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## The mouse: An "average" homeotherm

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journal homepage: [www.elsevier.com/locate/jtherbio](http://www.elsevier.com/locate/jtherbio)The mouse: An “average” homeotherm<sup>☆</sup>Christopher J. Gordon<sup>\*</sup>

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## ABSTRACT

Mice, rats, and nearly all mammals and birds are classified as homeothermic, meaning that their core temperature is regulated at a constant level over a relatively wide range of ambient temperatures. In one sense, this homeothermic designation has been confirmed by the advent of radiotelemetry and other techniques that allow for the remote monitoring of awake, unrestrained animals in laboratory or natural settings. This technology confirmed that, when averaged over many hours, core temperature of mammals is regulated at a nearly constant level. On the other hand, telemetric sampling in relatively small mammals such as mice and rats also revealed that their core temperature often varies markedly from hour to hour. In other words, the mouse could be defined as a homeotherm only when core temperature is averaged over a relatively long period. Many researchers ascribe equal homeothermic capabilities to mice and other small rodents as they do to humans. Such an assumption could lead to errors in extrapolating physiological, pharmacological, and toxicological findings from experimental test species to humans.

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## 1. Introduction

For the past three decades researchers have witnessed the development of hundreds of transgenic strains of mice possessing a variety of unique phenotypes. The heavy experimental investment in mouse models in recent decades has led to the development of a range of mouse-specific reagents (e.g., monoclonal antibodies to mouse proteins) vastly exceeding that available for other experimental species, of any size. The genetic tractability of mice allowing for the regulated or inducible expression of any gene has turned the mouse, in this post-genome era, into a genetic toolbox ideal for both reductionist and systems biology approaches. Indeed, the heavy investment in murine models used in government, university, and industrial research demands that we learn all we can about the physiology of mice as well as their similarities and dissimilarities to other mammals, including humans. With this in mind, temperature is the universal engine that affects all life processes and it behooves biomedical researchers to have a firm understanding of the nature of the thermoregulatory system of their test species. As will be shown in this paper, this tenet cannot be overstated for mice.

