USE OF EXTERNAL WARMING DEVICES & ANIMALS

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Introduction

Body temperature is a critical component of homeostatic regulation in warm-blooded (homeothermic) animals, including most vertebrate species. Temperature is an important variable in physical-chemical relationships (e.g. Boyle's Law, PV = nRT, where T = temperature) relevant to physiological functions, rate constants for biochemical reactions, trans-epithelial ion fluxes, etc.) and homeotherms tightly regulate their body core temperature at a set point value (thermostasis). Different species regulate their body core temperature to slightly different values (Table 1).

Table 1: Normal Body Temperature Ranges for Laboratory Animal Species

Species	**Normal Body Temperature (T°C, (T°F))**
Mouse	36.5-38 (97.7-100.4)
Rat	35.9-37.5 (96.6-99.5)
Guinea pig	37.2-39.5 (99-103.1)
Rabbit	38.6–40.1 (101.5–104.2)
Dog	37.9–39.9 (100.2–103.8)
Cynomolgus macaque*	37-39.5 (98.6-103.1)
Cat	38.1–39.2 (100.5–102.5)
Swine	38.7–39.8 (101.6–103.6)
Human	36.1-37.2 (97-99F)
Birds	40.6–43.0 (105.0–109.4)

*Laffins et al., 2017

Body temperature is controlled by thermoregulatory pathways emanating from the hypothalamus in the brain. These pathways optimize cellular and organ functions at rest and in response to the demands of behavior, environmental temperature challenges, and inflammation and infectious disease processes. Body temperature is used in experimental research and in clinical veterinary medicine to monitor status of thermostatic control, to diagnose inflammatory processes (e.g. infectious disease), and progress and effectiveness of treatments. Body size is the major determinant of body core temperature and rate of loss of body heat. Small animals have higher body core temperatures and greater rates of loss due to larger surface area to body mass ratio.

Thermostatic control is essential for animal health, diagnosis, therapeutic monitoring, and especially during anesthesiology. Thermostatic control is equally important for animals on experiment study for accurate research results and assurance of the animal's health. Hypothermia has been found to directly impair cellular and humoral immune functions of lymphocytes and production of cytokines. Hypothermia delays healing and promotes surgical-wound infection through the decreased oxidative capacity of neutrophils, coagulation, and vasoconstriction. Hypothermia is associated with hypokalemia, metabolic acidosis, hyperglycemia, and decreases the metabolic rate. Impaired immune responses may exacerbate a current subclinical infection, thus activating a disease to clinical signs or trigger unexpected variables to research results.

Drugs can impact thermoregulatory pathways and increases (pyremics) or decreases (antipyremics) in body temperature. Anesthetic agents and/or the state of anesthesia interfere with thermostatic control resulting in falling body temperature. Body temperature is a specific and sensitive endpoint used to detect blood-brain barrier penetration and potential impacts of experimental drugs on CNS functions (see ICH S7A).

Multiple and diverse strategies and devices are available to provide external warming for thermostatic support and the appropriateness of individual strategies and devices depends upon the intended use. We distinguish eight (8) categories of situations in research and veterinary practice wherein external warming is used to support thermostasis in research animals and small pets.

1. Acute Anesthesia: Anesthetic agents (barbiturates, sedatives, tranquilizers, gaseous agents) are used in experimental procedures wherein research (e.g. intracerebroventricular injections) and acute veterinary procedures (e.g. dental hygiene) would or could cause animals to experience pain or distress, and/or to prevent animal injuries to staff. Procedure durations range from acute to several hours. In acute anesthesia situations animals are accorded external warming for body temperature support to facilitate rapid recovery from administered agents, and to eliminate body temperature variation as a confounding variable whether the animal is to recover or be euthanized. In acute anesthesia settings animals are under constant observation and monitoring by trained staff, and animals are generally unresponsive and unable to reposition themselves with respect to an external warming device.
   Priority characteristics of warming devices used during acute anesthesia include surface temperatures that do not exceed normal body temperature and ability to integrate easily with the experimental or clinical procedure (e.g. for acute surgical procedures a device that can also serve as an operating surface). Anesthetized animals must be monitored closely for signs of hypothermia, or body temperature monitored.
2. Surgery: Surgical anesthesia (Stage 3) effectively suppresses body temperature regulation and external warming is needed to maintain normal body temperature, particularly in smaller animals. Maintenance of normal body temperature during experimental and clinical surgeries is necessary to promote best possible surgical outcomes and rapid recovery (e.g. metabolism and excretion of anesthetic agents). In surgical settings animals are under constant observation and monitoring by trained staff, and animals are unresponsive and unable to reposition themselves with respect to an external warming device.
   Priority characteristics of warming devices used in surgery are to produce surface temperatures that do not exceed normal body temperature and ability to integrate easily with the surgical setting (e.g. for surgical procedures a device that can also serve as an operating surface). Animals undergoing surgical procedures must be monitored closely for body temperature.
3. Acute Recovery: Acute recovery (e.g. post-surgery) is characterized by unconscious/unresponsive animals in the process of regaining consciousness (anesthesia Stages 3 →1). External warming is necessary to maintain body temperature, for rapid metabolism/clearance/excretion of residual anesthetic agents, and to promote healing processes. In acute recovery animals are under close but not necessarily constant observation and monitoring by trained staff, and animals are at least initially unresponsive and unable to reposition themselves with respect to an external warming device.
   Priority characteristics of warming devices used in acute postsurgical recovery are to produce surface temperatures that do not exceed normal body temperature and comfortable/conducive to prolonged animal contact. Animals recovering from surgery must be monitored closely for signs of hypothermia and/or body temperature monitored.
4. Prolonged Recovery: Prolonged recovery (e.g. post -surgery) is characterized by semi-responsive animals in the process of regaining full consciousness and mobility. External warming is necessary to maintain body temperature, to promote metabolism/clearance/excretion of residual anesthetic, analgesic, or other agents and to promote healing processes. In prolonged recovery animals are under periodic observation and monitoring by trained staff, but with increasing unobserved periods. In prolonged recovery animals are at least partially responsive and able to reposition themselves with respect to an external warming device.
   Priority characteristics of warming devices used in prolonged recovery are animal ability to reposition with respect to warming device for optimal external warming support and robustness to avoid damage by animals (e.g. punctures).

