Review Article

Intra-Family and Inter-Family Comparisons for Viral Susceptibility to Heat Inactivation

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Abstract

A systematic review of the viral heat inactivation literature for data compatible with modeling using the decimal reduction value/*z* value approach as well as a new approach based on the power function relationship between decimal reduction value and inactivation temperature is presented. The review has enabled us to conduct quantitative intra-family and inter-family comparisons for various heat inactivation characteristics for viruses, including *z* value, temperature in °C for 1 $\log_{10}$ and for 4 $\log_{10}$ inactivation in 30 seconds. The *parvoviridae* family is confirmed to be the most heat resistant of the various virus families for which data were analyzed.

Keywords: *D* value; Enveloped viruses; High-temperature short-time; Inactivation kinetics modeling; Non-enveloped viruses; Viral heat inactivation; *z* value

Introduction

Heat inactivation of viruses represents an important approach for mitigating the risk of viral contamination for food and drinking water protection [1-10], inactivation of vaccine viruses [11-15], inactivation of viruses of importance to agriculture and animal husbandry [16-30], and inactivation of viruses in blood products [31-33]. More recently, heat inactivation and more particularly high-temperature short-time (HTST) treatment have been evaluated as a barrier technology for mitigating the risk of introducing adventitious viral contaminants into biologics manufacturing processes through contaminated cell culture reagents [34-36]. For the latter studies, it has been assumed that a species from the parvoviridae family represents an appropriate worst-case model virus, and murine minute virus has been used as the prototypic species from this family [34-36]. This reflects the opinion [e.g. 24] that the parvovirus family is among the most resistant of the virus families to heat inactivation.

While it has been useful to use a parvovirus as a worst-case model, the empirical data on virus inactivation by heat treatment has not, heretofore, actually lent itself to inter-family or even inter-species comparisons of susceptibility to this inactivation modality. As discussed previously [37], this has been due to the fact that empirical studies of heat inactivation of viruses have not been performed at standardized conditions of temperature and time, and it turns out that both of these factors play important roles in determining heat inactivation efficacy. So even if the inactivation matrices have been duplicated or approximated across different studies, the exact conditions of temperature and time have rarely been directly comparable.

In a recent report [37], we have described a modeling approach intended to allow inter-study evaluation of heat inactivation results as a means of circumventing the difficulties in conducting the inter-family and inter-species comparisons described above. This approach is based on the power function relationship between decimal reduction value (*D*, the time required to inactivate 1 $\log_{10}$ of a virus) and temperature. In the present survey of the viral heat inactivation literature, this modeling approach has been used to facilitate direct comparison of heat inactivation susceptibility results for a number of virus families, including both enveloped and non-enveloped viruses. This survey is expanded greatly relative to the few examples discussed in our previous report [37]. The *z* value (a more traditionally used value corresponding to the temperature required to cause a one $\log_{10}$ change in *D*) obtained for each of the various viruses has also been assembled and compared. In addition, the existence of a rather extensive literature on the heat inactivation of caliciviruses has enabled the intra-species and inter-species variability of heat inactivation for this family to be assessed.

The results confirm that the parvovirus family is, in fact, the most resistant of the various virus families for which heat inactivation data exist.

Methods

Literature survey

The viral heat inactivation literature from the late 1950s forward was searched for reports containing the requisite results to enable the modeling approach described below. In particular, the studies must have investigated wet heat inactivation (inactivation of viruses in liquids) vs. time at three or more different fixed temperatures. No limit to upper temperature was applied. The limit to lower temperature was necessitated by the absolute requirement that at least one $\log_{10}$ inactivation of virus must have occurred (i.e., a *D* value must have been obtained for each temperature). These *D* values were in some cases reported by the authors in the paper. In other cases, inactivation vs. time plots displaying at least one $\log_{10}$ inactivation of the model virus at each of the three or more temperatures were provided. In the latter cases, we had to estimate the *D* values from the reported plots. As some degree of error was necessarily introduced through this *D* value-estimation process, the instances involving use of such estimates have been indicated in the data summaries to follow.

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The authors made every attempt to identify and to analyze all sources of literature satisfying the requirements listed above. No single search string was employed. Repeated attempts to retrieve literature meeting the modeling requirements were made, using various rearrangements of: heat inactivation, D value, and virus or specific virus names. Retrieving the various publications cited herein was one of the most difficult aspects of this survey. The literature obtained includes reports of the inactivation of a variety of non-enveloped [3-5,7-11,19,23-28,39] and enveloped [1,6,12,14-18,21,22,26,29-31,33] viruses. As might be expected, those viruses considered a threat to food safety are somewhat more highly represented in the heat inactivation literature.

