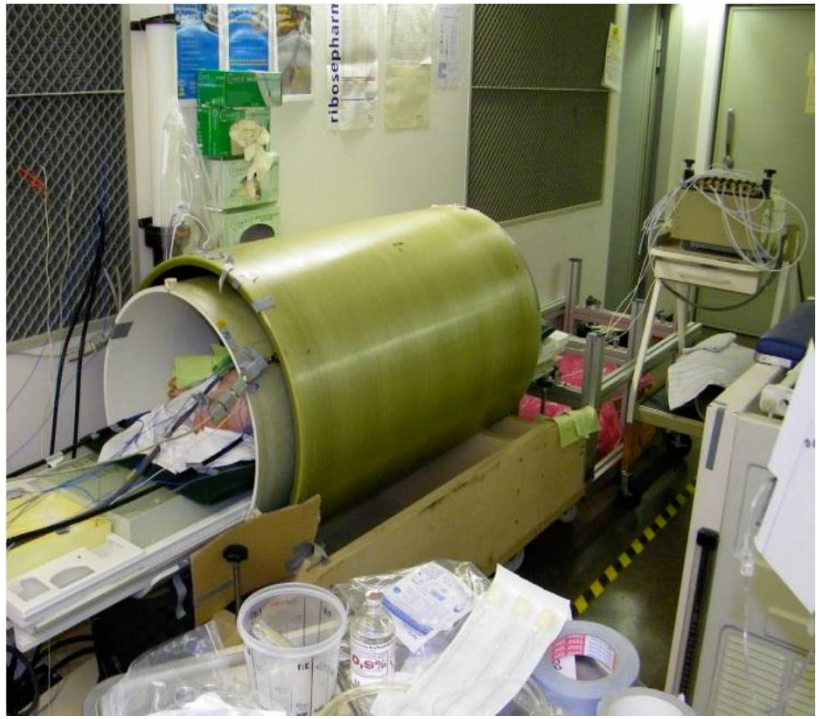
Muscle

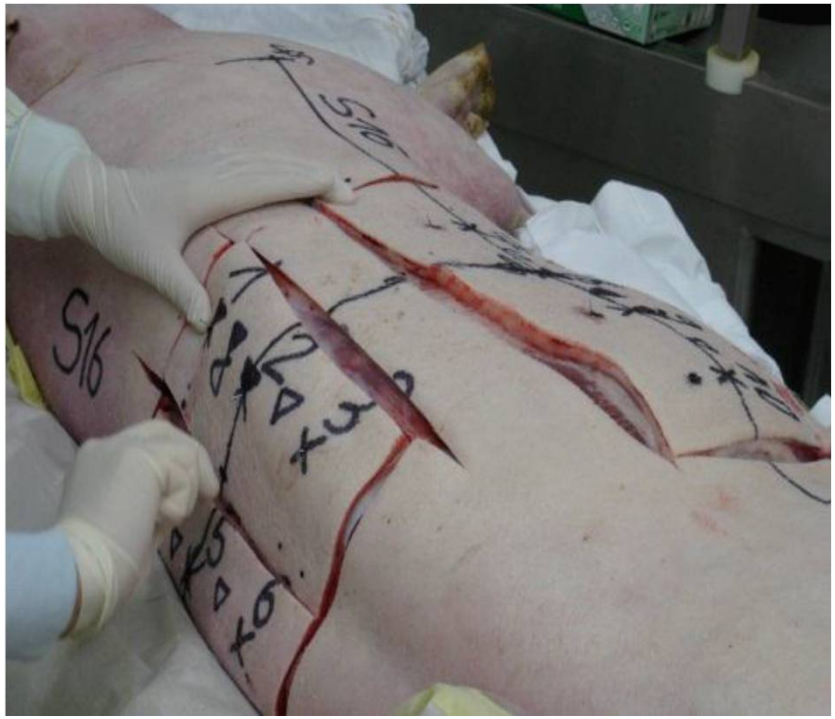


For muscle tissue, acute but minor thermal damage is reported to occur from 41 min CEM43 with the damage (haemorrhage and necrosis) becoming significant and chronic above 80 min CEM43.