5. Neonatal, juvenile, and geriatric animals: Neonatal, juvenile, and geriatric animals present separate challenges regarding maintenance of body temperature and requirements for external body warming. In general, these populations are under scheduled observation and monitoring by trained professionals but may have prolonged periods where unobserved. These populations are responsive and retain ability to position themselves for optimal external warming device support.
   Priority characteristics of warming devices used with neonatal, juvenile, and geriatric animals include animal ability to reposition with respect to warming device for optimal external warming, robustness against accidental damage by animals, and compatibility with the home environment.
6. Disease models: Diseased animal models present unique challenges as do human conditions regarding maintenance of body temperature and requirements for external body warming. In general, these populations are under scheduled observation and monitoring by trained professionals but may have prolonged periods where unobserved. These populations are responsive and retain ability to position themselves for optimal external warming device support.
   Priority characteristics of warming devices used with neonatal, juvenile, and geriatric animals include animal ability to reposition with respect to warming device for optimal external warming, robustness against accidental damage by animals, and compatibility with the home environment.
7. Exotic species: Exotic species present unique challenges regarding maintenance of body temperature and requirements for external body warming, depending upon natural environment characteristics. In general, these populations are under scheduled observation and monitoring by trained professionals but may have prolonged periods where unobserved. These populations are responsive and retain ability to position themselves for optimal external warming device support.
   Priority characteristics of warming devices used with exotic species include animal ability to reposition with respect to warming device for optimal external warming, robustness against accidental damage by animals, and compatibility with the home environment.
8. Transportation: Transportation relates to conditions associated with transportation of animals of all characteristics (see above) between external or within internal facilities. Animal in transport are subject to environmental and social stress and depending upon duration and maximums of temperature changes may require access to external warming for body temperature support. In general, these populations are under scheduled observation and monitoring by trained professionals but may have prolonged periods where unobserved. These populations retain ability to position themselves for optimal external warming device support and consistency with rehabilitation in home environmental conditions.
   Priority characteristics of warming devices used with animal transportation include animal ability to reposition with respect to warming device for optimal external warming and compatibility with conditions of transportation towards (e.g. electrical power availability).

Statement of Purpose

The purpose of this document is to review current technologies and strategies used to provide external warming in conjunction with research and veterinary procedures in small animals, to identify relative strengths and weaknesses, and to provide guidance where specific technologies/strategies may be best applied.

Electrical Resistance Warming Devices

Table 2: Examples of Electrical Resistance Warming Devices

Unit		Product ID
Induction/Warming Chamber	Animal Identification and Marking Systems	WW-CS, WW-CL, WC-S1, WC-S2
Temperature Controller/Monitors	Physitemp	TCAT-2AC, TCAT-2LV, TCAT-2DF
RightTemp® Temperature Monitor & Homeothermic Warming Control Module	Kent Scientific	PS-02

These devices represent a broad range of products loosely characterized as having a primary alternating current (AC) power source and electrical resistance heat generating unit. The device may be packaged in a solid surface (e.g. heating plate), a solid block (e.g. a warming 'rock') or a soft/flexible material (e.g. heating blanket or pad). These devices usually have a controller mechanism to regulate the surface temperature generated at the plate, rock, blanket or pad. Some devices are provided with or have functionality to be used with a temperature control device wherein the temperature on the surface (e.g. surface temperature) or within an animal (e.g. rectal temperature/body core temperature) is compared to a calibrated 'setpoint' temperature and the output of the heat generating unit increased or decreased to restore/maintain the setpoint.

Electrical resistance warming devices are the most frequently used class of external warming device found in laboratory and veterinary facilities. Certain units (e.g. warming plates or rocks) may be appropriate for responsive post-surgical neonatal, juvenile, geriatric, and diseased animals and exotic species so long as they are sufficiently conscious and mobile to adjust their position regarding the device for optimal temperature.

With unresponsive animals, users must measure the relevant temperature endpoint (e.g. device surface temperature or body core temperature) and adjust the device as appropriate to prevent hyperthermia and hypothermia. Further, it is strongly advised to monitor surface, setpoint, and/or body core temperatures regularly to detect and rectify malfunctions (e.g. rectal thermal probe displaced from rectum) before injury can occur. In general, the surface temperatures generated by these units should not exceed body core temperature of the species used with.

Electrical resistance warming devices must be monitored closely when used with responsive animals (e.g. those capable of changing their position regarding a heat source) as these devices pose hazards including but not limited to electrocution, burns, and death if animals damage components of electrical circuits. Users need to be aware that surface temperatures created by resistance warming units may not be uniform (e.g. hot and/or cold spots, Zang et al., 2017). Resistance warming units and warming rocks are not generally useful during transportation because of lack of suitable electrical power, lack of monitoring, and/or risks associated with electrical shock if the units become damaged.

Advantages of electrical resistance warming units are relatively common, robust, and simple to operate.

Disadvantages include their expense, potential to overheat if controller and/or temperature control systems are disrupted or fail, and electrical shock, burns and deaths if animals damage electrical circuits.

Recommendations for use: Electrical resistance warming units are generally appropriate for acute anesthesia surgery and acute recovery procedures because the units generate surface temperatures within the range of body core temperatures and are readily adaptable with thermo-controller units. These units must be used with caution for longer term applications without continuous observation because of possible animal damage to electrical components.

Table 3: Recommended Uses of Electrical Resistance Warming Devices

Unit	**Acute Anesthesia**	**Surgery**	**Acute Recovery (Prolonged)**	**Prolonged Recovery**	**Neonatal, Juvenile, & Geriatric Animals**	**Disease Conditions**	**Exotic Species**	**Transport**
Temperature controlled Electrical Resistance Warming Devices	√	√	√	×	×	×	×	×
Warming 'rocks'	×	×	×	√	√	√	√	×

Water Circulation Warming Devises

Table 4: Examples of Water Circulation Warming Devices

Unit	Manufacturer	Product ID
Heat Therapy Pump and pad	Adroit	HTP-1500 AP-D, AP-AV
ThermaZone Therapy Pump and pad	Innovative Medical Equipment	IP003-07, IP003-22
Intensive Care Units	Thermocare	DW-1N, DW-2N, DW-3N, FW-1N, FW-2N, FW-3N

These devices use electrical resistance to create and store heat as a reservoir of warm water. A pump circulates the water through solid radiators or flexible pads to transfer heat by direct (animal on pad) or indirect (air around the animal) contact. The units can either set and circulate water at the reservoir's temperature, or incorporate thermo-controller technology to regulate the temperature of the pad or air temperature of the cage

Advantages offered by water circulation units include more uniform surface temperatures on pads and in cages.

Disadvantages include the risk of punctures of radiators, pads, and tubing creating local flooding and animal drowning hazards. The organization e.g. geometry, directions of flow and flow rates in the pad can affect thermal performance; alternating flow in parallel tubes will promote a stable temperature across pad surface area due to countercurrent heat transfer; hair-pin loop configurations where there inward and outward flows are connected in close contact with each other can produce thermal gradients (counter-current isolation phenomena).