Our aim in the present paper was to survey the viral inactivation literature for heat inactivation in liquids and specifically for literature that contained the level of detail required for our modeling approach. The results of the survey will allow the research community to find, within one source, heat inactivation estimates of efficacy and, importantly, also z values, for 12 non-enveloped viruses and 15 enveloped viruses. Heat inactivation can be very matrix sensitive. In order to facilitate the inter- and intra-family comparisons that were of interest to the authors, it was felt advantageous to control for matrix variability to the greatest extent possible. Dry heat inactivation (inactivation of viruses on surfaces by heat), the heat inactivation of viruses within solid food items, and the heat inactivation of bacteriophage were therefore considered to be out of scope for this survey.

Modeling of viral heat inactivation

Historically, heat inactivation of microbes, and particularly, food pathogens, has been evaluated through calculation of D and z values [e.g., 38]. This approach has been used also for evaluating the thermal inactivation of viruses. The decimal reduction value (D) for a given inactivation temperature is obtained from a plot of $\log_{10}$ inactivation vs. time at that temperature, and reflects the amount of time required at that temperature to reduce the initial viral titer by 90%. In cases where the plots of $\log_{10}$ inactivation vs. time display first-order kinetics through multiple $\log_{10}$ of inactivation, the amounts of time required for higher levels of inactivation may be calculated easily using D, as 2 $\log_{10}$ inactivation will require $2D$, 3 $\log_{10}$ inactivation will require $3D$, and so on.

The z value is obtained from the slope (m) of the linear line equation for a plot of log D vs. temperature, and therefore in order to determine a reasonably accurate z value, inactivation must have been assessed and D values obtained at three or more different temperatures. The z value is obtained as:

$$Z = \frac{1}{|m|} \qquad (1)$$

The utility of the z value historically has been in calculating D values for inactivation temperatures other than those actually explored empirically. In order to accomplish this, one solves the following equation:

$$\log_{10} D_{predicted} = \log_{10} D_{ref} - \frac{T - T_{ref}}{z} \qquad (2)$$

where T is the temperature at which D is to be predicted, and T_{ref} is the temperature at which D_{ref} was actually measured [38]. As is apparent, in order to execute this calculation, one must arbitrarily select one of the three or more empirical temperatures to be T_{ref}, and the corresponding D value is used as D_{ref}.

The rationale for pursing a different approach for modeling heat inactivation susceptibility of viruses, and the approach itself, have been described in detail previously [37]. In brief, this alternative approach consists of assigning a power function line fit directly to a plot of D vs. temperature. As with the z value, this approach requires that inactivation must have been assessed and D values obtained at three or more different temperatures. The power function line fit may be obtained using Excel as:

$$D = a * temperature^{-b} \qquad (3)$$

where a and b are constants.

Once these power function parameters have been obtained, the equation may be solved either for D at a given temperature, as in (3), or for the temperature yielding a given D, as:

$$temperature \ (^{o}C) = \left(\frac{D}{a} \right)^{-\frac{1}{b}} \qquad (4)$$

As with the z value approach, the accuracy of the power function approach for estimating inactivation at temperatures other than those actually probed in generating inactivation data is dependent on a number of factors. These include the goodness of fit of the underlying line equations (indicated by R^2) and the breadth of empirical temperatures evaluated relative to the temperatures at which predictions are to be made. The advantages of the power function approach over the z value approach are that in the former case fewer steps are involved and the calculation of inactivation at non-empirical temperatures does not involve the arbitrary selection of a reference temperature and the subjectivity thereby introduced. An example of a power function fit to empirical temperature inactivation data is shown in Figure 1. Additional examples of the use of both the z value approach and the power function approach for modeling heat inactivation at non-empirical temperatures, based on the same data set, have been reported previously [37].

Results and Discussion

As part of the analysis for the present survey, it was considered appropriate to make comparisons for non-enveloped vs. enveloped viruses in order to allow, for the first time, quantitative comparison of efficacy for these two broad classes of virus. Such quantitative comparisons have not been possible in the past. We have selected one
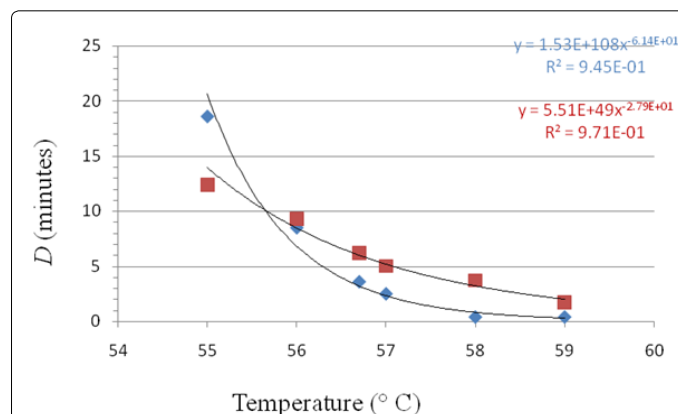
Figure 1: Modeling using the power function of the relationship between temperature and D (the time required to inactivate 1 $\log_{10}$ of virus). Data for avian influenza (blue symbols) or Newcastle disease virus (red symbols) [6].

