Principles of Thermal Dosimetry Thermal Thresholds for Tissue Damage and Neurocognitive Function An Update

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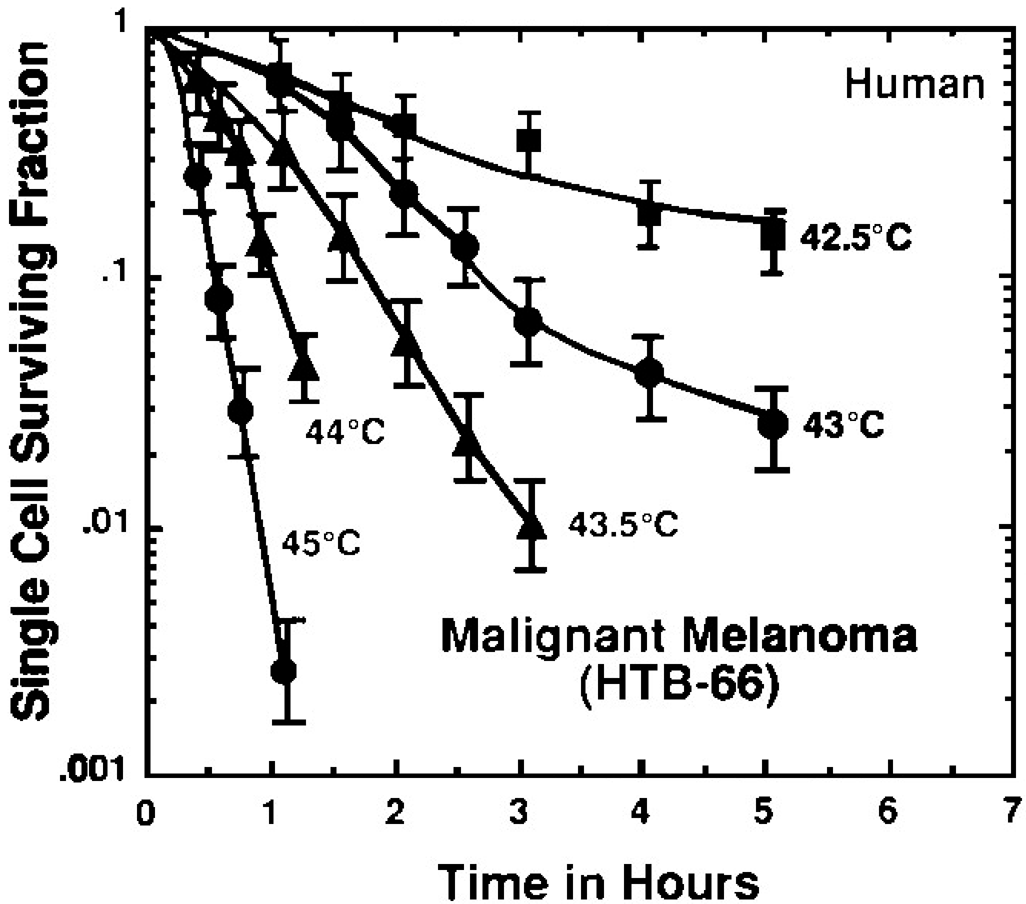
Eruditio et Religio

Objectives

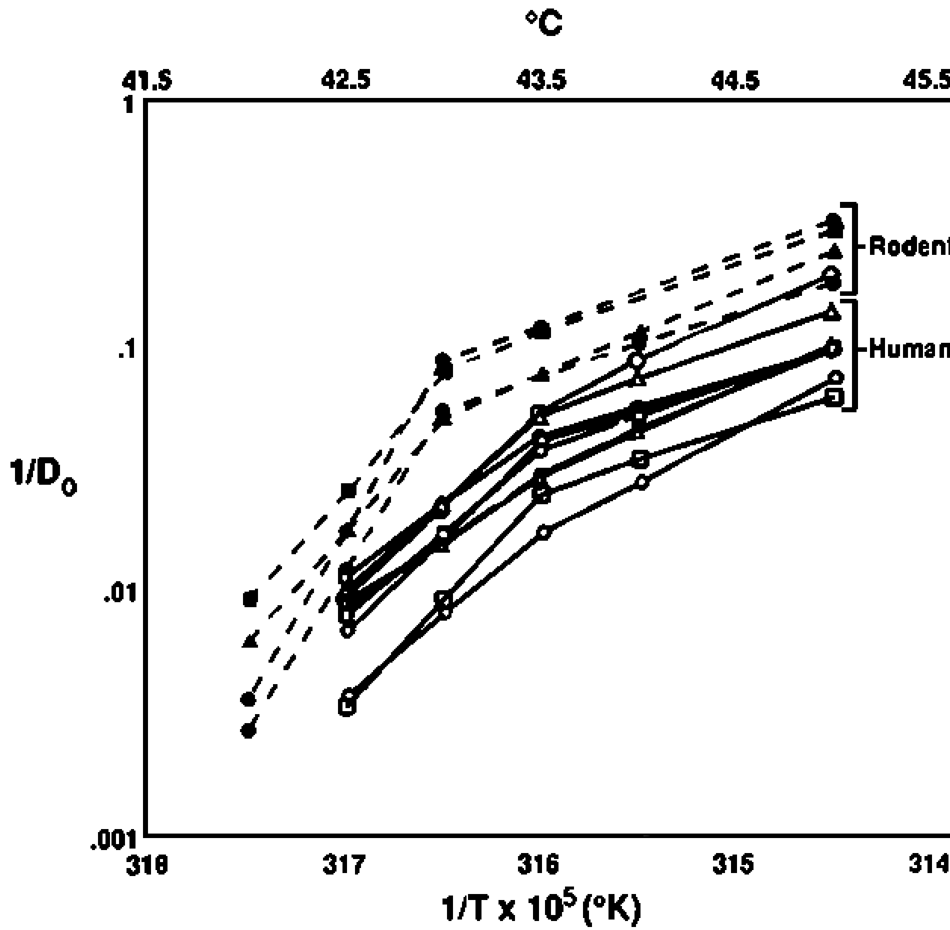
- Summary of prior work
- New review
  - Review criteria
  - Highlights of new tissue information
    - Brain
    - Testis
    - Other
  - Challenges
- Recommendations for future research