Recommendations for use: Direct contact water circulation units are generally appropriate for surgery and acute post-surgical recovery procedures, but not for longer term applications without continuous observation because of possible animal damage to the heated surface or tubing. Cage-top mounted water circulation units can be appropriate for longer-term recovery and for thermal stabilization of neonatal, juvenile, geriatric animals, exotic species and disease models because these units warm the air the animal is in contact with and are less susceptible to animal damage (w/caveat of potential drowning risk). Cage-top models may also be appropriate for animal transportation between laboratories and laboratory facilities, so long as electrical power is maintained.

Table 5: Recommendations for Use of Water Circulation Warming Devices

Unit	Acute Anesthesia	Surgery	Acute Recovery (Prolonged)	Prolonged Recovery	Neonatal, Juvenile, & Geriatric Animals	Disease Conditions	Exotic Species	Transport
Water circulation pads	√	√	√	×	×	×	×	×
Cage-mounted water circulation Units	√	×	√	√	√	√	√	√

Radiant and Far-Infrared Warming Devices

Table 6: Examples of Radiant and Infrared Warming Devices

Unit	Manufacturer	Product ID
Temp Controller w/heat lamp	Physitemp	TCAT-2AC, TCAT-2LV, TCAT-2DF, w/HL1
Heat Lamp	Physitemp	HL-1
Far Infrared Surgical Warming Pad	Kent Scientific	DCT-15, DCT-20, DCT-25
RightTemp® Temperature Monitor & Homeothermic Warming Control Module	Kent Scientific	PS-02

These units are radiant resistance heating units similar to heating plates, pads, blankets, and objects, except that they generate light wavelengths along the infrared red/visible/ultraviolet spectrum to provide heating. The simplest applications are egg incubators and radiant infrared heating for juvenile chicks (no products shown). Bulbs can be located underneath animal cages to provide warming. These units usually have a controller mechanism to regulate the ambient temperature generated by the heat generating unit. Some units are provided/used with thermo-control units wherein ambient temperature or temperature within an animal (e.g. rectal temperature) is compared to a calibrated 'setpoint' temperature and the output of the radiant unit increased or decreased to maintain the setpoint. Depending upon the primary wavelengths generated by the unit and absorption they can preferentially heat the air surrounding the animal (visible thru near infrared wavelengths) or transfer energy preferentially to the animal (far infrared, See Far Infrared Surgical Warming Pad, Kent Scientific)

Advantages of radiant units include ability to heat the animal indirectly or directly (depending upon wavelength), that most units do not require contact with the animal e.g. no equipment for the animals to damage, and the units used allow responsive animals to adjust position depending upon their warming preferences.

Disadvantages of radiant units include disruption of circadian cycling through continuous exposure to visible light, damage to eyes and skin (and internal organs if used during surgery) if precautions are not taken to prevent animal exposure to ultraviolet wavelengths. When used with photoreactive chemicals radiant units may elicit phototoxicity.

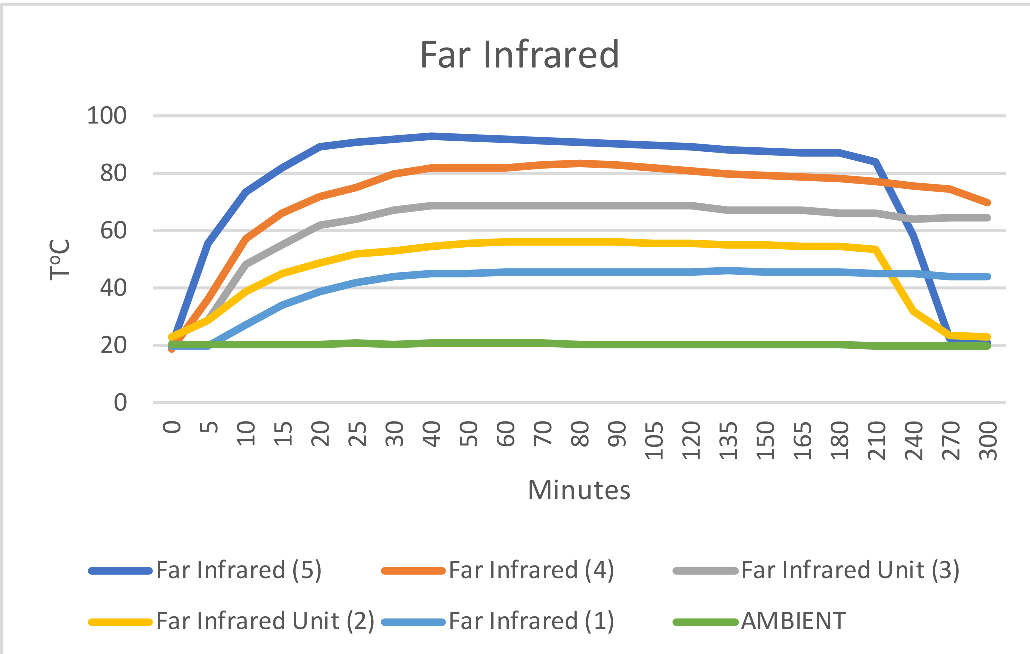
Recommendations for use: Radiant infrared heating units generally not appropriate for acute anesthesia surgery or acute recovery as unresponsive animals are unable to adjust their positions for optimal warming and the wavelengths generated may superheat exposed organs. They are the most commonly used for thermal support for juvenile, geriatric, and diseased animals and some tropical species. Users must know the wavelengths produced by the units used in order to anticipate and avoid unwanted consequences, e.g. phototoxicity, photocarcinogenicity. 24-hr exposure to even low level visible light may disrupt circadian rhythms. Bulbs generating ultraviolet wavelengths may damage the eyes and exposed skin (ultraviolet wavelengths are known carcinogens)

Users of radiant devices must know the surface and/or air temperature needed for their specific application(s), and measure the temperature produced and adjust as appropriate to prevent hyperthermia and hypothermia. Further, it is strongly advised to monitor surface, setpoint, and/or animal temperatures (a pocket infrared thermometer – IR-TW2) regularly to detect and rectify malfunctions.

Far Infrared Radiation

An example of a unit advertising far infrared (FIR) warming radiation (Kent Scientific DCT-15) was evaluated using a standard protocol. Following collection of an ambient temperature measurement, a laboratory grade mercury thermometer was wrapped inside the 6" by 8" FIR pad and measurements commenced for 300 minutes at the five (1-5) power settings. Data are presented in Figure 1.