heating time (30 seconds) as an example in displaying the utility of the modeling approach. This time reflects our own bias that a short time at temperature may cause less damage to the types of inactivation matrices that we are interested in (i.e., biologicals). But it should be noted that this modeling approach (equations 3 and 4 and modeling parameters for each virus) will allow the reader to calculate inactivation efficacy at conditions of time and/or temperature relevant to their own applications.

Heat inactivation results for non-enveloped viruses

Literature describing the heat inactivation of four families of non-enveloped viruses (parvoviridae, caliciviridae, picornaviridae, and birnaviridae) was identified and analyzed. Two or three species were represented for each virus family. The heat inactivation characteristics (inactivation matrices, z values, power function parameters, and modeled temperatures yielding 1 $\log_{10}$ or 4 $\log_{10}$ inactivation following 30 seconds heating) for the various non-enveloped viruses for which appropriate literature was identified have been assembled in Table 1. These data have been arranged by virus family, with the various families listed in approximate order of particle size. Intra- and inter-family variability in the determined heat inactivation susceptibilities for the non-enveloped viruses is discussed below.

The relatively extensive literature on heat inactivation of the caliciviruses feline calicivirus (FeCV) and murine norovirus (MNV) enabled a more detailed examination of the intra- and inter-species variability in heat inactivation susceptibility. The results of this evaluation are shown in Figure 2. The temperatures required to cause 1 $\log_{10}$ inactivation in 30 seconds were 70.9 ± 12.1°C (mean ± SD, $n=5$) for murine norovirus and 70.9 ± 13.7°C (mean ± SD, $n=4$) for feline calicivirus. These indicate a relative standard deviation of 17% and 19%,

respectively. The mean temperature values required for inactivation of 1 $\log_{10}$ in 30 seconds were not significantly different between the two calicivirus species ($P=1.00$ by ANOVA). The variability in the determined z values was also assessed. The z values were found to be 10 ± 3°C (mean ± SD, $n=5$) for murine norovirus and 11 ± 2°C (mean ± SD, $n=4$) for feline calicivirus. The relative standard deviations associated with these values, which were not significantly different ($P=0.80$ by ANOVA), were 30% and 18%, respectively.

Heat inactivation results for enveloped viruses

Literature describing the heat inactivation of eight families of enveloped viruses (rhabdoviridae, herpesviridae, flaviviridae, coronaviridae, retroviridae, poxviridae, paramyxoviridae, and orthomyxoviridae) was identified and analyzed. Two or three species were represented for each virus family except in the case of flaviviridae, retroviridae, and orthomyxoviridae, for which only a single species has been represented. The heat inactivation characteristics (inactivation matrices, z values, power function parameters, and modeled temperatures yielding 1 $\log_{10}$ or 4 $\log_{10}$ inactivation following 30 seconds heating) for the various enveloped viruses for which appropriate literature was identified have been assembled in Table 2. These data have been arranged by virus family, with the various families listed in approximate order of particle size. Where the data allowed, intra- and inter-family variability in the determined heat inactivation susceptibilities for the enveloped viruses were assessed and have been discussed below.

