

- **Hyperthermia is a demonstrated teratogen in rodent laboratory animal (*e.g.*, rats, mice, guinea pigs) and fowl (*e.g.*, chickens) systems.**
- **Neural tube closure (NTC) is especially sensitive to thermal insult; other embryological or fetal stages are also sensitive.**
- **This type of work is labor-intensive.**
- **There are inadequate data on thresholds, or attempts to define a thermal threshold, and on thermodynamics. Mechanistic approaches have merit.**
- **There had been no concept of thermal dose for hyperthermia-induced birth defects. There is now.**
- **Hyperthermia is a teratogen in humans.**

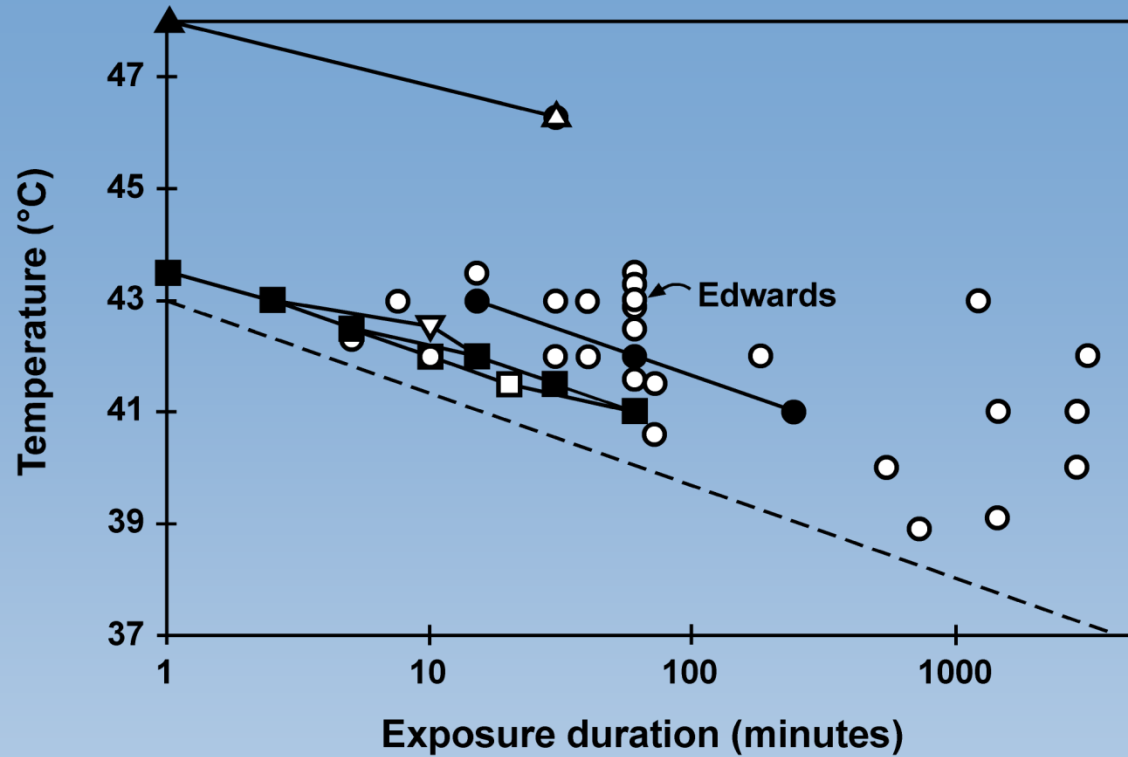


Figure 3. A plot of thermally produced biologic effects, listed in Table 4 of Miller and Ziskin (1989), that have been reported in the literature in which the temperature elevation and exposure duration are provided. Each point represents either the lowest temperature reported for any duration or the shortest duration for any temperature reported for a given effect. (—) Multiple data points relating to a single study; (---) a lower boundary ($t_{43} = 1$) for observed biologic effects. The arrowed “Edwards” indicates the exposure temperature (43.0°C):exposure duration (60 min) for the Edwards (1969) exposure metrics for hyperthermia treatment of pregnant guinea pigs.