Figure 1: Evaluation of a Battery-Powered Far Infrared Heating Device



Legend for Figure 1: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). The Far Infrared device was folded over an individual mercury laboratory grade thermometer and activated after collection of time = 0 temperature, and the unit activated. Separate temperature profiles were collected for five power settings (1-5). Ambient temperature was recorded using separate thermometer. Temperatures were recorded at 5 to 60 min intervals for 300 minutes.

The data show a positive relationship linking relative battery power (1-5), thermometer temperature, and duration. The unit tested required approximately 30 min to generate a steady state temperature which was maintained for at least 3 hours. Following exhaustion of its battery power unit, temperature within the pad fell rapidly towards ambient levels (see Figure 1).

Even at its lowest power level (1), the infrared unit generated temperatures more than 40°C, too high for direct contact during acute anesthesia, surgery or acute post-surgical recovery. Because of the temperature range generated the FIR unit tested would be utilized with animals having ability to adjust their body position relative to the unit to achieve optimal body core temperature. Far infrared warming devices used in conjunction with thermocontrol technology may produce lower surface temperatures appropriate for use with unconscious/immobile animals.

Table 7: Recommendations for Use of Radiant and Infrared Warming Devices

Unit	**Acute Anesthesia**	**Surgery**	**Acute Recovery**	**Prolonged Recovery**	**Neonatal, Juvenile, & Geriatric Animals**	**Disease Conditions**	**Exotic Species**	**Transport**
Visible & Near-Infrared	×	×	×	√	√	√	√	√
Far-Infrared	×	×	×	√	√	√	√	√

Passive Radiant Warming Devices

Table 8: Examples of Passive Radiant Warming Devices

Unit	Manufacturer	Product ID
Grabber® Warmer	Grabber (Dalton GA 30722)	n/a
SpaceGels®	Spacedrapes	SPGL-S, SPGL-M
SpaceDrapes®	Spacedrapes	SP-TS, SP-DR
Deltaphase® Isothermal Pad	Braintree Scientific	39-DP
SnuggleSafe®	Lenric (UK)	n/a

These devices either reflectively attenuate the loss of body heat (e.g. SpaceDrapes) or generate heat thru an exothermic chemical reaction (e.g. oxidation of elemental iron to iron oxide) or phase change reaction. The amounts of energy (heat) released and temperatures generated by exothermic chemical reactions are functions of the amounts of reactants available. Thus, to use exothermic reactions to generate specific amounts of heat and temperatures that reactants and reaction conditions must be tightly controlled.

Energy is also absorbed or released in phase change reactions, e.g. solid to liquid and liquid to solid phase changes relevant for these products. The difference between phase change and exothermic chemical reactions is that with the former energy absorbed or released occurs isothermally (e.g. at constant temperature) until the phase change is complete. The temperatures at which phase changes occur are a physical characteristic of the molecules undergoing phase changes (e.g. a melting temperature (e.g. melting point) is a characteristic used in identification and purification of a specific molecular structure). Energy release at constant temperature associated with solid to liquid phase changes is the principle behind several of the passive radiant warming products (e.g. SpaceGel™, Deltaphase ®and SnuggleSafe®, Figure 1).

SpaceDrape®

The SpaceDrape® is a thin plastic film with a metallic finish that reflects but does not generate heat. When an anesthetized or immobilized animal is covered or wrapped with the drape the rate of loss of body core temperature is reduced. The SpaceDrape® can be used in potentiate warming effects of electrical resistance, water circulation, and passive warming devices. The SpaceDrape® is most appropriate for anesthetized and immobile animals.

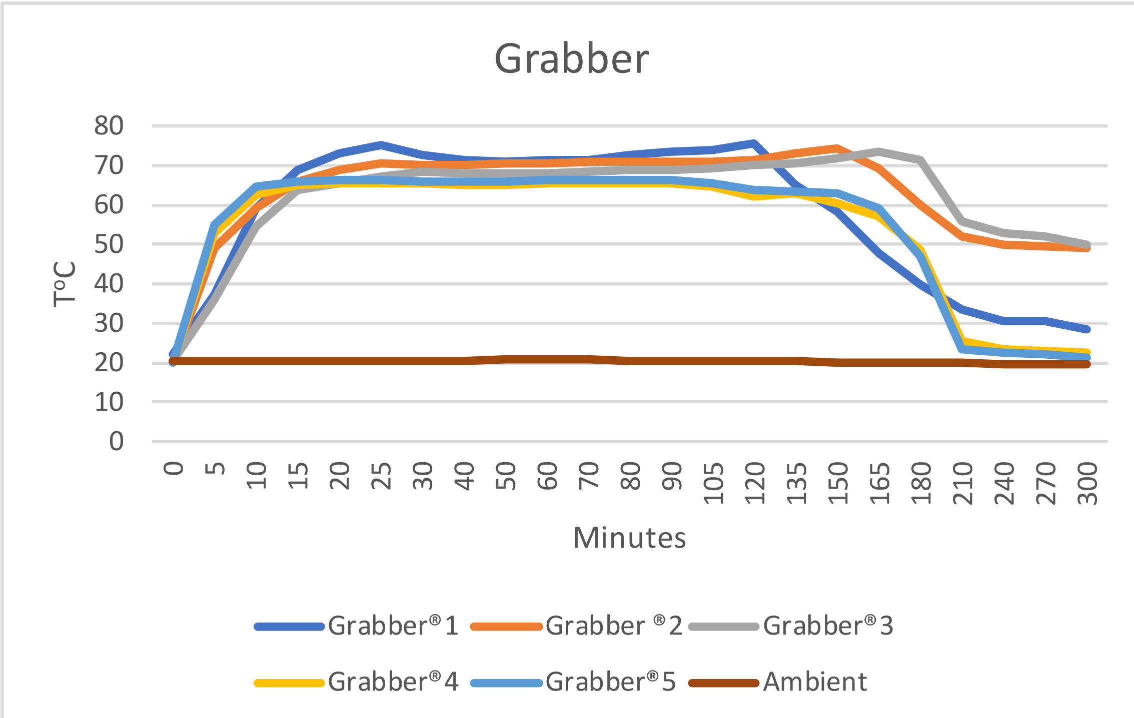
Grabber® Warmer

The Grabber® uses heat generated by the exothermic oxidation reaction following air exposure of fine iron particles. The Grabber® illustrates the principle of warming generated by exothermic inorganic chemical reactions. Figure 2 shows temperature generation profiles of 5 units using one (4, 5) or two (1-3) packets used per profile. Following exposure to air the surface temperature generated by one or two packets increased to approximately 70 degrees and was maintained for 2-3 hours. Two packets generated slightly higher temperatures than single units, consistent with the expected thermodynamics of exothermic chemical reactions.