(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Muscle





Range for thermal damage in muscle 67 – 235 min CEM43

(Nadobny et al., Int. J. Hyperthermia 2015; early view

Bone

- Thermal damage in bone tissue was mainly studied out of interest in high-speed drilling and medical devices implantation.
- In the second review the experimental data obtained with the use of a titanium thermal chamber implanted in a rabbit tibia approximated the thermal damage threshold for bone at 16 min CEM43.

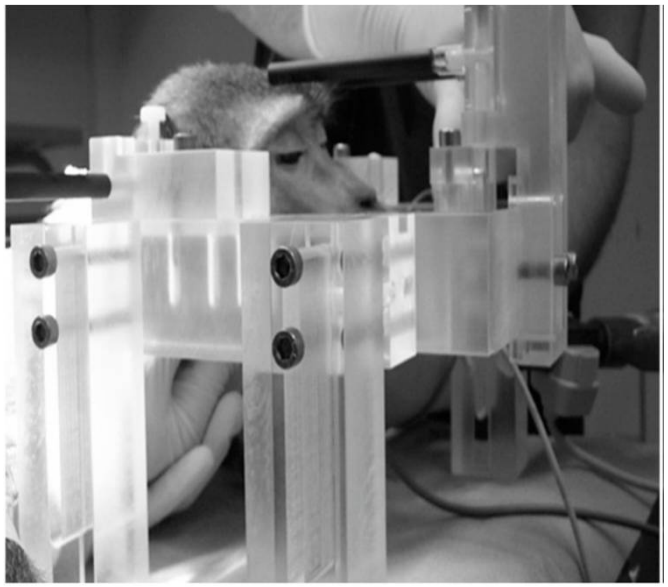
(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