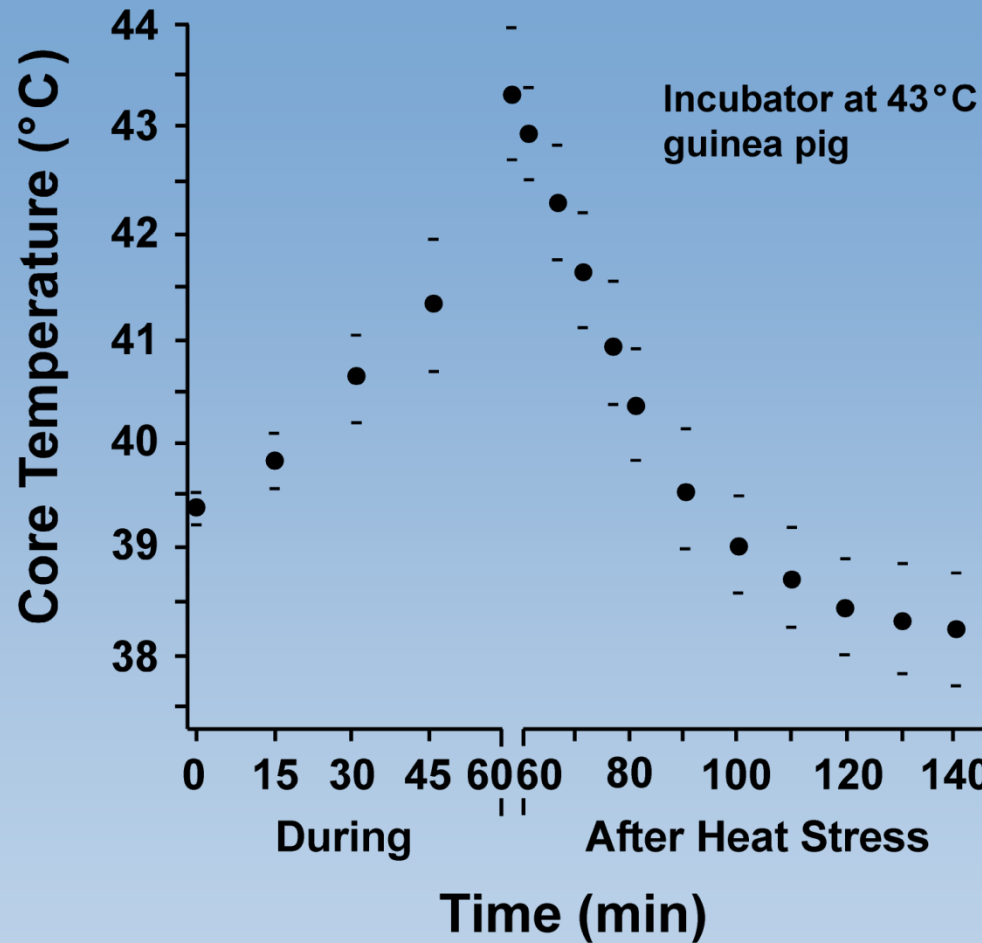


Figure 1. Core temperature (mean \pm SD) as determined by a rectal thermometer in conscious guinea pigs during heat treatment from 0-60 min in an air convection incubator at 43°C, and subsequent recovery after heat treatment (60-150 min). Redrawn from Edwards¹⁷, with permission.

Table 1. A $t_{3.5}$ analysis of the heating:cooling profile in figure 1 (from Edwards¹⁷), in which modified procedures of Sapareto and Dewey⁴ are employed; equation (2) was used with $R = 0.25$, since the temperature increase is less than 6.0°C .

Temperature ($^{\circ}\text{C}$)		Time (t) in min		Coefficient	Exponent	$t^{5.5}$ (min)
T	ΔT^a	t^b	Δt^c	R	for R	$R^{(3.5-\otimes T)} \times \Delta t$
					$R^{(3.5-\otimes T)}$	
43.0	3.5	2	2	0.25	0.0	2.00
42.5	3.0	7	5	0.25	0.5	2.50
42.0	2.5	15	8	0.25	1.0	2.00
41.5	2.0	23	8	0.25	1.5	1.00
41.0	1.5	35	12	0.25	2.0	0.75
40.5	1.0	47	12	0.25	2.5	0.38
40.0	0.5	61	14	0.25	3.0	0.22
39.5						