With Grabber® and similar devices oxygen in the air reacts with elemental iron powder to yield iron oxide and heat, as much as 163 degrees Fahrenheit. Military-grade warmers (for heating MREs) can generate upwards of 200 degrees. (https://www.wired.com/2014/12/whats-inside-hot-hands/).

Grabber® similar units have not been designed or recommended for use with animals and because of the high and relatively unregulated temperatures generated compared to body temperature, the technology is only appropriate for use with conscious animals that can adjust their position relative to the unit, and then only with close technical supervision.

Figure 2: Evaluation of a Chemical Reaction Warming Unit (Grabber®)

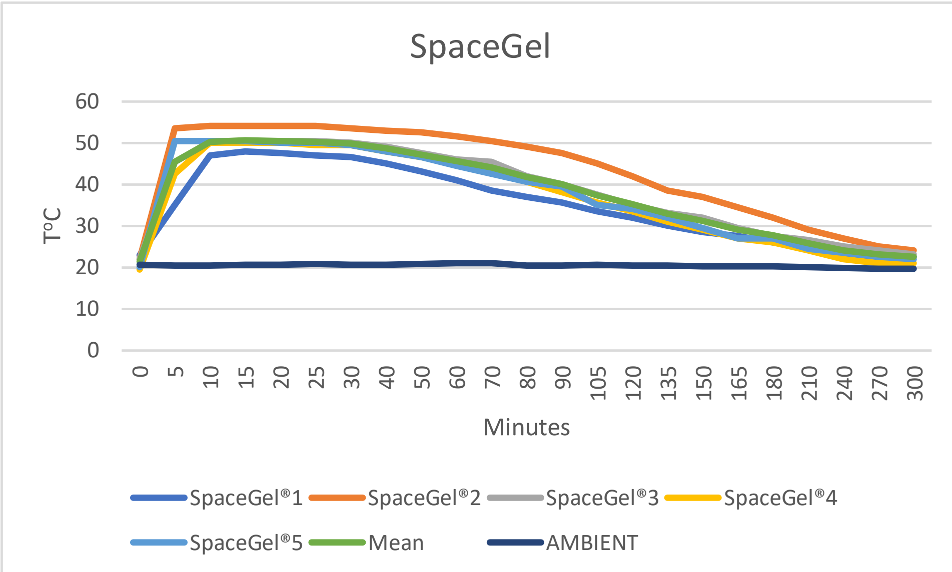


Legend for Figure 2: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). After collection of time = 0 temperature Grabber® devices (1, 2, and 3, two packets) were activated, and positioned above and below the bulb of an individual laboratory grade thermometer. After collection of time = 0 temperature Grabber® devices (4 and 5, one packet each) were activated, and positioned above the bulb of an individual mercury laboratory grade thermometer. Data for five (1-5) activations are presented. Ambient temperature was recorded using separate thermometers. Temperatures were recorded at 5 to 60 minute intervals for 300 min.

SpaceGel®

SpaceGel® is a supersaturated salt solution sealed with a stainless steel trigger in a flexible plastic pouch. The trigger mechanism activates a chain reaction crystallization of the salt molecules releasing energy associated with the liquid to solid phase change. Figure 3 shows temperature profiles generated with 3 sequential activations of a SpaceGel® device.

Figure 3: Evaluation of a Crystallization Phase Change Warming Unit (SpaceGel®)



Legend for Figure 3: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). Repeated (5) profiles of a SpaceGel® device on separate days, following activation after collection of time = 0 temperature and centered over a laboratory grade thermometers. Ambient temperature was recorded using separate thermometers. Temperatures were recorded at 5 to 60 min intervals for 300 min.

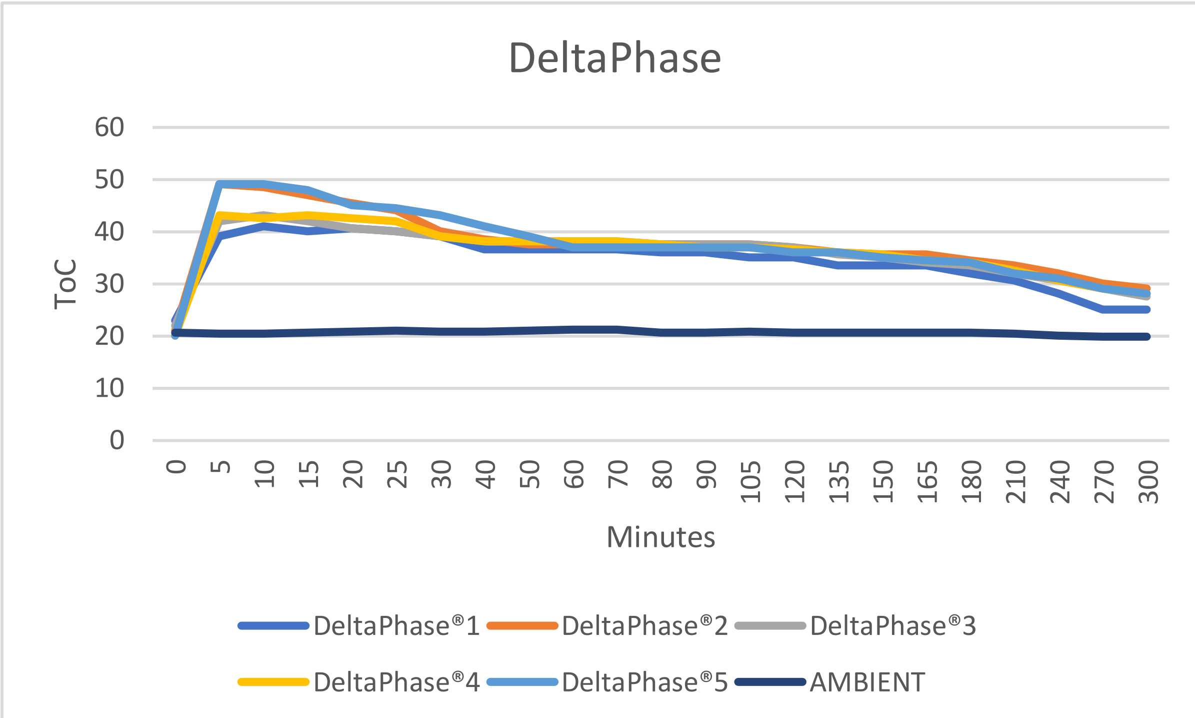
Following activation surface temperature rises rapidly and plateaus at approximately 50 degrees C. The isothermal plateau is maintained for approximately 30 minutes wherein the crystallization reaction is completed, and surface temperature then decreases towards ambient temperature. The period post activation wherein SpaceGel® delivers a useful therapeutic warming temperature is approximately 3 hours. Several minutes emersion in boiling water is the preferred method for reactivation. N.B.: The SpaceGel® pad contains a metal trigger and cannot be activated in a microwave oven.