HT survival of Human Cells



From Roizin-Towle

Characteristics of Arrhenius plot - rodent vs. human cells

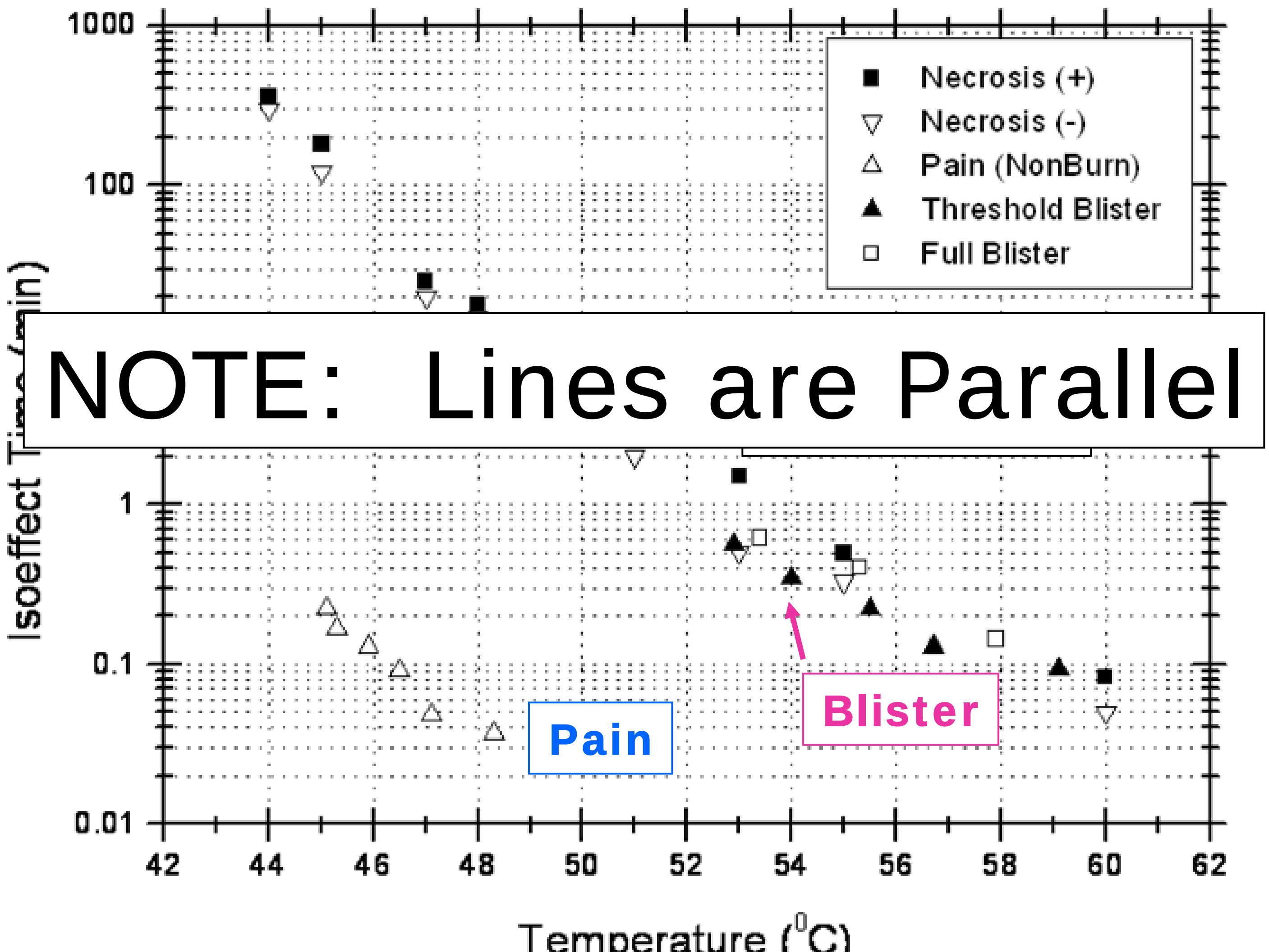


Basis for thermal isoeffect dose

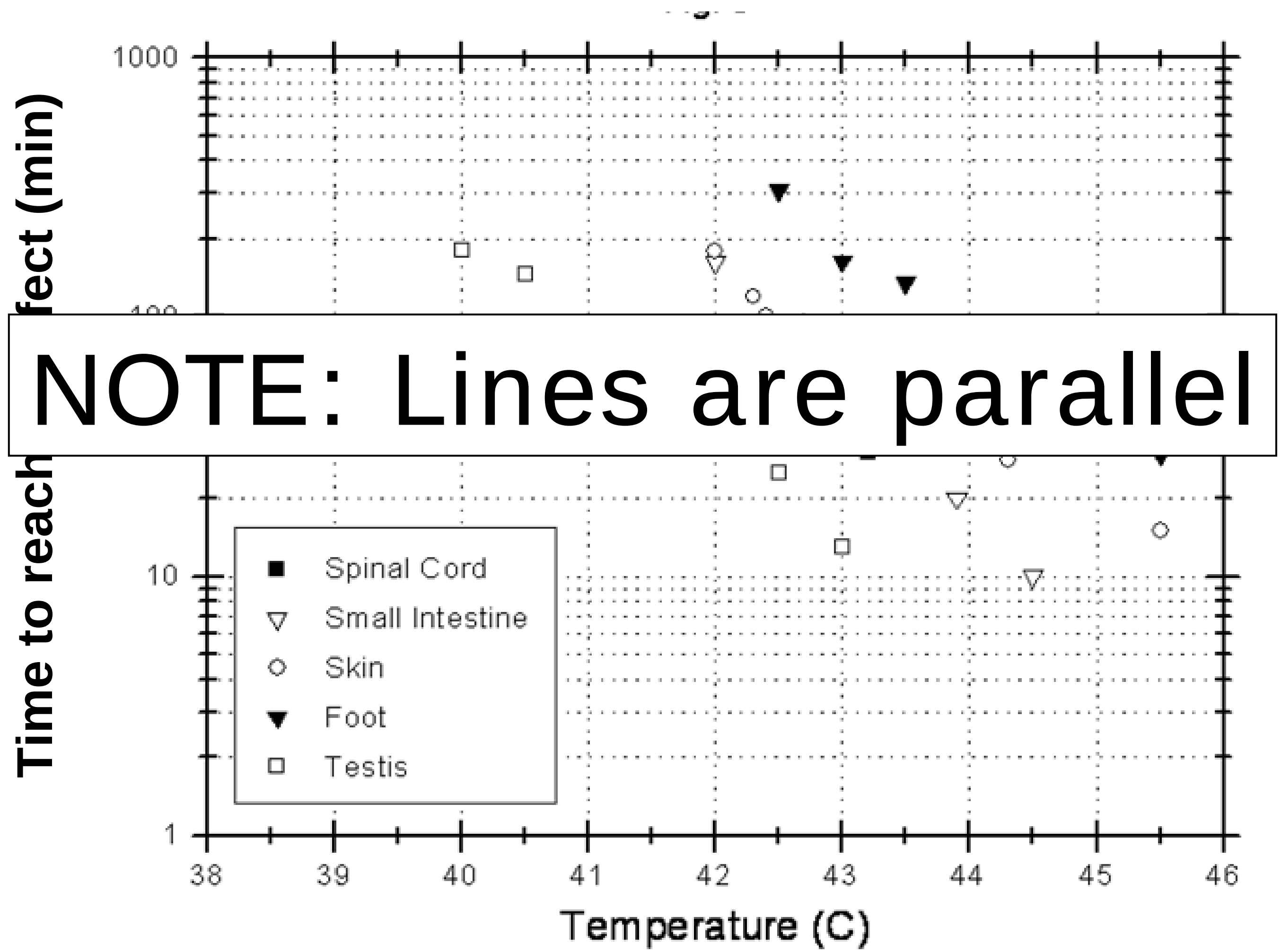
$$CEM\ 43°C = \Delta t R^{(43-T_{avg})}$$

Advantages	Challenges
Convert time-temp combination to standard Threshold for thermal damage can be established Can establish t-T isoeffect line to avoid thermal damage	Arrhenius plot slopes may vary by - Tissue - Endpoint - Species Need to have at least 1 time-temp comb for threshold - Endpoint dependent

Isoeffect lines for pain vs. thermal damage – human skin



Comparison of time-temperature thresholds across tissue types for mouse



Arrhenius slope characteristics for mouse vs. human cells

		R value	
Species	Breakpoint	<Breakpoint	>Breakpoint
Mouse	43.0°C	0.25	0.5
Man	43.5°C	0.13	0.72

NOTE: Because of the variety of species studied, however, we used characteristics of mouse cells for CEM 43°C calculations. This provides a more conservative estimate of thresholds for damage

Search Criteria

463 papers identified

Table 1. Keywords used in database searches.		
hyperthermia damage	laser burn	skin
heat damage	heat	tendon
high temperature damage	soft tissue	muscle
heat exposure damage	adipose tissue	epicardium
hyperthermia injury	liver	bone
heat injury	esophagus	spine
high temperature injury	intestine	fat
heat exposure injury	testis/testes	foot
high temperature tissue destruction	prostate	tail
high temperature tissue damage	bladder	spleen
heat tissue destruction	urethra	bone marrow
heat temperature tissue damage	kidney	brain
heat inflammation	eye	spinal cord
heat exposure damage	cornea	blood vessels
heat exposure injury	retina	gonads
CNS/Central Nervous	lens	ovaries/ovary
blood brain barrier	iris	gonads
peripheral nerve system	eyelids	burn injury

Recursive searches were also done, looking for papers
That cited our 2003 IJH review

117 Papers included in current analysis

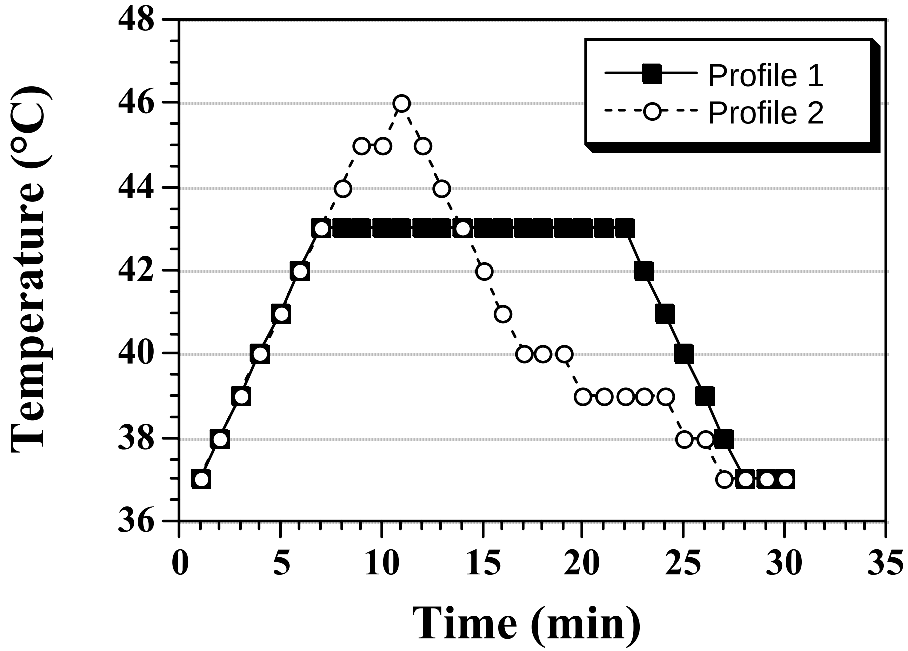
Table 4. Papers included in this review categorized by tissue type and heating method.