Intra-and inter-family comparisons of heat inactivation susceptibility

For cases in which at least two different species of virus were

Virus	Family	Matrix	z (°C)	Power Function Parameters			Temperature (°C) for Inactivation in 30 seconds		Ref
				a	b	R²	1 log₁₀	4 log₁₀	
mouse minute virus	parvoviridae	culture medium	35†	8.00×10^{8}	4.28	0.99	141	196	[19]
		water	16†	1.19×10^{23}	11.6	0.99	104	117	[27]
bovine parvovirus		water	8.2*	2.23×10^{41}	21.1	0.90	94	101	[24]
canine parvovirus		water	12†	1.59×10^{28}	14.2	0.99	102	112	[23]
feline calicivirus	caliciviridae	PBS	14*	9.9×10^{14}	7.80	1.00	91	109	[7]
		culture medium	9.3*	3.43×10^{28}	15.9	0.94	65	71	[4]
		culture medium	9.8†	1.07×10^{24}	13.5	0.89	63	70	[5]
		culture medium	9.3*	8.58×10^{26}	15.1	0.94	64	70	[10]
murine norovirus		PBS	13*	5.41×10^{15}	8.16	0.98	92	109	[7]
		culture medium	12*	2.53×10^{21}	12.0	0.94	64	72	[4]
		PBS	9.5†	7.08×10^{22}	12.6	0.97	69	77	[9]
		culture medium	9.3*	1.38×10^{27}	15.2	0.93	64	70	[10]
		culture medium	6.4*	1.20×10^{35}	19.5	0.99	65	70	[39]
foot and mouth disease virus (strain OPN)	picornaviridae	PBS	35*	1.24×10^{9}	5.27	0.94	61	79	[28]
foot and mouth disease virus (strain OBFS1860)		culture medium	11*	4.50×10^{24}	13.5	0.95	71	78	[26]
foot and mouth disease virus (strain A119)		buffer pH 7.5	5.9*	6.19×10^{35}	20.3	0.98	60	64	[11]
hepatitis A virus		PBS	10*	5.30×10^{25}	13.6	0.96	82	91	[7]
coxsackie B-5 (Faulker strain)		culture medium	6.1†	1.11×10^{43}	24.4	0.95	60	63	[3]
infectious pancreatic necrosis virus	birnaviridae	PSM	9.9*	1.96×10^{31}	16.2	0.99	89	97	[8]
infectious bursal disease virus		peptone broth	17†	5.96×10^{18}	10.0	0.95	81	93	[25]

PBS, phosphate buffered saline; PSM, peptone salt medium
*D (decimal reduction) values used to calculate the z values and power functions were reported in the reference.
†D values used to calculate the z values and power functions were estimated from the published inactivation vs. time plots.

Table 1: Heat inactivation characteristics for various non-enveloped viruses.

represented in a given family of non-enveloped or enveloped viruses, the intra-family variability in heat inactivation characteristics was assessed (Table 3). These comparisons apply strictly to inactivation of viruses in liquids. Extrapolation of these results to viruses adsorbed to surfaces, or to viral aggregates or viruses suspended in aerosols may not be appropriate. The same applies to viruses in matrices other than liquids (purés, solid foods, surfaces, etc.).

For the temperature required to cause a 1 $\log_{10}$ inactivation in 30 seconds, the relative standard deviation values ranged from 4% for paramyxoviruses to 19% for parvoviruses. The overall value for this modeled inactivation parameter for non-enveloped viruses (four families) was $83 \pm 20°C$ (relative standard deviations=24%), compared to $70 \pm 8.9°C$ (relative standard deviations=13%) for enveloped viruses (five families). The overall value for non-enveloped viruses was not

significantly different from that for enveloped viruses (P=0.23 by ANOVA).

For the temperature required to cause a 4 $\log_{10}$ inactivation in 30 seconds, the relative standard deviation values ranged from 3% for birnaviruses to 33% for parvoviruses. The overall value for this modeled inactivation parameter for non-enveloped viruses (four families) was $96 \pm 25°C$ (relative standard deviations=26%), compared to $82 \pm 13°C$ (relative standard deviations=16%) for enveloped viruses (five families). The overall value for non-enveloped viruses was not significantly different from that for enveloped viruses (P=0.32 by ANOVA). As with inactivation of 1 $\log_{10}$ in 30 seconds, much of the variability observed for the temperature required to cause a 4 $\log_{10}$ inactivation in 30 seconds would appear to represent inter-study variability.