Because of the relatively high stable surface temperature generated compared to body temperature, SpaceGel® is most appropriately used with conscious, mobile animals that can adjust their position relative to the device.

DeltaPhase®

DeltaPhase® is a eutectic formulation of salt, water, and polyethylene glycol in a flexible plastic pad. The formulation is designed to undergo solid-to-liquid phase change (melting) at approximately 38°C. The DeltaPhase® pad is activated (e.g., contents melted) in boiling water or a microwave oven. The unit tested in our analyses was readily activated after 1.5 minutes exposure in a microwave oven (~ 1200 watts). The effects of 5 sequential activations of a DeltaPhase® unit are shown in Figure 4. Upon microwave activation (1.5 to 2 min plus hand kneading to mix contents at 45 second intervals), the DeltaPhase® formulation is completely melted and contents appear transparent and exhibits a temperature above (in this case >40°C) its melting point, depending upon strength and duration of activation. Temperature of the DeltaPhase® formulation then falls at ambient temperature over approximately 30 min until liquid-solid phase change (freezing) begins. Thereafter, the DeltaPhase® pad maintains a constant surface temperature of 37-38°C for 2 to 3 hours. Once the phase change reaction is completed the pad temperature decreases slowly towards ambient temperature.

Figure 4: Evaluation of a Eutectic Phase Change Unit (DeltaPhase®)



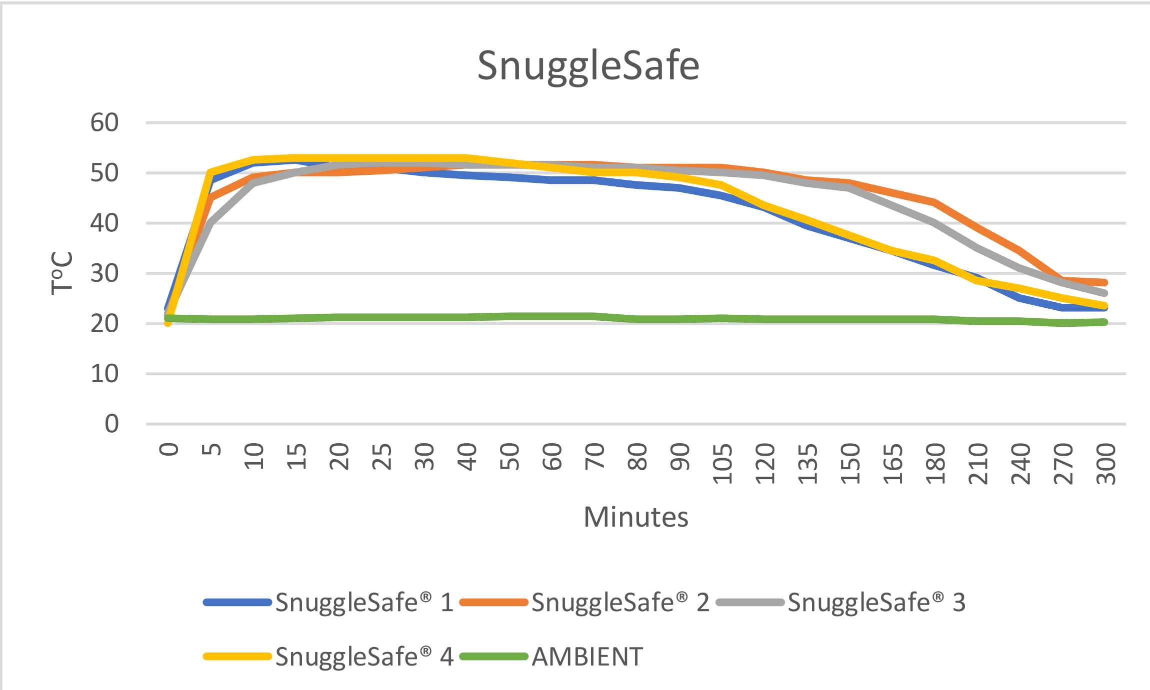
Legend for Figure 4: Vertical axis is surface temperature (ºC), horizontal axis is time (minutes). DeltaPhase® was activated by microwave radiation (1-2 min at 1200 watts) and centered over a laboratory grade thermometer, after collection of time = 0 temperature. Data for five (1-5) separate activations is presented. Ambient temperatures were recorded using separate thermometers. Temperatures were recorded at 5 to 60 min intervals for 300 min.

With its surface temperature of approximately body core temperature, DeltaPhase® is appropriate used with anesthetized, immobile, and conscious mobile animals. The non-toxic nature of its components allows use with minimal animal supervision, including transportation. The sturdiness of the DeltaPhase® formulation lends itself as a suitable warming platform upon which to perform surgical procedures.

SnuggleSafe®

SnuggleSafe® contains Thermapol® sealed in a solid opaque plastic pad. The product is activated by heating in a microwave oven for approximately 2-3 minutes (1200 watts). Because the pad is opaque it is not possible to visually monitor the activation process (see activation 1). Four sequential activations (1-4) of a SnuggleSafe® device are shown in Figure 5. Once activated, SnuggleSafe® surface temperature is maintained at approximately 50ºC for two hours before falling rapidly towards ambient levels. The heat retaining characteristics of the Thermapol® formulation are much shorter than those of the Deltaphase® formulation (compare w/Figure 4).