Tissue (All Species)	Local Heating	Whole Body Heating
Bladder	1	
Bone	1	
Bone Marrow		1
Brain	3	8
Ear		2
Esophagus	1	
Eye (Cornea, Retina, Eyelids)	4	
Kidney	4	
Liver	6	1
Mammary Gland	1	
Muscle	8	1
Prostate	6	
Skin	4	
Small Intestine		2
Testes	8	3
Thymus		2

Reasons for Exclusion from Analysis

- Lack of adequate thermal data
  - 131 papers
    - Temperature not measured adequately
    - Temperature not measured at site of damage assessment
- Laser data with doses that grossly exceeded threshold for damage
- Modeling papers without data
- Reviews
- Experiments done on excised tissues

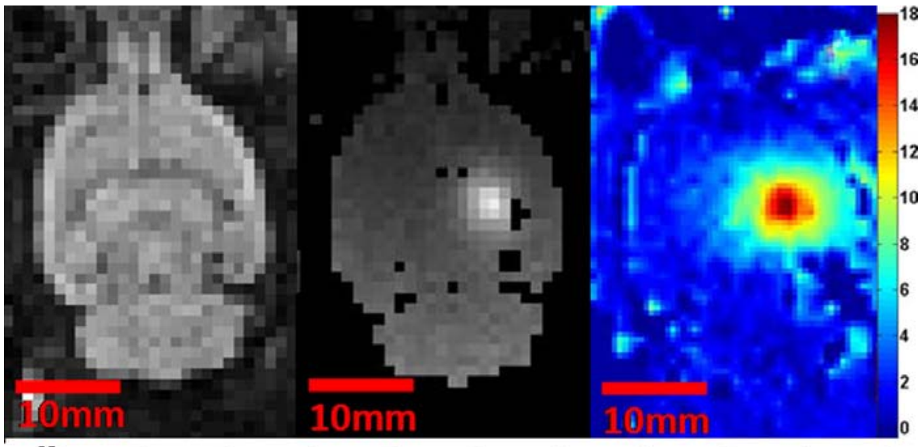
Accurate calculation of CEM 43°C requires full thermal history – At location of damage assessment



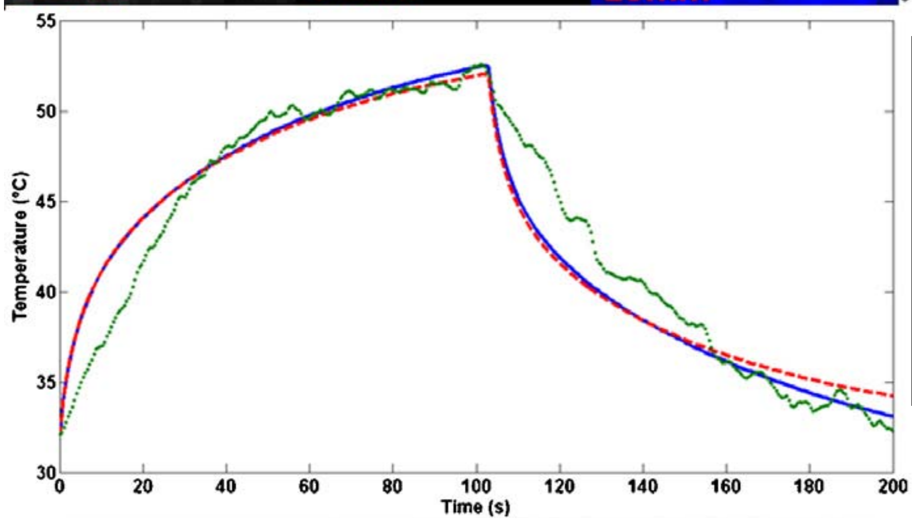
Which profile has the highest CEM 43°C?

Profile 1 = 17 CEM 43°C
Profile 2 = 27 CEM 43°C

Full thermal data can be obtained from MRI, but are most often not reported



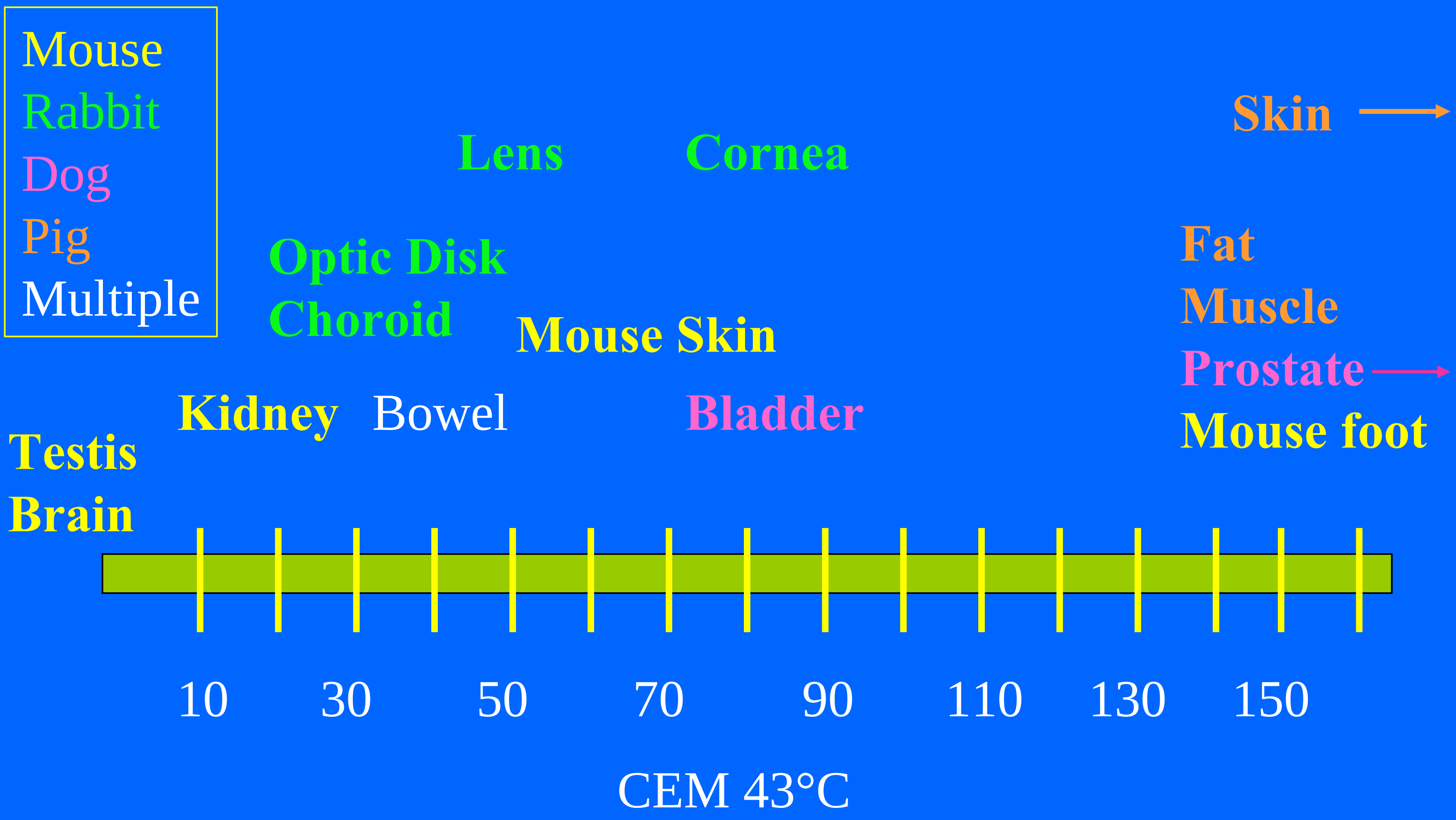
Example-
Rat brain thermal ablation
With HIFU