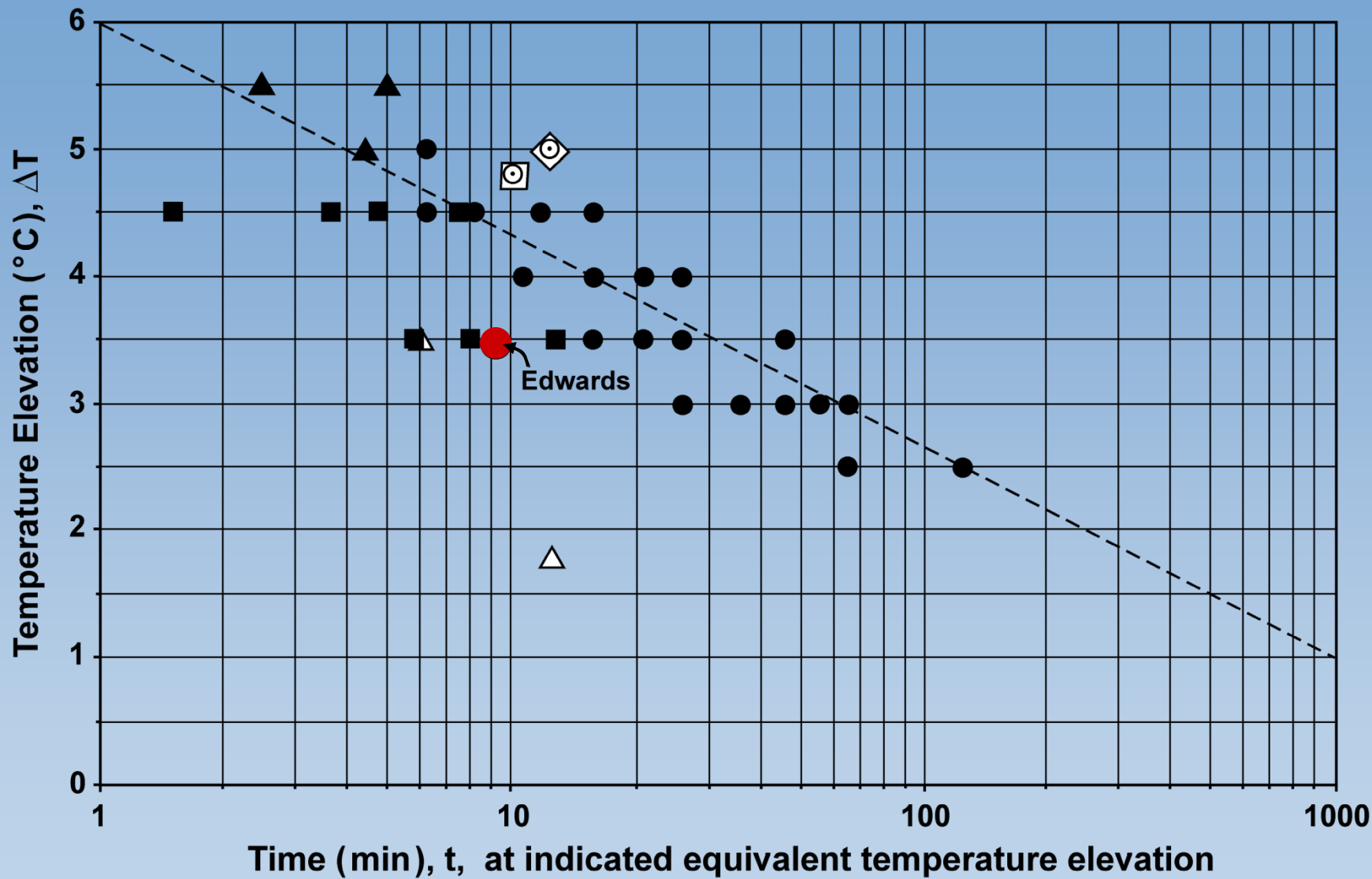
$t_{3.5} = 8.9 \text{ min}$

^a ΔT = increase in temperature above starting level.

^b t = total time at or above a core temperature T_c .

^c Δt = time at one interval minus time at next higher interval (*e.g.* t at 43.0 and 42.5°C are 2 and 7 min. respectively; hence $7 - 2 = 5$ min for $\otimes t$ at 42.5°C). By summing the $t_{3.5}$ (min) values for each 0.5°C increment, a value of $t_{3.5} = 8.9$ min is obtained for the temperature profile in figure 1. From equation (2), this also corresponds to $t_{4.0} = 4.5$ min.