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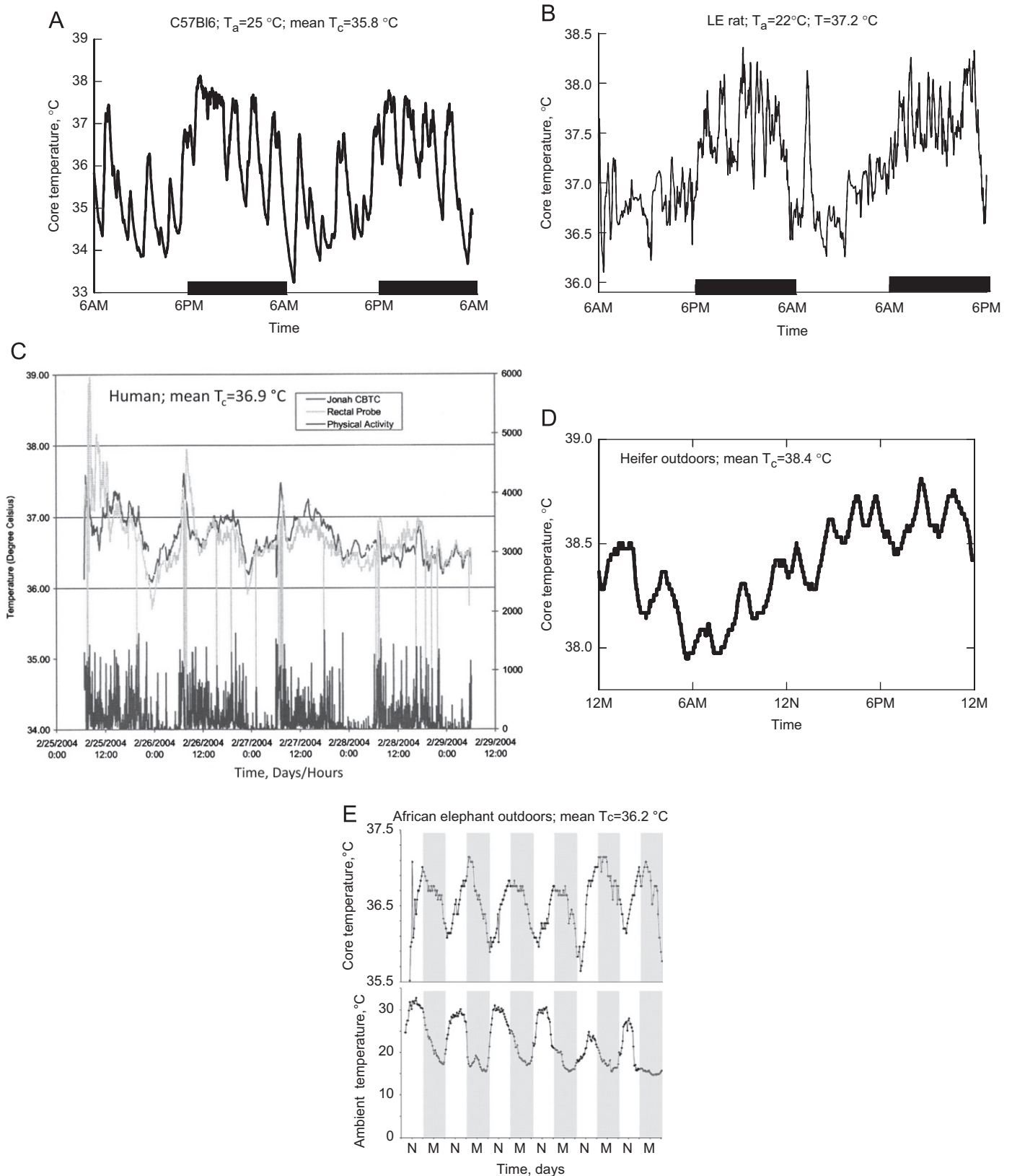
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In the study of thermal homeostasis, core temperature is ultimately regarded as *the* regulated variable. It would be remiss to not to mention that some researchers consider total body heat content and heat flow and not core temperature, to be regulated parameters in human thermoregulation (Webb, 1995). Nonetheless, the consensus among thermal physiologists is that a key function of the thermoregulatory system is the regulation of the core temperature (e.g. brain, aortic, or intra-abdominal). Radiotelemetry and data logger technology now allow researchers to monitor minute-to-minute changes in core temperature of species ranging from mouse to elephant. Most importantly, this technology affords monitoring of temperature and other physiological processes in unstressed and undisturbed animals while housed in either an artificial settings or allowed to move about freely in their natural habitat. This technology gives researchers the ideal tool to evaluate the performance of the thermoregulatory system in ways that were not possible with the conventional techniques requiring restraint, tethering or periodically disturbing the test subject to collect data. Moreover, this technology provides researchers with a powerful tool to test theories or long-accepted principles of thermal homeostasis, such as proportional control.

## 2. Thermal homeostasis: do all species use the same strategy?

It is proposed that the concept of average core temperature can be misleading in terms of the nature of the CNS mechanisms



**Fig. 1.** Time-course of core body temperature monitored by radiotelemetry or data loggers of a mouse, rat, human, steer, and elephant. A-C57BL6 male mouse; data collected at 1 min intervals; ambient temperature =  $25^\circ\text{C}$ ; Gordon, 2009; (B) Long-Evans male rat; data collected at 1 min intervals;  $22^\circ\text{C}$ ; Gordon, 2009; (C) human volunteer; four days of temperatures recorded every 15 s with an ingested data logger as well as with a rectal probe. Motor activity (right axis) also plotted. Gray downward lines represent slippage of rectal probe. Mean  $T_c$  calculated for entire study group; graph modified from McKenzie and Osgood (2004); (D) 24 h of core temperature of a cross bred heifer ( $\sim 450\text{ kg}$ ) monitored by telemetry (vaginal temperature data logger) maintained outdoors in Omaha, Nebraska, USA, during month of June; temperature data collected every minute (see Hillman et al., 2009). Data provided courtesy of Dr. Tami Brown-Brandt, USDA, Clay City, NB; (E) five days of core temperature in adult female African elephant monitored with an ingested data logger; ambient temperature on natural cycle; data collected every 20 min; mean  $T_c$  calculated for entire study group; modified from Kinhan et al. (2007).

of thermoregulation. There is a plethora of text books and review articles with data tables and summaries of average core temperature of mammals and birds (Altman and Dittmer, 1962; Folk, 1974; Hart, 1971; Gordon, 1993). The data are typically presented as the mean and standard deviation, standard error, and/or range from a sample of several animals of a particular species or strain collected at a specified time of day. Of course, mean core temperature is species specific and is generally maintained over a wide range of ambient temperatures, provided that the thermoregulatory system is not overwhelmed from severe heat or cold stress.