Beautiful data, but
only temperature data are in the center of the ablation zone –
We need data at the margin and outside the ablation zone to set thresholds

Larrat et. al. Phys Med Biol, 2010

Relative Ranking of thermal sensitivities



Example of new data compared with original review

For the most part, thresholds for thermal damage for organs did Not change from original review

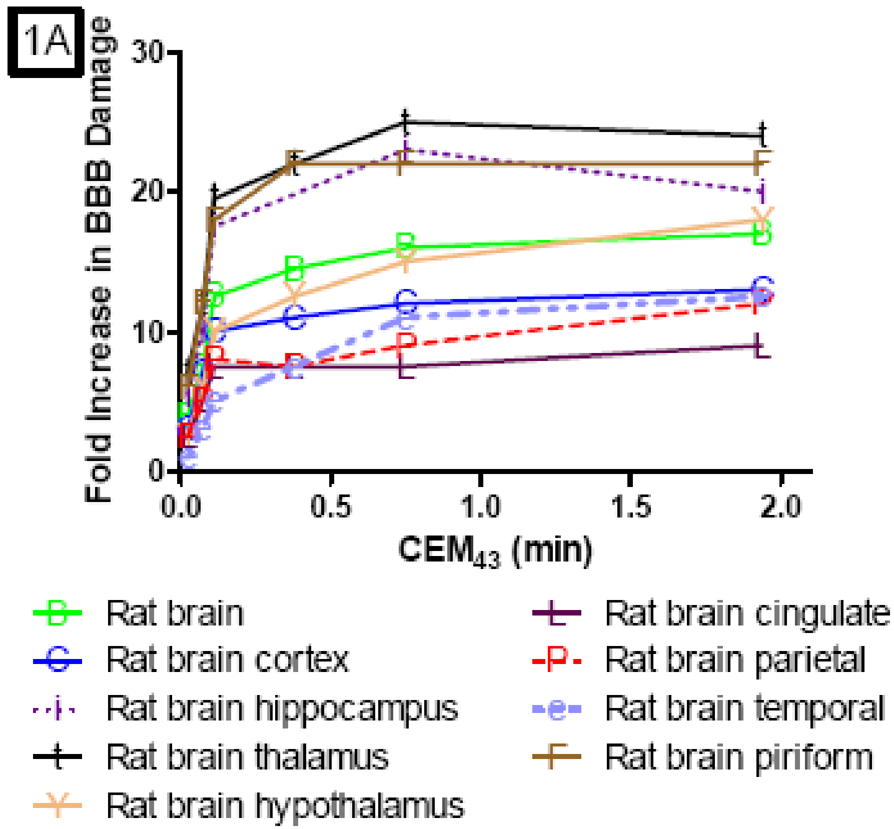
Table 5. Comparison of data compiled in the earlier review with the newer literature.

		Type and degree change						
		Acute		Chronic				
CEM_{43} (min)	**Tissue type**	**Minor**	**Significant**	**Minor**	**Significant**	**Species**		**Reference**
0-20	BBB		H*/F, H/F			Rat/Rabbit	Dog	[4-7]
	Bone				G	Rat		[8]
	Bone Marrow	F/H	H*			Rat	Mouse	[9]
	Brain	H/H	H	H		Rat/Rabbit	Dog/cat	[5, 7, 9-11]
	Cornea		F			Human		[12]
	Esophagus		H			Pig		[13]
	Kidney	H	F			Rabbit	Rabbit	[14]
	Muscle		F*/H			Human/Pig		[15, 16]
	Retina			G/H			Rabbit	
	Testis	F, F/H	H, H/F/G	F, H	F, F	Mouse	Mouse	[17-20]
	Testis		G, H*			Rat		[11, 21]
	Thymus		H*			Rat		[9]
	Small Intestine		F/H			Rat		[22]
	Nerve		F			Rat		[23-25]

H = histology
F = Function
G = Gross assessment

NOTE: Very few assessments made of chronic consequences of thermal damage

Both local and whole body heating were examined in this review – in prior review we did local only



Data from Sharma et al., indicate very low threshold for change in BBB permeability – but threshold is likely to be much higher for local heating- Estimates from Hoopes in dog – 10-20 CEM 43°C

Sub-regions of brain vary in thermal sensitivity – age and time of assessment are important

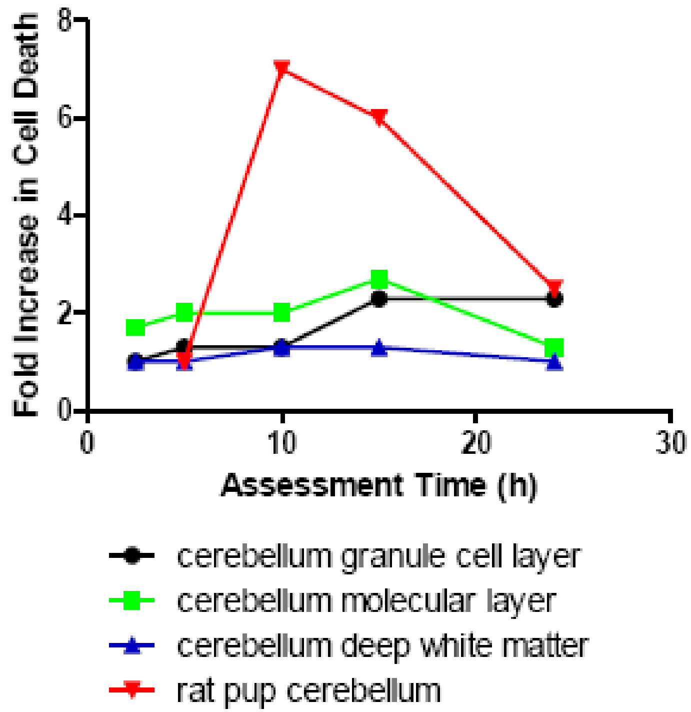
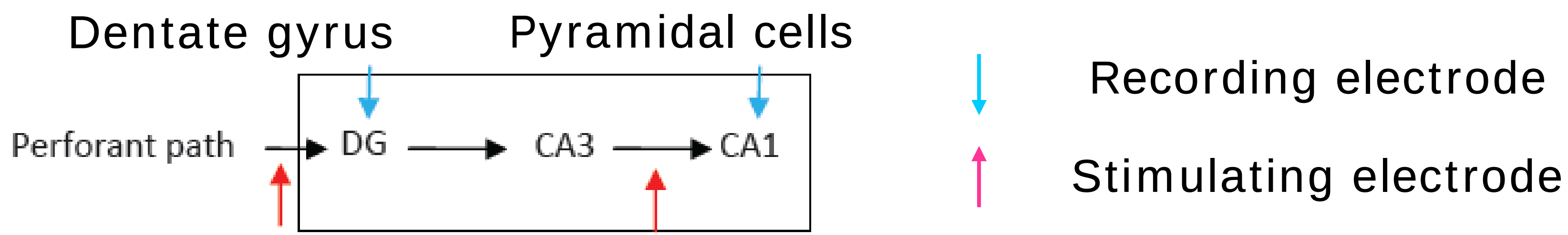
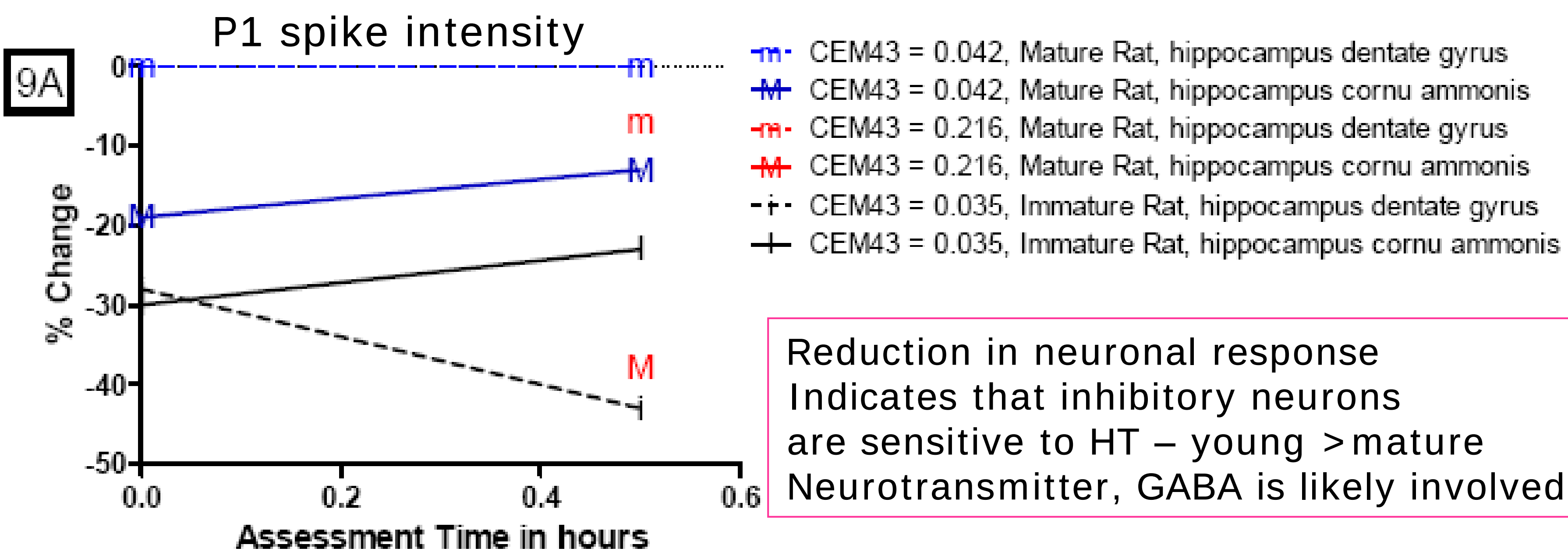