Mammalian Core Temp °C		43°C ΔT
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Human	37.0	6.0
Mouse	37.5	5.5
Rat	38.0	5.0
Guinea Pig	39.5	3.5



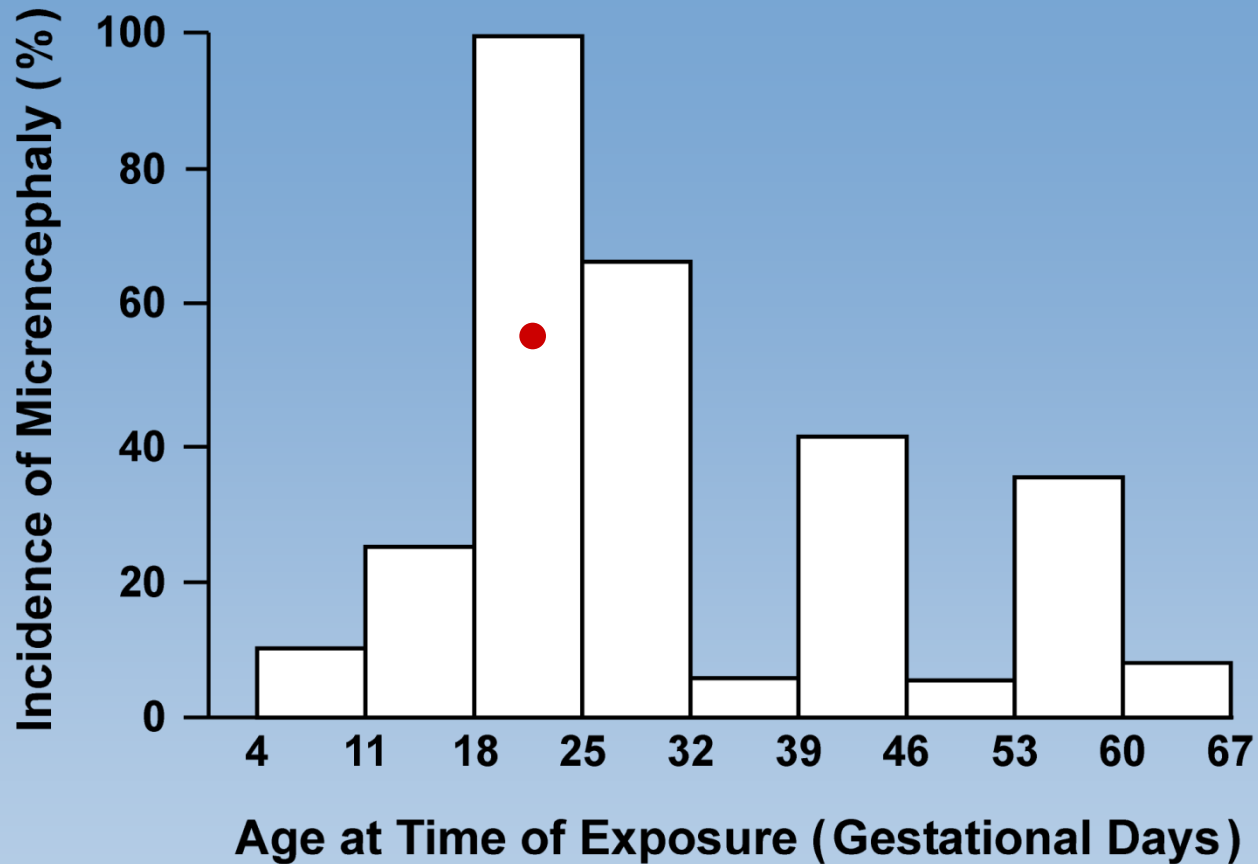


Figure 2. The incidence of micrencephaly found in newborn guinea pigs following eight consecutive daily exposures of the mother to hyperthermia at various stages of gestation between 4 and 67 days (from Edwards, 1981).

Notation: A single exposure at day 21 (NTC) yielded 55% micrencephalic fetuses.

Arrhenius Isodose Values

For Marsh Edwards' Heating: Cooling Profile

(R = 0.25 from Sapareto & Dewey)

- $t_{3.5} = 9$ min.
- $t_{2.5} = 36$ min
- $t_{1.5} = 144$ min
- $t_{1.0} = 288$ min
- $t_{0.5} = 576$ min

What some thermal doses during the obstetrician's watch?

1. **Fever.**
2. **Third trimester 0.5 °C fetal ΔT .**
3. **Third trimester with 24-h fever.**
4. **Labor.**
5. **Labor plus epidural.**

Situation #1. Fever

Assume an average fever is 2.5 °C above normal physiological temperature, and its duration is 24 hours. Thus, the thermal dose for this fever is:

$$t_{2.5\text{ }^{\circ}\text{C}} = 24\text{ hr} = 1440\text{ min.}$$

Ratio #1.