While mean core temperature of the mammalian fauna varies between species by just a few degrees Celsius, the same cannot be said for the control of core temperature over time within a species (Fig. 1). Plotted is the time-course over several days of the core temperature for a mouse, rat, human, heifer, and elephant. The mean core temperatures of these species are amazingly similar, exhibiting a range of approximately 2.7 °C despite a 280,000-fold range in body mass. The mean core temperature of the mouse (also see Fig. 2) and elephant is essentially the same, with a value of approximately 36.2 °C; however, variability over a 24 h period differs markedly between these two species. The core temperature of the mouse can wax and wane by as much as 2–4 °C from one hour to the next. The rat is also quite variable but not as much as the mouse. A recent study on the stability of core temperature in rodents showed that, depending on strain, temperature regulation of mice is approximately 50% more unstable compared to rats (Gordon, 2009). The time course of core temperature measured each minute of the steer (Fig. 1D) shows oscillations but it is important to note that the temperature scale of this figure spans 1.2 °C whereas the scales for mouse spans 6 °C.

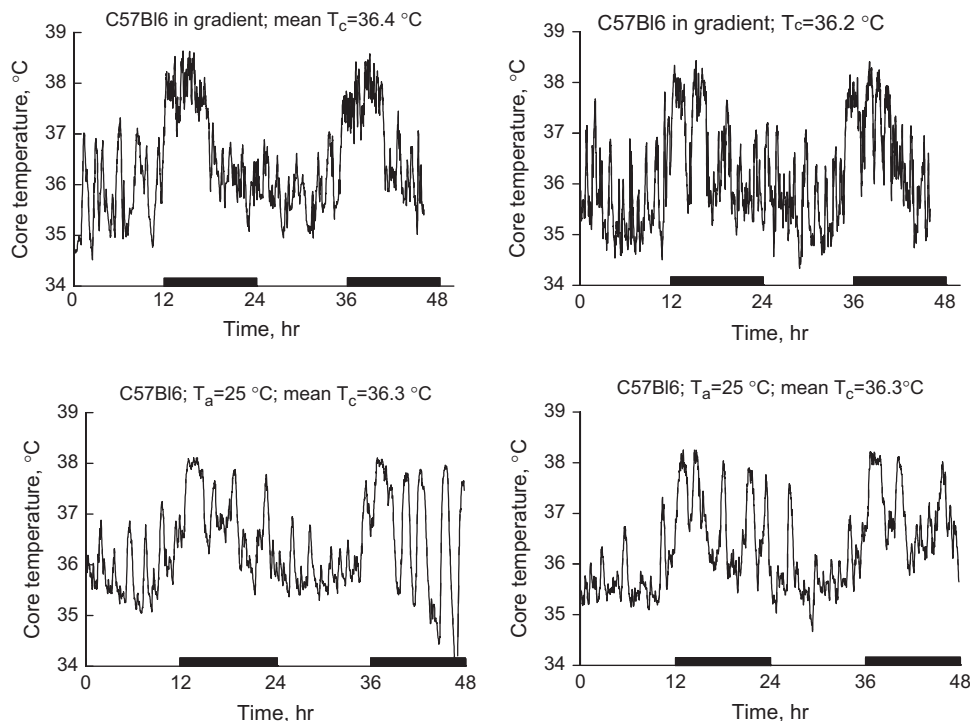
One important point to take from the aforementioned is that, based on mean core temperature, one would conclude that the thermoregulatory systems of the mouse, rat, human, and elephant are similar. On the other hand, based on the pattern of core

temperatures over time, one would surmise that these species have markedly different thermoregulatory mechanisms. It is important to note that core temperature in the elephant was collected every 20 min, which may minimize the variations in core temperature over time. Because of the elephants' mass, little variation in temperature is expected from one time point to the next. The temperature data for the human subjects was collected at 15 s intervals; compared to the mouse and rat, there is relatively little variation with time.