Figure 4. Assessment of cell death in several brain regions at multiple assessment times after whole body hyperthermia treatment in rats at a CEM_{43} of 5.9 minutes [11].

Effects of HT on hippocampal neuronal excitability – has implications regarding seizure activity

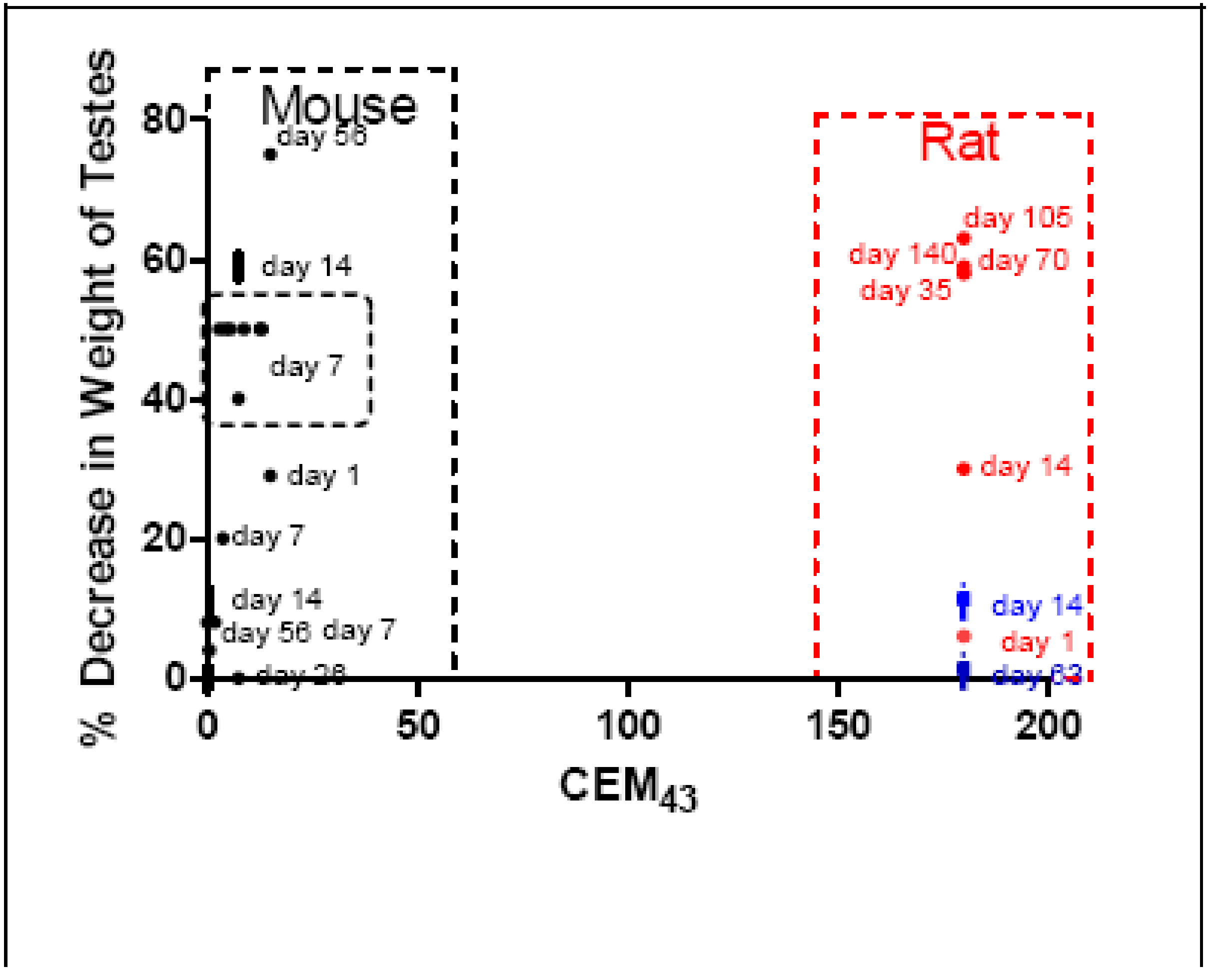


Inhibitory neurons function to dampen excitatory response

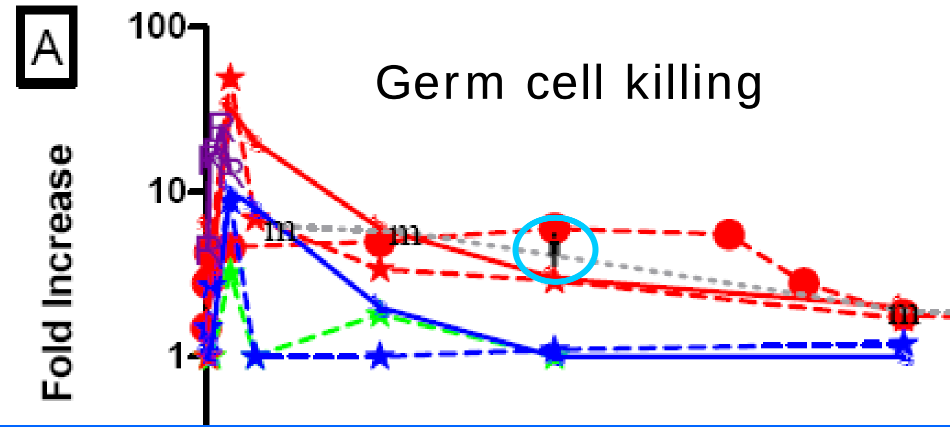


Reduction in neuronal response
Indicates that inhibitory neurons
are sensitive to HT – young >mature
Neurotransmitter, GABA is likely involved

Effects of HT on testis – mouse data may not accurately reflect sensitivity of human