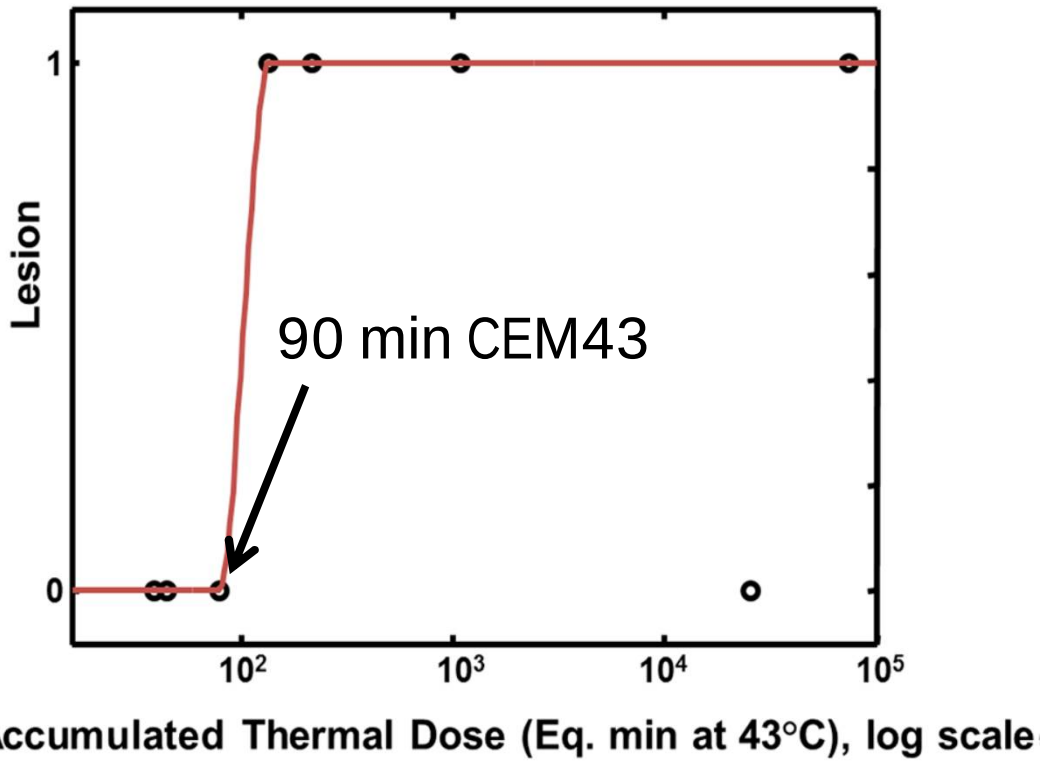
Peripheral tissues - Summary

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

(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

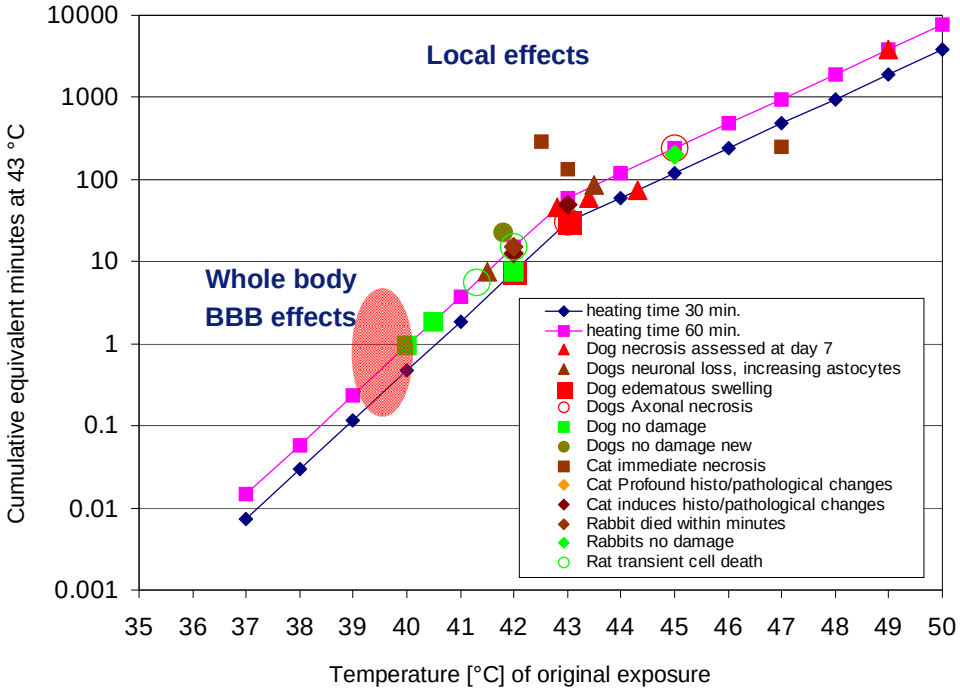
Brain





(Marquet et al., J. Acoust. Soc. Am. 2013; 134(2):1632-1639)