Figure 5: Evaluation of a Thermapol® Phase Change Unit (SnuggleSafe®)



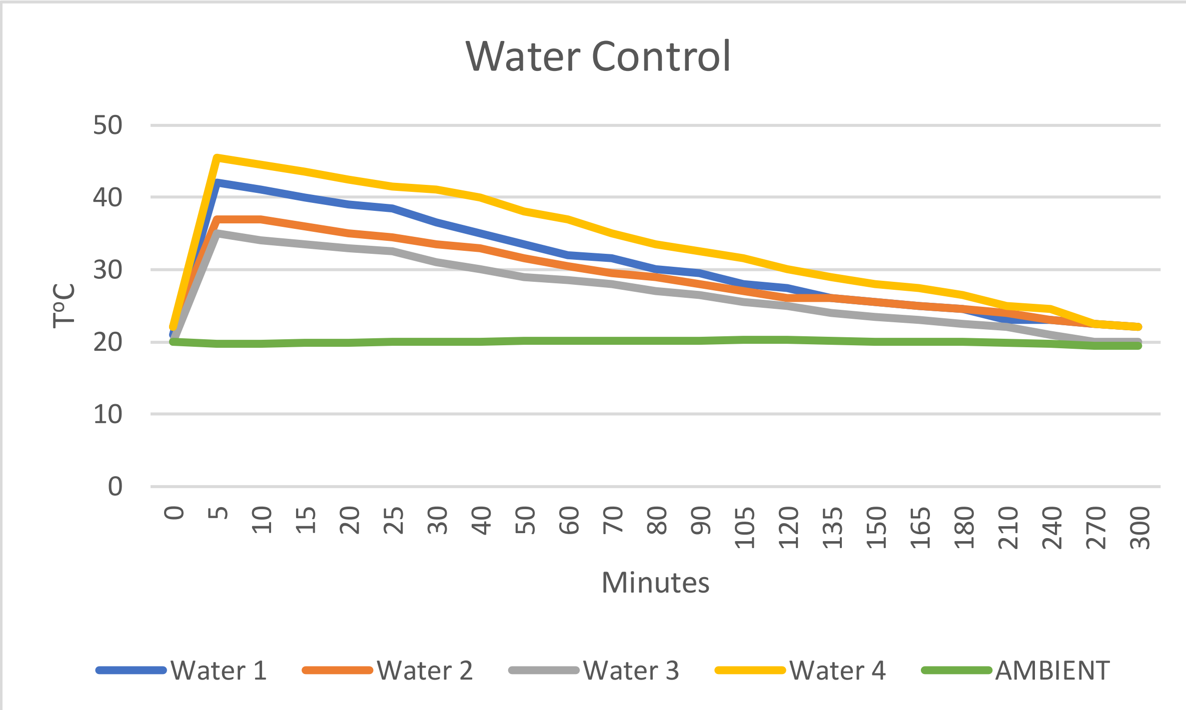
Legend for Figure 5: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). SnuggleSafe® was activated by microwave radiation (2-3 min at 1200 watts) and centered over individual mercury laboratory grade thermometer after collection of time = 0 temperature. Data for three (1-3) activations is presented. Ambient temperatures was recorded using separate thermometers. Temperatures were recorded at 5 to 60 min intervals for 300 min.

Because of the relatively high surface temperature generated compared to body temperature, SnuggleSafe® is most appropriately used with conscious, mobile animals that can adjust their position relative to the device.

Water Control

A traditional clinical warming device is a container filled with warm water (e.g., hot water bottle). Therefore, we measured the surface temperature profile over time of an amount of warm (~40°C) water contained in a small plastic bag and approximately equivalent in weight to DeltaPhase® and SpaceGel®. As expected, this device loses its heat in a linear fashion as a function of time (Figure 6).

Figure 6: Evaluation of a Water Control Unit

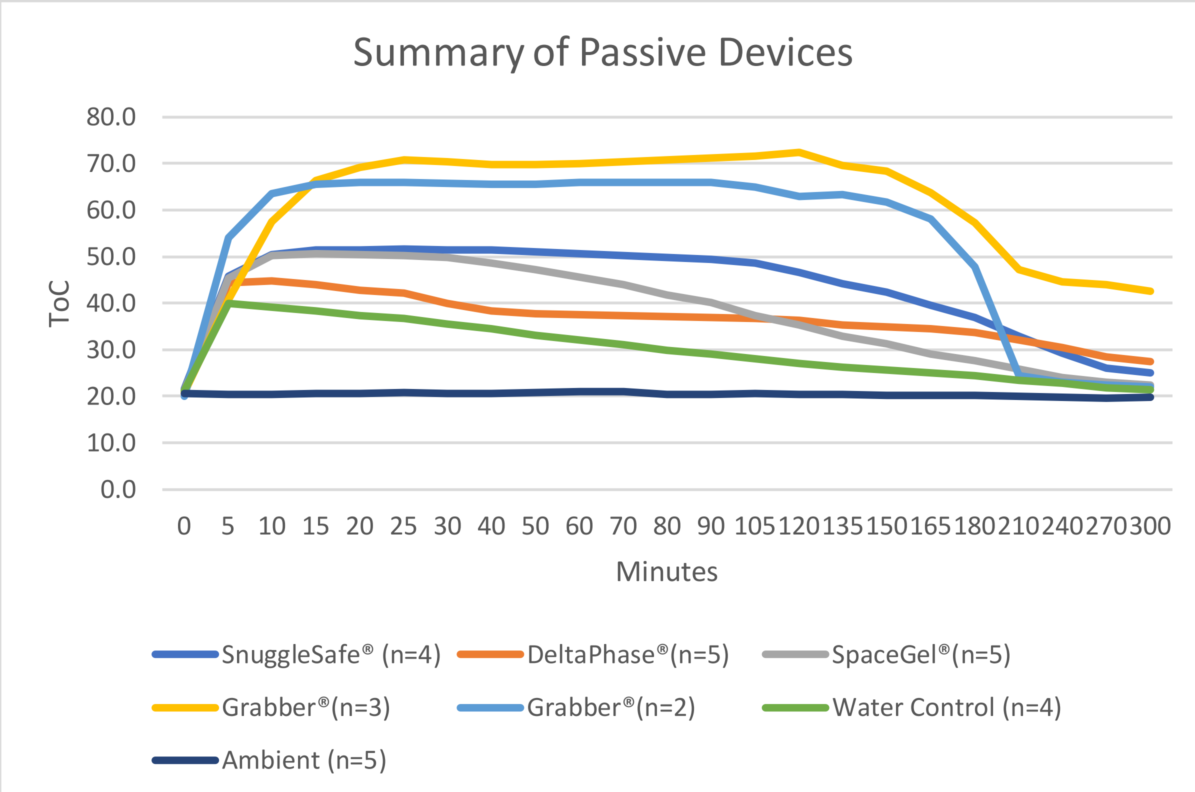


Legend for Figure 6: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). Water control was ~12 oz warm tap water (35-45 °C and approximately the weights of SpaceGel® and DeltaPhase® units) in a plastic bag and centered over a laboratory grade thermometer after collection of time = 0 temperature. Data for four (1-4) experiments are presented. Ambient temperatures were recorded using separate thermometers. Temperatures were recorded at 5 to 60 min intervals for 300 min.