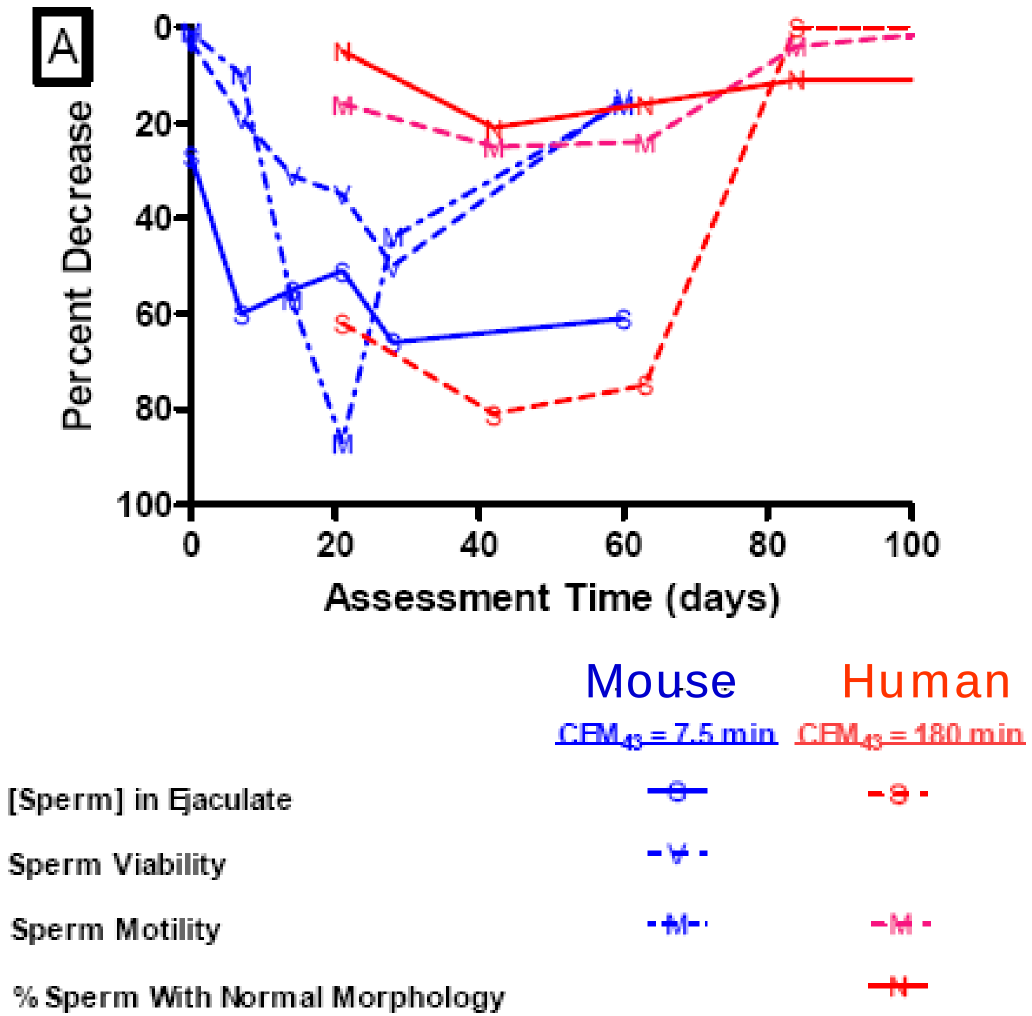
Effect of HT in testis dependent upon time after exposure



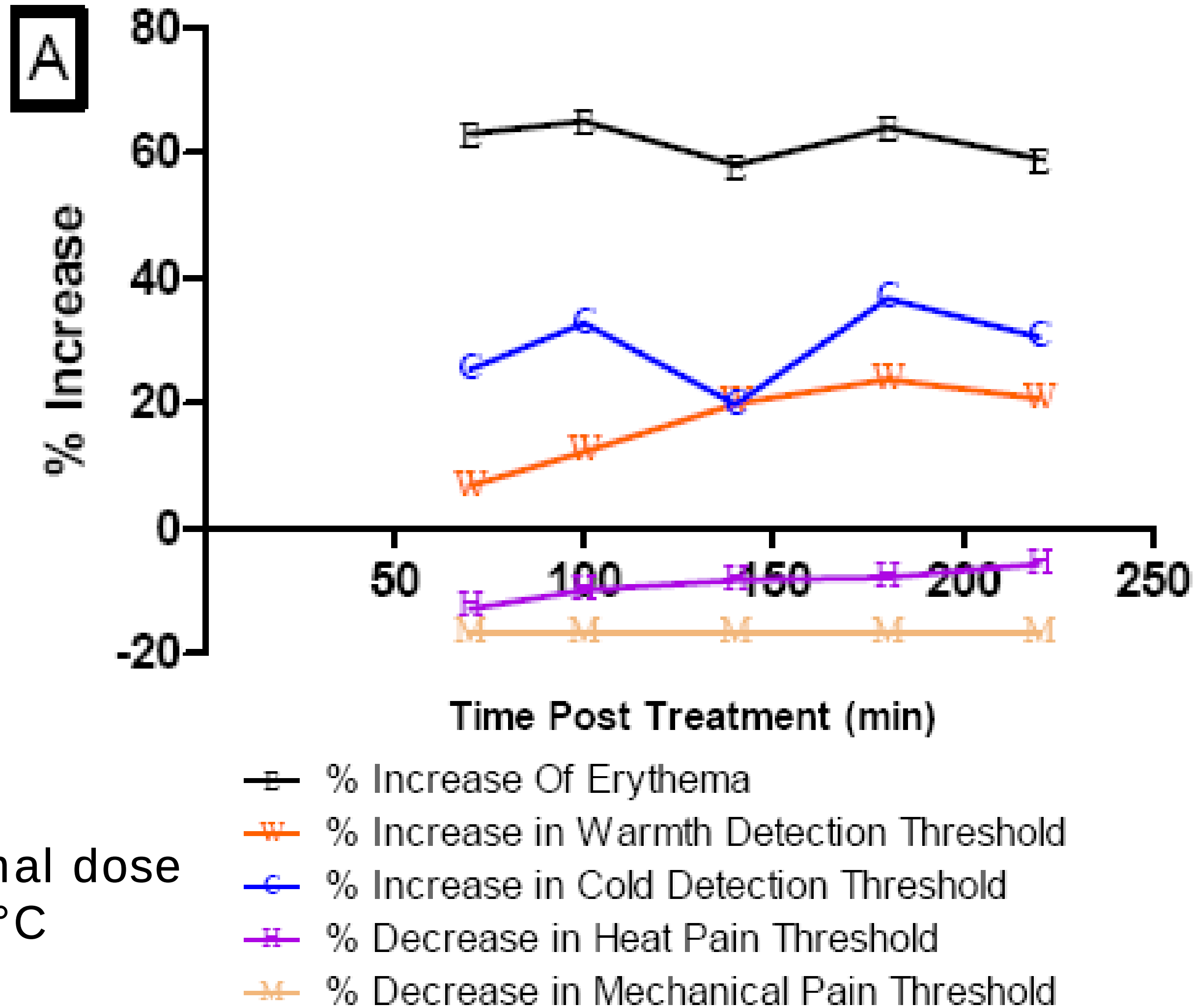
Note:
A threshold for sperm damage is not yet determined particularly for humans. Monkey and human data are similar. So, this could be done using monkeys

		0.03	0.05	5.9	7.5	60	180
Mouse	Testes germ cell death [17]				---●---		
	Testes germ cell death [19]	--★--	--★--		--★--		
	Overall cell death In testes [18]		--§--		--§--		
Rat	Cell death In seminiferous tubules [11]			R			
Monkey	Testes germ cell death [31]					··m··	
Human	Testes Germ Cell Death [36]						i

HT effects on sperm function show recovery over time



Skin- Thresholds for pain are dependent on prior thermal exposure



Initial thermal dose
112 CEM43°C

Assessment of thermal damage using Damage Index

Derived from Arrhenius relationship, assumes that damage occurs with 1st order Kinetics

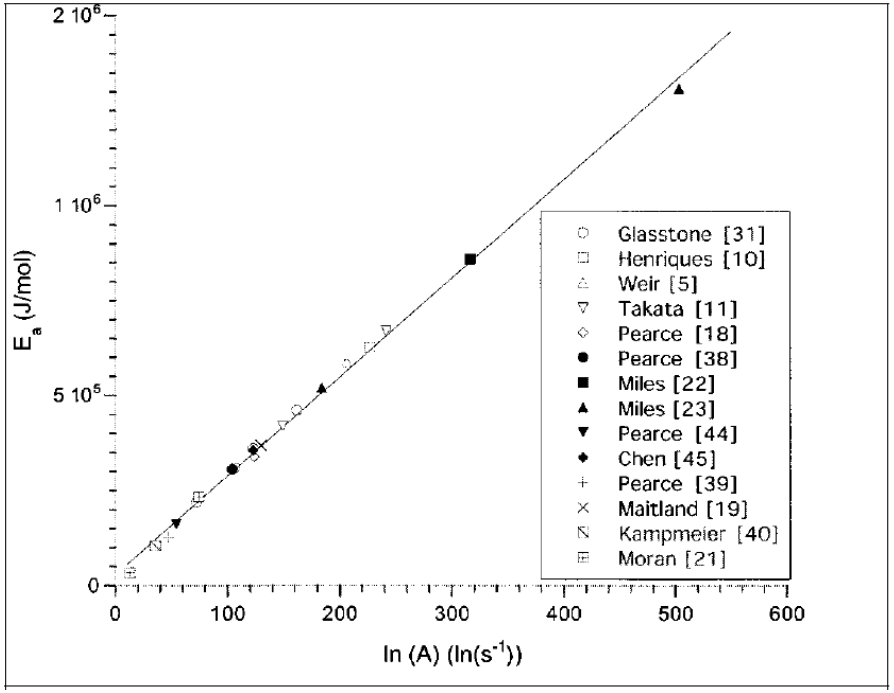
$$Rate\ \ of\ \ damage = {dC(t)}/{dt} = K \cdot C, \quad K = A \cdot \exp\left(\frac{-E_a}{RT(t)}\right)$$