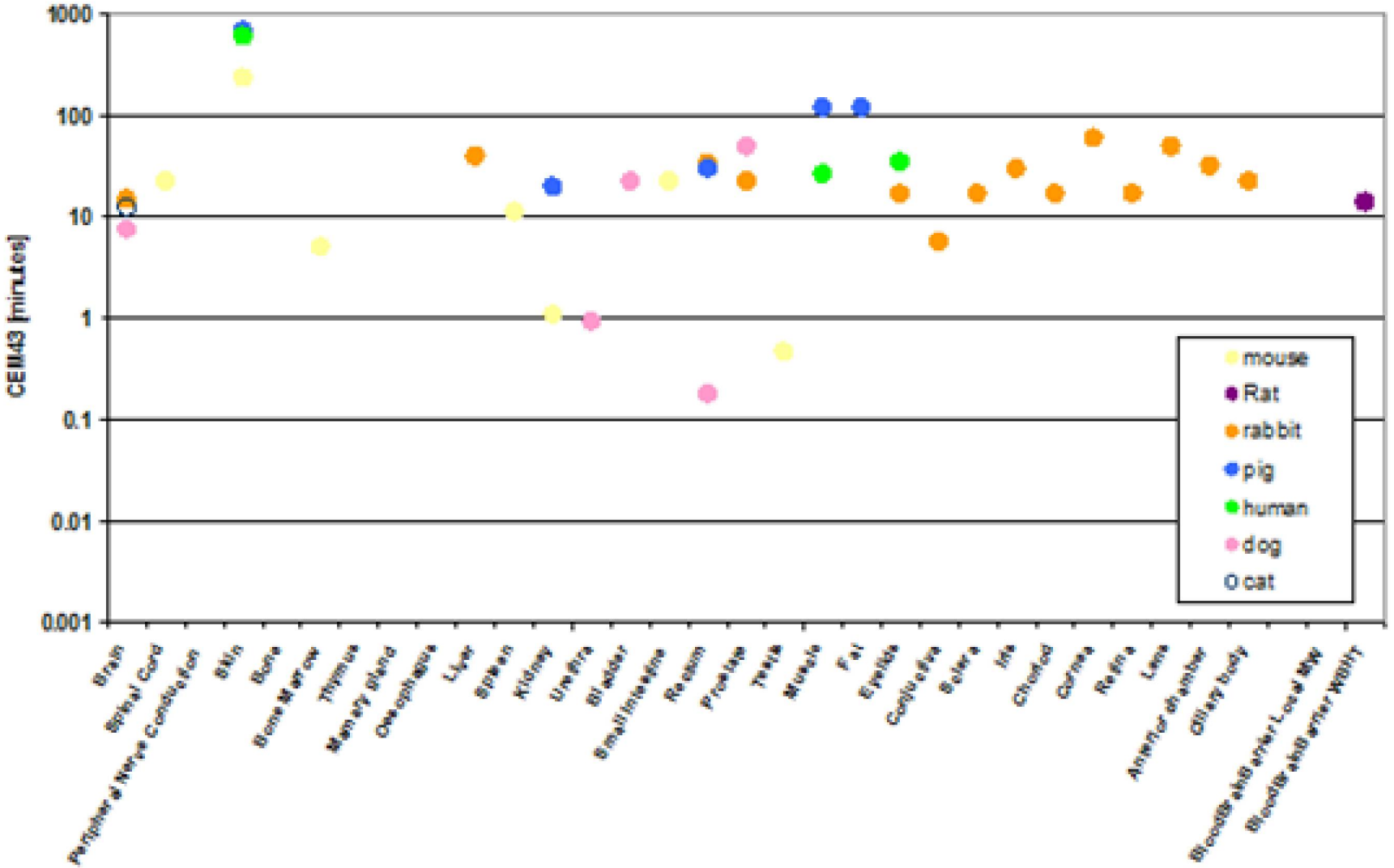
Brain



The importance of whole body heating is illustrated here, because effects are reported for lower CEM43°C doses.