### 3. Reconciling conventional and telemetric data

If one removes the cover from a cage of 10 mice that are undisturbed and begins measuring their rectal temperature one at a time, a progressive elevation in core temperature from mouse number 1 to mouse number 10 will be observed with temperature rising steadily from ~37 to nearly 39 °C (Zethof et al., 1994). As one mouse is picked up and its core temperature is measured, the other mice awaken and begin to move about the cage, developing a predictable stress-induced hyperthermia. The so-called mean core temperature of the cage of mice is over 38 °C using this method, yet we know that this is not a correct reflection of the animal's true homeostatic behavior. Indeed, the authors of this study developed this technique as a means of quantifying stress and were not reporting these data as a measure of the species' true core temperature.

The above example with a cage of mice serves to demonstrate that the mean colonic or rectal temperature determined by averaging data from several animals is clearly not a reflection of the true nature of the pattern of core temperature in rodents as evident by the telemetry data shown in Fig. 1. If one measures the colonic or rectal temperature of mice or rats and does this quickly without allowing the animal to respond to the stress of handling or disturbance of being near the cage, then the temperatures



**Fig. 2.** Examples of time-course of core temperature of mice monitored by radiotelemetry while maintained in either at constant ambient temperature or allowed to select from a range of temperatures while housed in a temperature gradient. Note the periods where core temperature is maintained at a relatively stable level for brief periods, especially during the night when motor activity is elevated. Unpublished data provided courtesy of Dr. Lisa Leon, U.S. Army Research Institute, Natick, MA, USA).

would fall somewhere along the range of temperatures as shown for individual animals in Fig. 1. The mean of these core temperatures would ostensibly represent a physiologically relevant measurement of the regulated body temperature. Clearly, the telemetric data indicate a more unstable regulated variable. Overall, the data collected by telemetry or data logger confirms what many researchers would expect but is rarely documented or discussed; namely, the core temperature of a relatively small homeotherm will vary more over time than that of a large homeotherm.

#### 4. Proportional control and core temperature stability

Thermoregulation has been a hallmark regulatory system that pioneers in physiology used to understand the principles of homeostasis. Decades of research in the 20th century led to the development of models of CNS control of thermoregulation that incorporate the principle of proportional, negative feedback control systems (Stolwijk and Hardy, 1974; Bligh, 1998, 2006). That is, the response of an effector or motor response ( $R_1$ ) over and above the baseline response ( $R_0$ ) is equal to the difference between a theoretical set point for thermoregulation ( $T_{\text{core-set}}$ ) and the actual brain or core temperature ( $T_{\text{core}}$ ) multiplied by a proportionality constant ( $\alpha$ )

$$R_1 - R_0 = \alpha(T_{\text{core-set}} - T_{\text{core}}) \quad (1)$$

$R_1$  and  $R_0$  can represent the values of any number of thermoeffectors, such as skin blood flow, metabolic heat production, sweating, panting, or an index of behavioral thermoregulation. The processing of thermal stimuli and control of the activity of thermoeffectors also involves changes in skin temperature and the proportional equation is often expressed to take into consideration the combined impact of changes in brain and skin temperature that are either added or multiplied depending upon the model (e.g., Johnson and Elizondo, 1979; McEwen and Heath, 1974)

$$R_1 - R_0 = \alpha(T_{\text{core-set}} - T_{\text{core}}) + \beta(T_{\text{skin-set}} - T_{\text{skin}}) \quad (2)$$

where  $T_{\text{skin-set}}$  is a set-point or reference temperature for skin temperature,  $T_{\text{skin}}$  is actual skin temperature, and  $\beta$  is a proportionality constant. The value of  $T_{\text{skin}}$  is typically a measure of mean skin temperature; however, it can be further refined into skin temperature of specific sites of the body, each site having its own proportionality constant. Proportional control is a starting point to understand the fundamentals of physiological homeostasis, including the regulation of blood pressure, water balance, blood glucose, and many others (e.g. Schmidt-Nielsen, 1975; Stolwijk and Hardy, 1974).

Although there has been considerable work on the thermal physiology of rodents (e.g., Gordon, 1993, 2005), the work leading to the development of proportional control of body temperature was performed primarily in large mammals such as dogs, goats, rabbits, and sheep (Hammel, 1968; Bligh, 1998, 2006). These larger species were amenable to the stereotaxic implantation of thermodes and other probes into the CNS needed for the control and measurement of selected sites in the CNS for studying the thermoregulatory reflexes. There is also a considerable data base on CNS thermoregulatory control in rodents using stereotaxic techniques. Responses between small and large mammals are comparable but our concepts of thermal homeostasis and CNS control are better established in the larger species.