C= % undamaged tissue
K = 1st order reaction constant
t= time
A= frequency factor 1/s
Ea = activation energy (J/mole)
R = universal gas constant
T= time dependent function of temperature, K

Assessment of thermal damage using damage index

$$Damage \quad Index = \Omega = \ln\left(\frac{C(0)}{C(\tau)}\right) = \int_0^{\tau} A \cdot \exp\left(\frac{-E_a}{RT(t)}\right) dt$$

Ω = Ratio of damage at time 0 vs. time (τ)



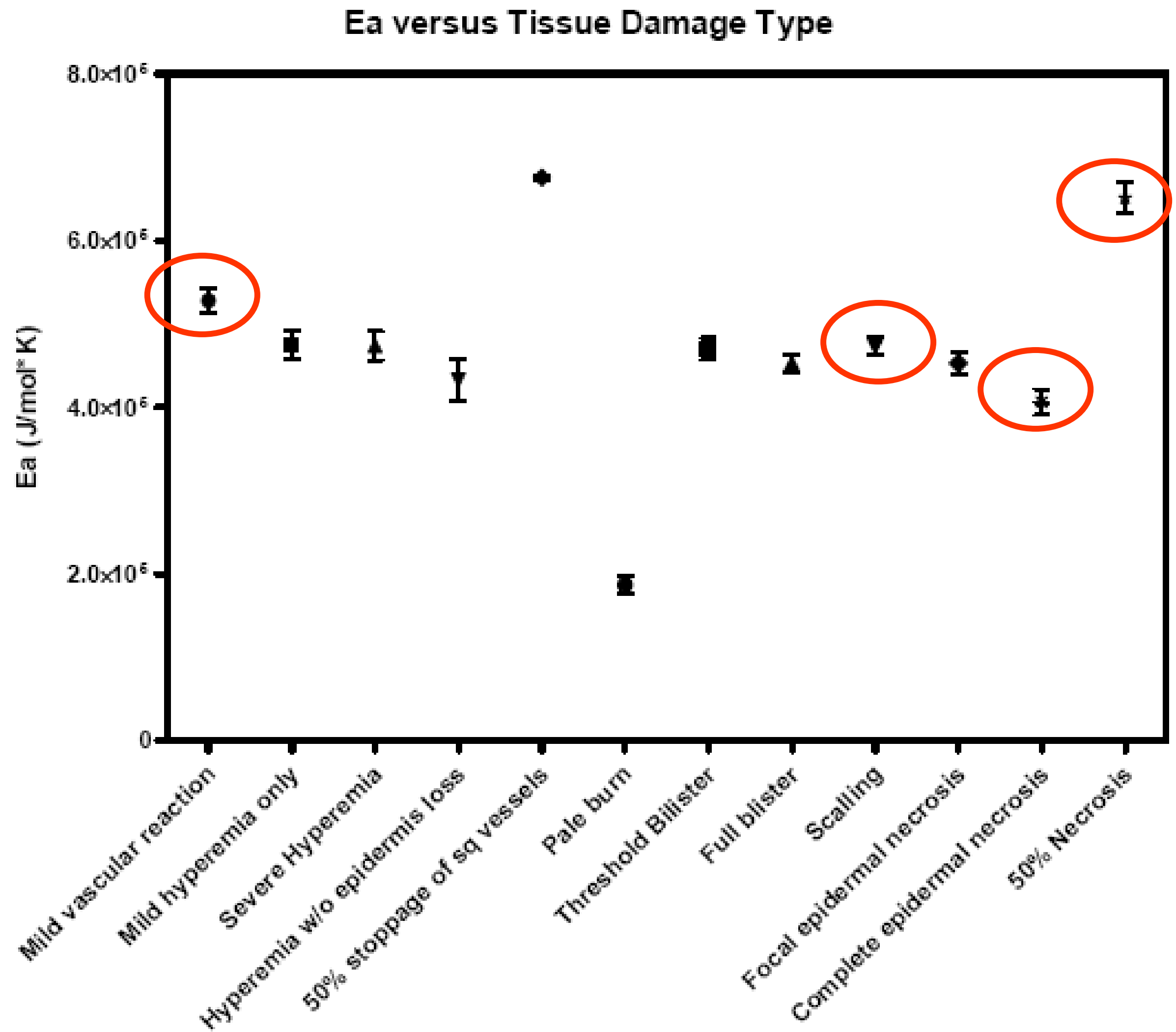
For complete necrosis or collagen Denaturation there is a log-linear relationship between Ea and A(ln (s^{-1}) across many tissues

Wright, N.T., *On a relationship between the Arrhenius parameters from thermal damage studies.* J Biomech Eng, 2003. 125(2): p. 300-4.

Requirements to establish damage index as common platform to compare across tissues

- Need to establish a range of time-temperature combinations that yield the same isoeffect
  - Such data are difficult to find
- Need to see a predictable relationship between Ea and severity of damage

Severity of skin damage does not exhibit intuitive relationship with Ea.