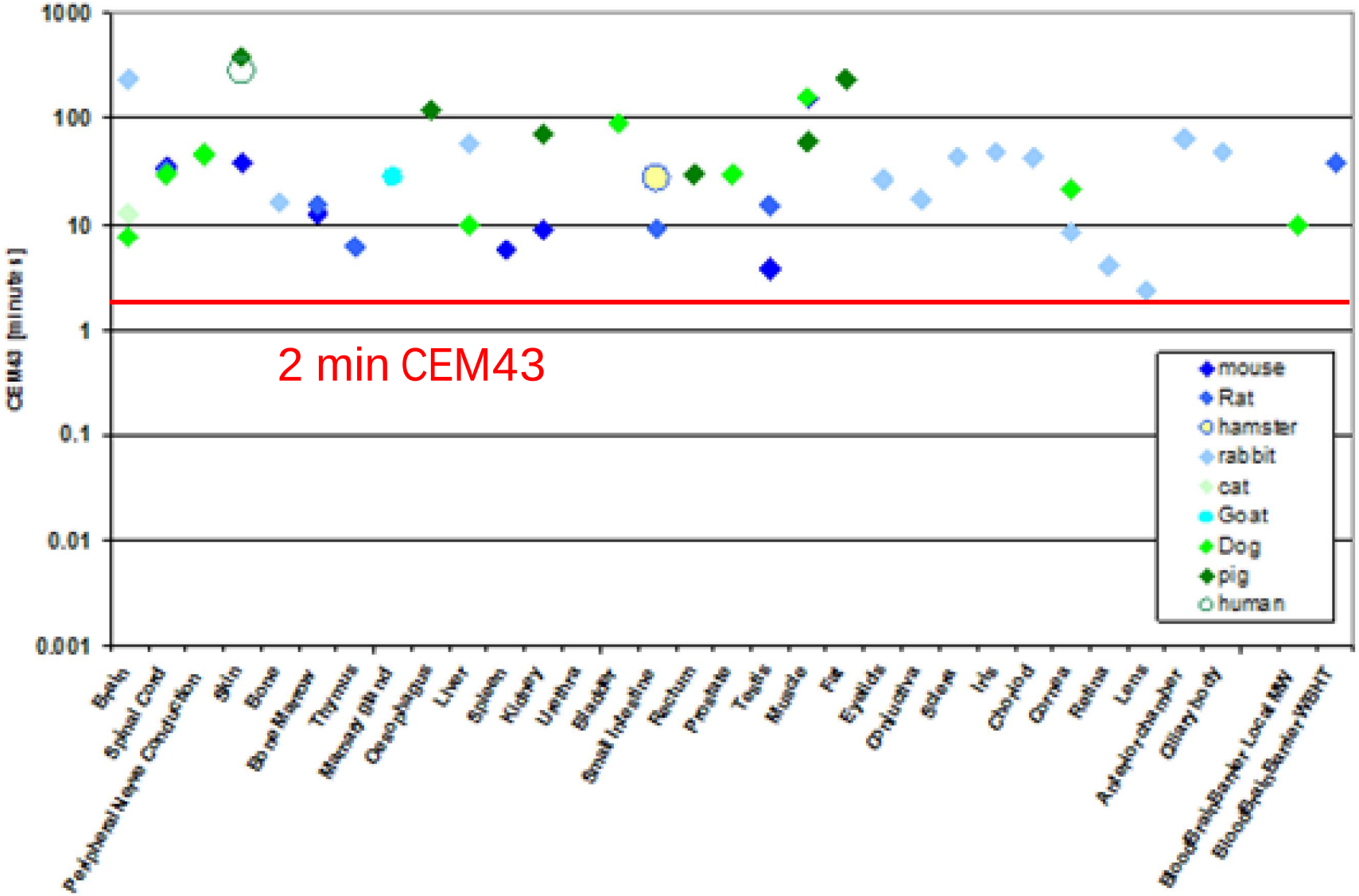
(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Highest CEM43°C - No observed thermal damage (all species)