Comparison of Passive Warming Devices

The surface temperature profiles of SpaceGel®, DeltaPhase®, SnuggleSafe® are compared to that of an equivalent volume of water sitting at ambient temperature. All three devices exhibit isothermal release of heat consistent with phase change; however, only DeltaPhase® is designed for isothermal release at approximate body core temperature (~38°C).

Figure 7: Summary of Passive Warming Devices



Legend for Figure 7: Vertical axis is surface temperature (°C), horizontal axis is time (minutes). Water, SpaceGel®, DeltaPhase®, SnuggleSafe® devices were activated after collection of time = 0 temperature and centered over laboratory grade thermometers. Water control was ~12 oz water (approximately the weights of SpaceGel® and DeltaPhase® units) in a plastic bag. Ambient temperature was recorded using separate thermometers. Values are means of repetitions (n=2-5). Temperatures were recorded at 5 to 60 minute intervals.

Table 9: Recommendations for Use of Passive Radiant Warming Devices

Unit	**Acute Anesthesia**	**Surgery**	**Acute Recovery**	**Prolonged Recovery**	**Neonatal, Juvenile, & Geriatric Animals**	**Disease Conditions**	**Exotic Species**	**Transport**
Grabber®	×	×	×	×	×	×	×	×
SpaceGel®	×	×	×	√	√	√	√	√
DeltaPhase®	√	√	√	√	√	√	√	√
SnuggleSafe®	×	×	×	√	√	√	√	√

Summary and Recommendations

In this document we have outlined the critical importance of body temperature and thermostasis for health and welfare of homoeothermic species, focusing upon laboratory in vivo animal experimentation and veterinary practice. While the physiological, pharmacological, and pathogenic aspects of thermostasis are common to all homeotherms, we focus upon species with smaller body mass because: a) Smaller species must generate disproportionately more energy (heat) per unit body mass to maintain thermostasis; and b) Smaller species loose body temperature more rapidly when thermostasis mechanisms are disrupted.

We have described 8 general classes of situations in small animal husbandry and research and veterinary practice wherein external warming to assist body thermostasis is necessary: Acute anesthesia, Surgery, Acute Recovery, Prolonged Recovery, Neonatal Juvenile and Geriatric Animals, Exotic Species, and Animal Transportation. While some of these classes share similar features and constraints for external warming, each has unique features.

Finally, we have organized the available external warming devices and technologies into four categories: Electrical resistance, water circulation, radiant and far infrared, and passive warming devices. We have reviewed each of the categories of devices for suitability in each of the eight classes of situations and have made specific recommendations summarized in the tables presented above. In general:

a) Electrical resistance warming devices are most appropriately used with unconscious and/or unresponsive animals with continuous technical monitoring due to serious risks associated with animal damage to electrical components. An exception may be made for so-called 'warming rock' devices that are used with conscious/responsive animals, so long as provisions are made to protect against animal damage to electrical components. The surface temperatures and temperature control mechanisms associated with electrical resistance devices are appropriate for surgical and acute care applications to maintain normal thermostasis, and electrical heating plates and pads are readily compatible with the surgical theater.
b) Water circulation warming devices are also most appropriately used with unconscious and/or unresponsive animals with continuous technical monitoring due to serious risks associated with animal damage to water circulation components. An exception may be made for cage-top water circulation devices that provide indirect warming when used with conscious/responsive animals, so long as provisions are made to protect against animal damage to electrical and water circulating components. The surface temperatures and temperature control mechanisms associated with water circulation devices are appropriate for surgical and acute care applications to maintain normal thermostasis, and water circulation heating plates and pads are readily compatible with the surgical theater.
c) Radiant devices using visible and near-infrared wavelengths are most appropriately used with conscious and/or responsive animals with periodic technical monitoring because these devices are used to heat the air in the cage and/or skin of animals and do not have components that can be damaged by animals and cause injury. Care must be taken to provide and insure that radiant devices do not overheat the environment, and that in combination with caging a heating gradient is provided wherein animals can select a zone providing optimal warming. An exception is the far-infrared heating pad (Figure 1) which provides surface temperatures significantly in excess of normal body temperature ranges and should be used with caution with unconscious or unresponsive animals or in surgery to prevent hyperthermia. The far infrared unit is inappropriate for use with conscious animals unless closely monitored because its battery power pack connector poses an electrical shock risk if damaged.
d) Passive warming devices generate heat thru chemical reactions and/or physical liquid to solid phase change (Figures 2-7). The Grabber® warmer unit was never intended for use with animals and is shown only to illustrate the heat generated by the iron to iron oxide chemical redox reaction. The physical phase change devices (SpaceGel®, SnuggleSafe®, and Deltaphase®) are appropriately used with conscious and/or responsive animals with periodic technical monitoring because they do not pose risks to animal health if damaged. However, SpaceGel® and SnuggleSafe® devices generate surface temperatures significantly in access of normal body temperature range must be used with caging that permits animals to position themselves at distances to achieve optimal warming and avoid hyperthermia. Similarly, these devices are not appropriate for surgery and used only with continuous monitoring unconscious/unresponsive animals. The exception is the DeltaPhase® device which during phase change generates a surface temperature of approximately 38°C for a duration of several hours. This device is appropriate for use with conscious/responsive animals and with unconscious/unresponsive animals to prevent hypothermia

without risk of hyperthermia. The design of the device and consistency of its eutectic formulation facilitates its use as a thermally-controlled surgical operating surface. DeltaPhase® is the only product that could be recommended for use in all 8 of the classes of situations identified above wherein external warming is necessary to assist thermostasis.

Conclusions

In using external warming devices in experimental animal research or clinical veterinary practice investigators and clinicians must match the characteristics of the animal species and situation with the attributes of individual device options. Some devices generate surface temperatures that are controlled to provide thermostasis without risking hyperthermia, other devices generate surface temperatures always in access of thermostatic need and require that animals or investigators adjust position relative to the device to prevent hyperthermia. Some devices pose serious risks to animals if damaged, other devices lack those risks. Some devices are easily integrated with specific situations (e.g. heated plates or pads as surgical operating surfaces), some are less easily integrated or incompatible. Only the DeltaPhase® device, if used according to manufacturer's specifications is applicable for all eight applications because it maintains surface temperature in the range of animal body core temperature, contains no acute hazards when used with animals, and provides a suitable working surface for surgical procedures.

It is the responsibility of investigators and clinicians to be knowledgeable of the needs of animals under their care and specific situations, the characteristics of specific external devices, and to make choices that are appropriate to maintain thermostasis and animal safety.

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