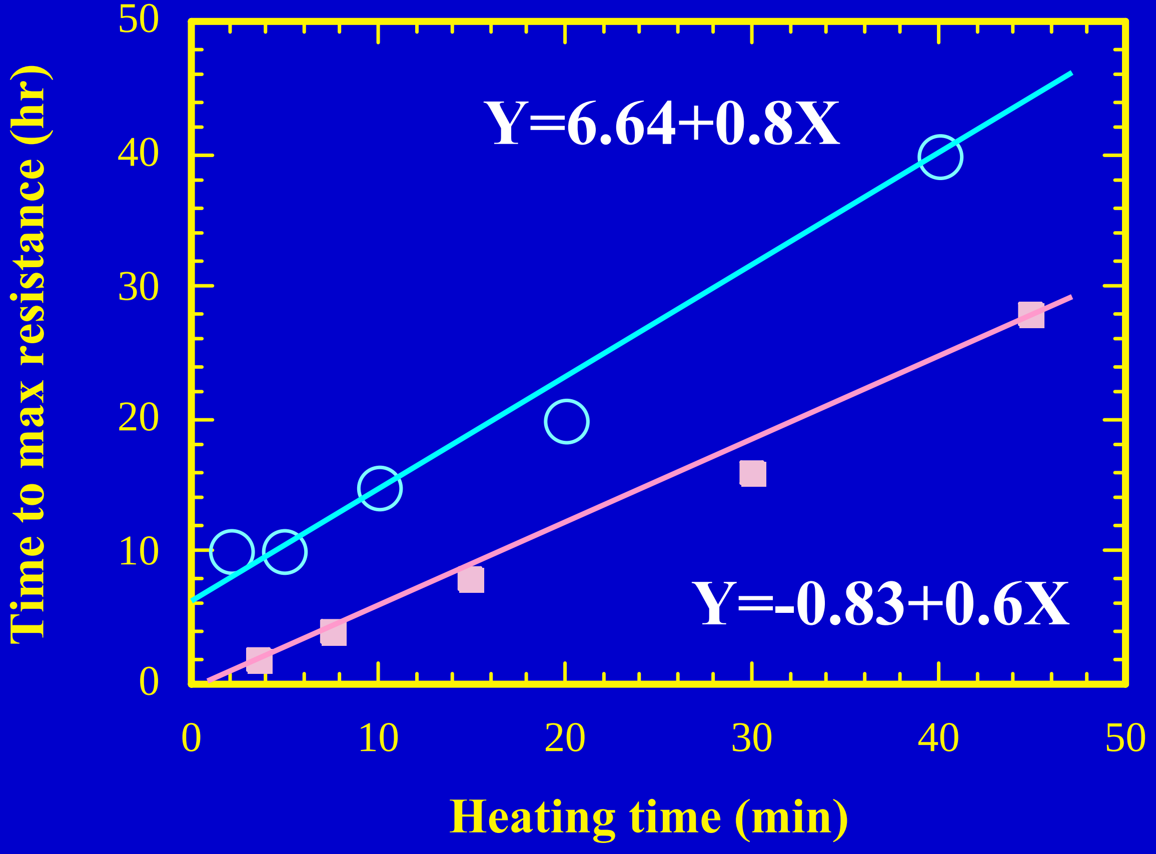


Data from Moritz

Future Directions

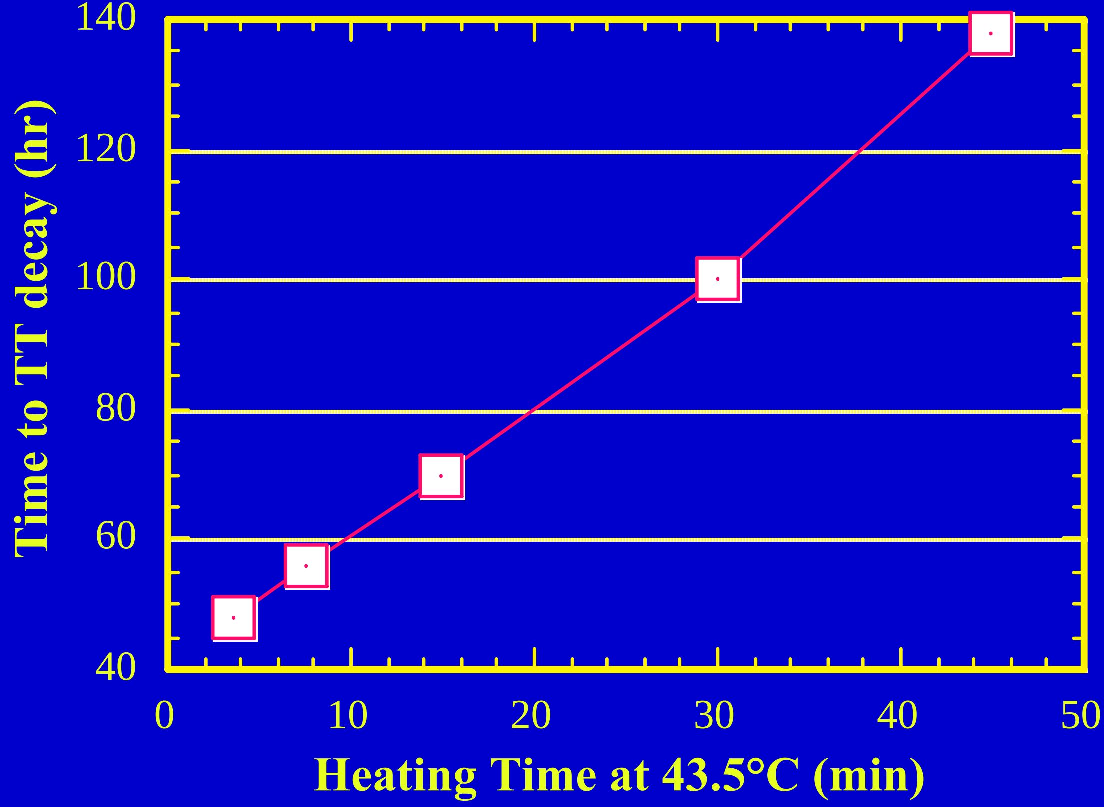
- Important to assess temperature at sites above and below threshold for damage
- Important to utilize standardized isoeffects
  - Identify various levels of severity of effect
- Insufficient data between 40-300 CEM43°C for many organs and tissues
- Assessment time after exposure is critical
  - Few data on chronic effects
- Virtually no data on repeated exposures

Time to max thermotolerance dependent severity of initial exposure



Data from: Nielson, 1982 & Law, 1979

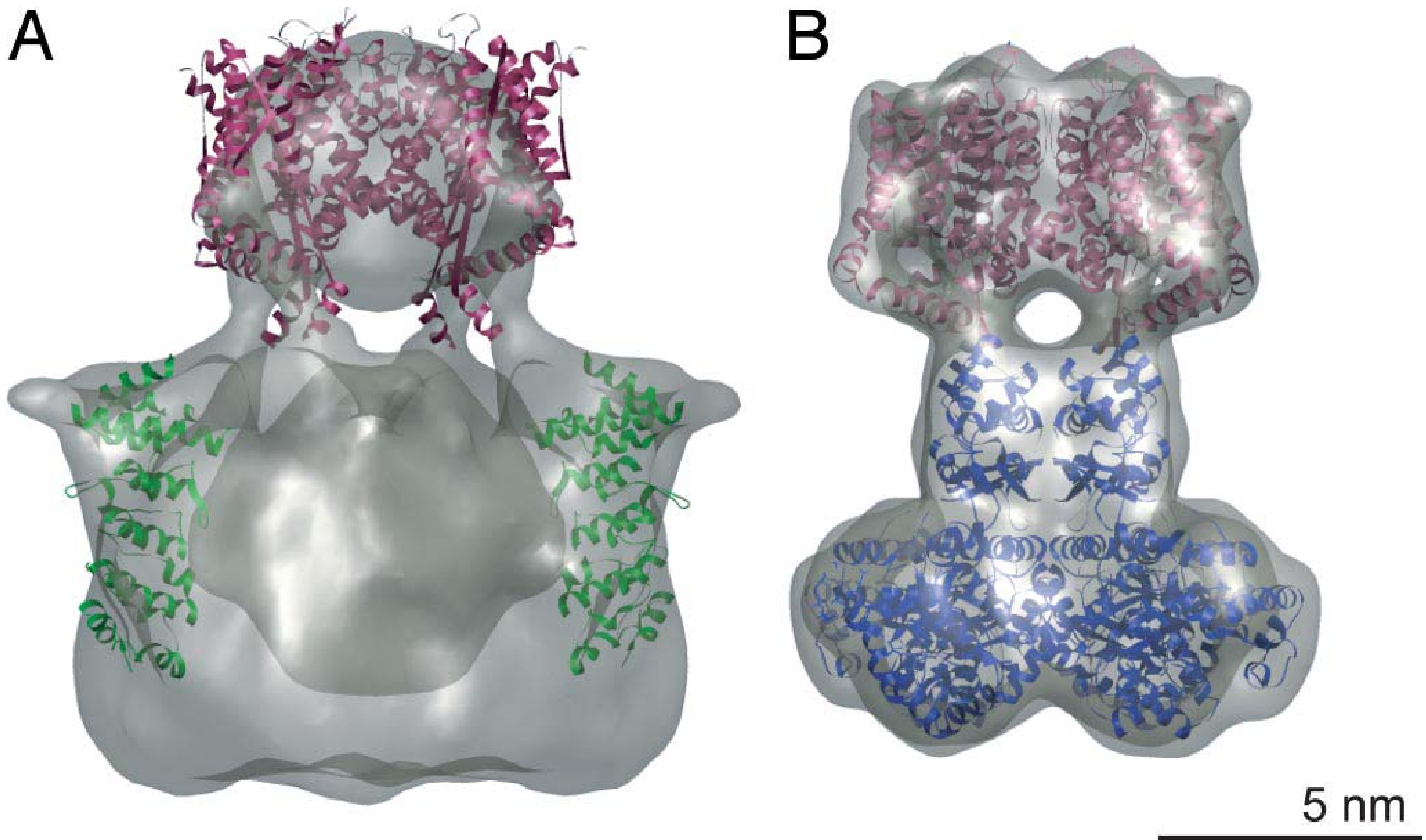
Kinetics of thermotolerance decay



From Nielson, 1982

Summary of report on neurocognitive effects

William Wetsel, PhD, Duke University



Central point of discussion is on role of TRPV receptors on temperature sensing and thermoregulation

TRPV1 is a negative regulator of fat generation

Activation of TRPV1 channel is necessary to prevent preadipocyte-to-adipocyte differentiation. TRPV1 activation may ultimately reduce the number and size of fat cells, and therefore reduce the tendency for fat to develop

Capsaisin is known to activate this channel – giving rise to efforts to develop pharmacologic agents that could activate the channel as a means of weight control

Functions of TRPV1 – 1 of a family of such receptors

- Sensor for temperature, low pH, inflammatory lipid metabolites, capsaisin and other vanilloids
- Knockout mice for TRPV1 have lower baseline body temperature
- Are subject to regulation by other stimuli
  - Inflammatory pain
  - Phosphorylation
  - These effects can alter thresholds for detecting temperature change
- Channel activation can influence hippocampal excitation
  - Increase propensity toward febrile seizures

Highlights of Wetsel report

- Discussed effects of neonatal and perinatal hyperthermia(39°C)/hypoxia exposure on behavior later in life
- Updated literature relating to thermal exposure and cognitive function in humans
  - Points to inadequate statistical design in several studies
  - Heat stress can decrease motor function, which could influence performance on cognitive tests that involve motor function
- Endpoints
  - Emphasized need to include a battery of different neurocognitive tests for this type of research
    - Several papers were deficient in this regard, making conclusions difficult to reach