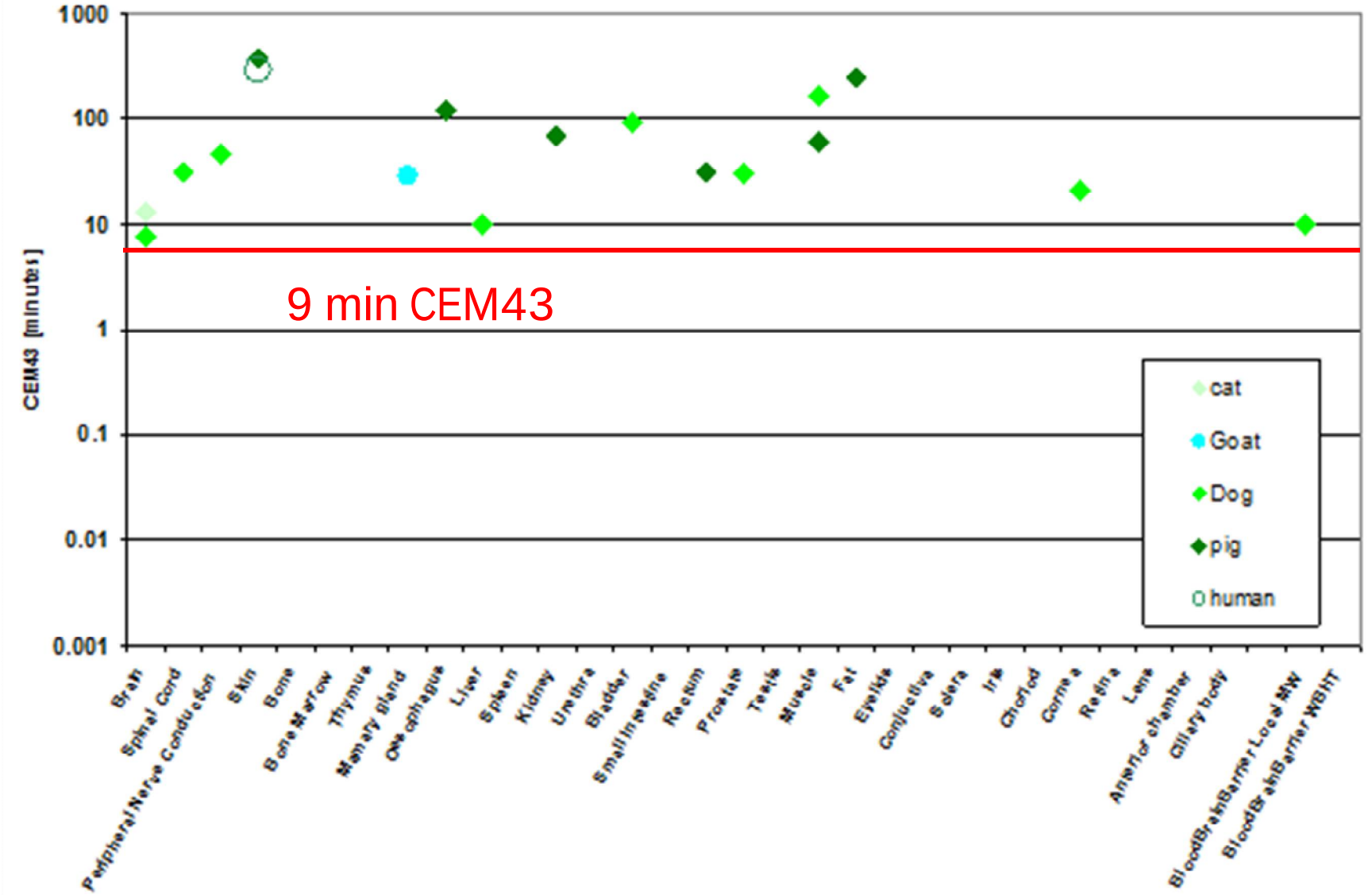
(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Lowest CEM43°C - Observed thermal damage (all species)



(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Lowest CEM43°C - Observed thermal damage (excl. rodents)



(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

Proposed guidelines

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)