Comparison: Human Fever Fetal Thermal Dose
Effective Guinea Pig Thermal Dose

Human: $t_{2.5C} = 1440$ min

Guinea Pig: $t_{2.5C} = 36$ min

The Human Fever Fetal Dose is 40 times greater than the highly effective Guinea Pig Dose!

Question

- This single illustration includes an apparently “normal” or “routine” obstetric procedure and occurrence, and approximated thermal doses.
- In drug testing situations, where with animal systems one can use substantially higher-than-clinically-used doses of some drug (which can lead to observations of teratogenic effects) the manufacturer and the clinician will note that these doses are not clinically relevant and that no such observations have occurred in clinical trials or practice. See the PDR (Category C).
- **In terms of routine thermal dose obstetric settings, this situation is reversed! During the obstetrician’s watch there are many instances in which the thermal dose to the fetus is far in excess of what has been observed to lead to defective offspring in carefully studied animal systems.**
- Are there “defective human bodies” whose numbers are such that it is reasonable to hypothesize that these thermal doses are biologically effective?

Answer – Yes!

There are ~4,000,000 babies born/year in the USA.

Of these:

For “high income” nations the birth defect rate is 10%, with about half of the defects having some genetic association, and half not presently known to be associated with genetic mechanisms. (March of Dimes Global Report; 2006). For “low to middle income” nations the overall birth defect rate is about 12%.

“Bodies”

Assume a defect rate of 10% for all infants (birth, 1-year, school age). Thus, 10% of 4,000,000 is 400,000 per year! Over a ten-year period this translates to 4,000,000 defective individuals. Some of these defects are known to be genetically driven (*e.g.*, trisomy 21). But, for most, the mechanism causing the effect is not known. And all are the result of chemical processes, and all would require an activation energy for initiation. An increased thermal burden would foster the occurrence of those “bad” reactions.

Table 4**A comparison of activation energies for thermally induced biologic effects**

Endpoint	Species/ System	E_a (kcal/mol)	R	$1/R$	Source
Micrencephaly	Guinea pig	680	0.031	32.48	Edwards <i>et al.</i>, 1969a,b [Miller <i>et al.</i>, 2005]
Microphthalmia	Rat	700	0.027	36.73	Germain <i>et al.</i>, 1985 [Miller <i>et al.</i>, 2005]
Cell killing	Cultured cells	365^a 148^b	0.150 0.470	6.67 2.13	Dewey <i>et al.</i>, 1977
Cell killing	Cultured cells	265^{a,c} 132.5^{b,d}	0.250 0.500	4.00 2.00	Sapareto and Dewey, 1984
Focal necrosis	Cat brain	85 – 135	0.617	1.62	Carstensen <i>et al.</i>, 1974
All defects	Various	316	0.195	5.13	Best-fit from Fig. 6

^a for $T < 43^\circ \text{C}$;

^b for $T > 43^\circ \text{C}$;

^c calculated from the value for R assuming $T = 37^\circ \text{C}$;

^d calculated from the value for R assuming $T = 43^\circ \text{C}$.

Church CC and Miller MW, 2007. Quantification of risk from fetal exposure to diagnostic ultrasound. *Prog Biophys & Mol Biol* 93: 331 – 353.

Table 5**Estimated ultrasound-induced increase in prevalence rate for a representative birth defect**

Duration (min)	Temperature Rise (°C)	Relative increase in prevalence rate		
		$E_a = 265$ (kcal/mol)	$E_a = 316$ (kcal/mol)	$E_a = 700$ (kcal/mol)
5	0	0.000%	0.000%	0.000%
5	1	0.004%	0.005%	0.048%
5	2	0.019%	0.033%	1.838%
5	3	0.077%	0.172%	67.571%
5	4	0.302%	0.869%	2425.585%

Church CC and Miller MW, 2007. Quantification of risk from fetal exposure to diagnostic ultrasound. Prog Biophys & Mol Biol 93: 331 – 353.

Conclusions

- **The Arrhenius equation does not invoke thresholds – any T for any t has an effect.**
- **There is congruency between “animal data” and “human data,” including dose response relations.**
- **Birth defects have background rates of occurrence. The issue of thermal thresholds therefore seems moot.**
- **Hyperthermia does not introduce “new” anomalies. Hyperthermia provides energy to enhance anomalous outcomes.**
- **Thermal episodes (doses) during the obstetrician’s watch can be substantially larger than a teratogenic-effective thermal dose in a well-studied, controlled animal system. This is very worrisome.**
- **The ΔT thermal dose concept is (a) mechanistically oriented, (b) supported by preliminary data, and (c) testable.**