#### 5. Assumptions of proportional control across species

When not exercising, the human, elephant, and other relatively large homeotherms display relatively fine regulation of core

temperature with a  $\sim 1$  °C magnitude circadian rhythm. With this smooth pattern of change in temperature, one can visualize how a proportional type regulator would be operative in these large species as predicted by Eqs. (1) or (2). But the unstable nature of core temperature in the mouse and rat should compel thermal physiologists to question if the smaller species use the same strategy of proportional control. If they follow the same principles of regulatory control, then one would predict a very dynamic thermoeffector response in mice and rats and other small mammals as their systems continuously attempt to correct for the temperature oscillations. For example, considering the time course of core temperature of the mouse in Fig. 1A, one would expect vigorous shivering and seeking of warmer temperatures when core temperature dips to a nadir followed with peripheral vasodilation and seeking of cooler temperatures as core temperature peaks.

#### 6. Rodents are metabolic strategists

Phillips and Heath (1995), using infrared analysis of skin temperature in a variety of species observed that as body mass increases, there is a greater reliance on peripheral vasomotor control of skin temperature for thermoregulation. They coined the phrase “metabolic specialist” to describe the nature of the thermoregulatory strategy of small mammals, meaning that because of their large surface area: mass ratio, smaller mammals rely more on changing their metabolic heat production to regulate core temperature. Small rodents also control heat loss through modulation of peripheral blood flow but their reliance on metabolic heat production to maintain core temperature as steady as possible is evident. As mass and thermal inertia increase, metabolic heat production per unit body mass decreases and adjustment in skin temperature of vascularized, furless areas to control heat exchange with the environment becomes more critical for thermoregulation (Phillips and Heath, 1995). To further illustrate, Ootsuka et al. (2009) monitored core temperature and interscapular brown adipose tissue (BAT) temperature simultaneously by telemetry and found that both temperatures oscillated with any change in BAT temperature preceding the change in core temperature. They concluded that the waxing and waning of the temperature of BAT, a highly metabolic tissue, is the main source of heat to warm the core. It is possible that metabolic strategists have evolved to endure the waxing and waning of core temperature that can only be minimized with increasing body size or by exposure to relatively warm ambient temperatures.

#### 7. Mice are capable of maintaining steady core temperatures

One should not conclude from the above discussion that mice and other small rodents are incapable of maintaining a relatively stable core temperature. Telemetric recordings from mice under various environmental conditions show how their core temperature can be maintained relatively stable for several hours. (Fig. 2). This stability is especially apparent at night when the animals are more active and they have a higher metabolic rate. Maintaining a stable core temperature in a relatively small mammal is probably quite costly and can only be achieved for relatively short periods of time. The waxing and waning of core temperature, especially during the inactive cycle is likely to be an ideal strategy for a small mammal to maintain a reasonable level of thermoregulatory control with minimal energy expenditure. This speculation warrants further research in this area of thermoregulatory control.

## 8. Significance of the mouse as an “average” homeotherm

In view of innate waxing and waning of core temperature of small rodents, it is likely that their thermoregulatory signals are processed differently in the CNS as compared to larger mammals. For example, a 2–4 °C rise and fall in core temperature over a period of 30 min in a 0.025 kg mouse is probably inconsequential in terms of eliciting a thermoeffector response compared to the same swing in temperature occurring in an 80 kg human or 7000 kg elephant. The thermal mass of the larger mammals simply limits any change in core temperature of this magnitude. If it were to occur, it would be expected to generate a marked thermoregulatory effector response. In terms of the theoretical proportional control system, the error signal to the mouse thermoregulatory center would exhibit extraordinary waxing and waning. Does this error signal drive thermoeffector responses in the same way as in larger species? Probably not but further research is needed. Furthermore, if thermal homeostasis mechanisms are radically different between small and large mammals, then how might this apply to other homeostatic processes such as blood pressure, respiration, and blood glucose? Considering the widespread application of murine models in biomedical research, it is imperative that we draw upon techniques, such as telemetry and related technology, which will allow us to observe and better understand the performance of the regulatory systems, including temperature, in these species. This will undoubtedly improve our ability to extrapolate results of rodent test models to humans.

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