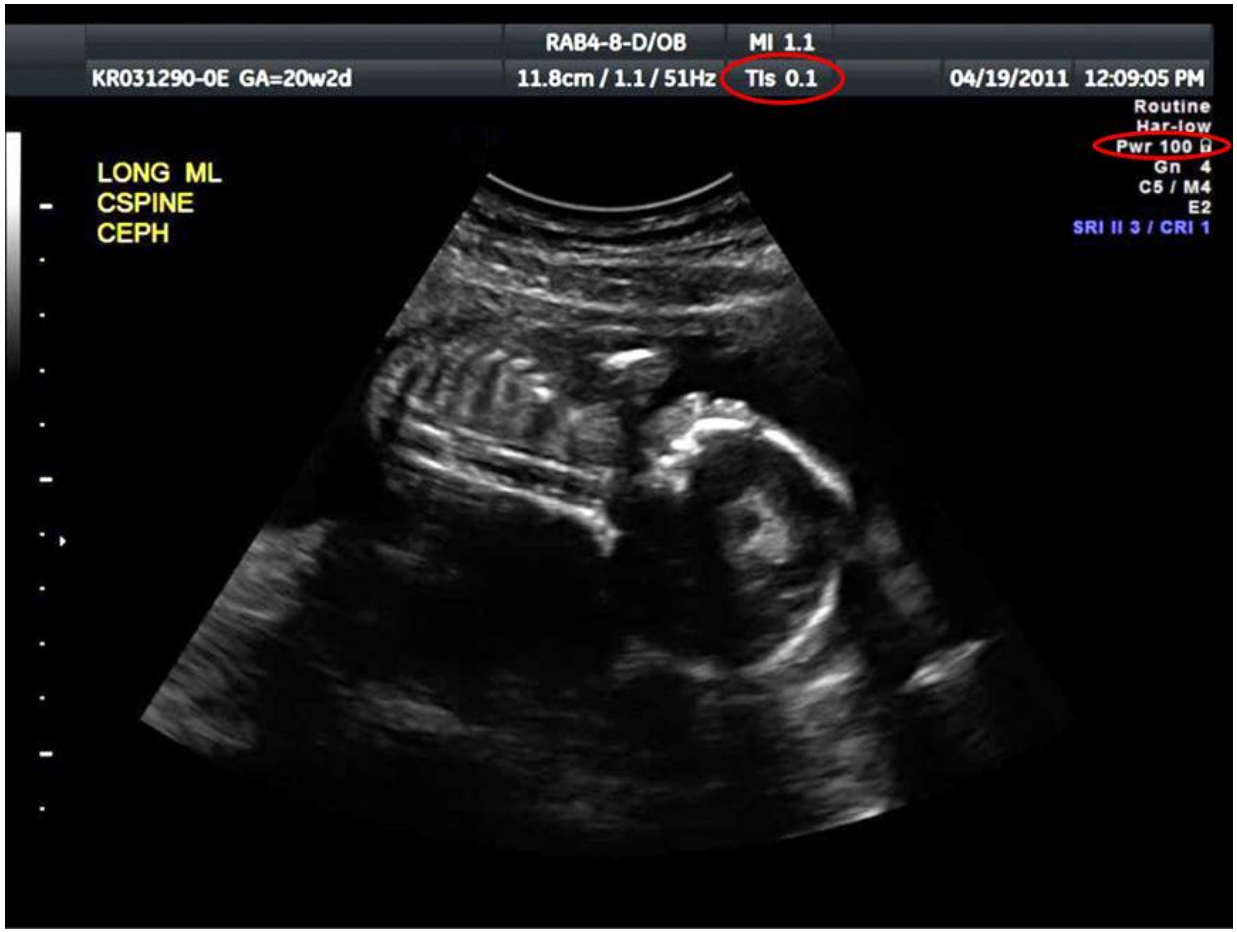
Controlled conditions	A medical doctor or a dedicated specifically trained person is available to respond instantly and adequately to heat-induced physiological stress and patient complaints during MR
Compromised thermoregulation	All persons with impaired systemic thermoregulation (elderly, young children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

(Van Rhoon et al., European Radiology 2013; 23(8):2215-2227)

The approach in US imaging: Thermal Index

$$TI = \frac{W_p}{W_{deg}}$$

Thermal index in soft tissue, bone and skull.



American Institute of Ultrasound in Medicine (2008):
1 CEM43°C for exposure > 5s
10 CEM43°C for longer exposures

Cautions when translating thresholds to guidelines

- The CEM43 model is not always valid for very low or very high temperatures.
- The value of *R* is still under discussion.
- The definition of “thermal damage” may change between therapy (cancer treatment) and safety.
- The exposure to RF during MRI is transient and can have a complex time pattern. However, effects like thermotolerance, or potential thermosensitization by physical (e.g., radiotherapy treatment) or chemical (e.g., medical drugs) agents are not incorporated in the model.
- The guidelines derive from thresholds of all tissues and not the mostly exposed peripheral tissues.

Cautions when translating thresholds to guidelines

- How good are animal models for extrapolation to humans?
  Humans are not mice...

Thank you!

“Trouble with mice is you always kill 'em.”

John Steinbeck, *Of mice and men*