Virus	Family	Matrix	z (°C)	Power Function Parameters			Temperature (°C) for Inactivation in 30 seconds		Ref
				a	*b*	R²	1 log₁₀	4 log₁₀	
hepatitis C virus	flaviviridae	culture medium	9.8†	4.26×10^{20}	11.4	0.97	69	77	[33]
HTLV-III	retroviridae	culture medium	5.6*	3.61×10^{37}	21.4	1.00	59	63	[31]
transmissible gastroenteritis virus	coronaviridae	HEPES	8.9†	4.38×10^{20}	10.9	0.97	83	95	[21]
Berne virus		culture medium	9.6†	6.04×10^{16}	9.16	0.98	73	85	[22]
canine coronavirus		culture medium	31†	1.23×10^{9}	4.92	0.86	81	107	[29]
avian influenza	orthomyxoviridae	fat-free egg	2.1*	1.53×10^{108}	61.4	0.95	58	60	[6]
rabies (Pasteur)	rhabdoviridae	PBS	12†	3.16×10^{19}	11.0	0.99	63	72	[14]
rabies (ERA)		PBS	8.2*	8.68×10^{21}	12.4	0.99	62	70	[15]
vesicular stomatitis virus		PBS	8.5*	5.68×10^{20}	11.9	0.97	59	66	[15]
		culture medium	4.4*	3.62×10^{40}	23.6	1.00	54	57	[30]
herpes simplex 1	herpesviridae	Tris	9.0†	2.43×10^{15}	8.40	0.89	74	87	[17]
cytomegalovirus		Tris	13†	5.10×10^{11}	6.13	0.97	91	114	[17]
pseudorabies virus		culture medium	7.7†	1.19×10^{32}	17.9	1.00	64	70	[26]
variola	poxviridae	PBS	18†	2.07×10^{11}	6.04	0.99	84	105	[16]
vaccinia (Lister)		buffer	10†	5.38×10^{22}	12.7	0.91	65	73	[12]
respiratory syncytial virus	paramyxoviridae	water	10*	2.17×10^{17}	9.73	0.99	65	75	[18]
Newcastle disease virus		allantoic fluid	9.4†	5.64×10^{21}	12.4	0.89	60	67	[1]
		fat-free egg	4.7*	5.51×10^{49}	27.9	0.97	62	65	[6]

HEPES, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid); PBS, phosphate buffered saline; Tris, tris(hydroxymethyl)aminomethane.
*D (decimal reduction) values used to calculate the *z* values and power functions were reported in the reference.
†D values used to calculate the *z* values and power functions were estimated from the published inactivation vs. time plots.
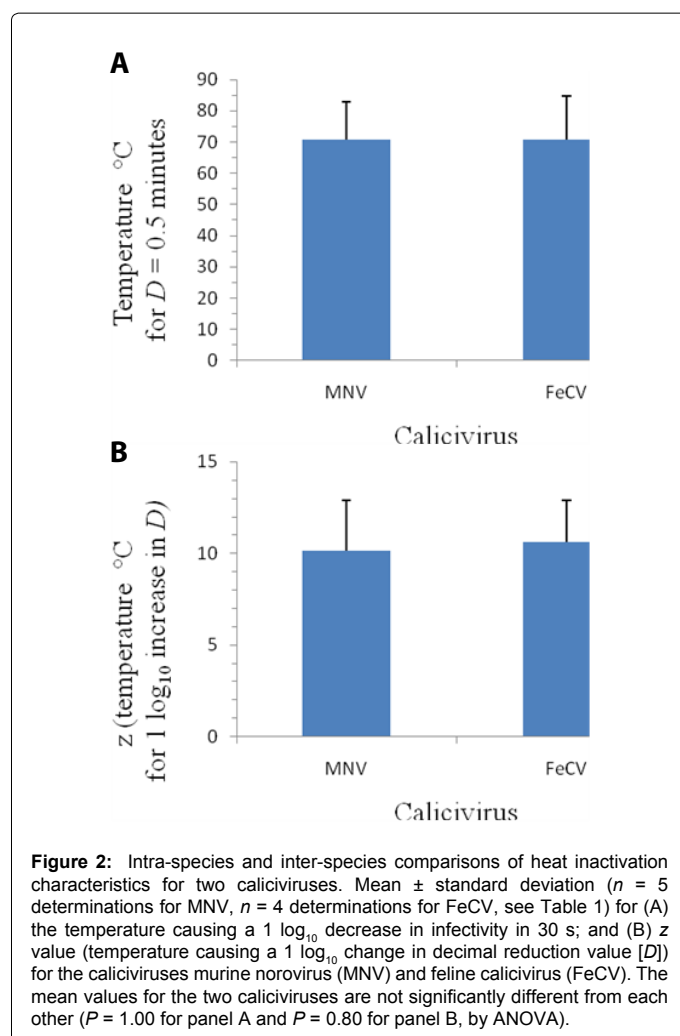
Table 2: Heat inactivation characteristics for various enveloped viruses.

Family	Temperature (°C) Inactivating 1 log₁₀ in 30 seconds				Temperature (°C) Inactivating 4 log₁₀ in 30 seconds				z (°C)			
	Mean	*n*	SD	RSD	Mean	*n*	SD	RSD	Mean	*n*	SD	RSD
parvoviridae	110	4	21	19	131	4	43	33	18	4	12	66
caliciviridae	71	9	12	17	80	9	17	21	11	9	2.4	22
picornaviridae	67	5	10	15	77	5	11	15	13	5	12	94
birnaviridae	85	2	5.9	7	95	2	3.0	3	14	2	5.2	38
non-enveloped viruses	83	4	20	24	96	4	25	26	14	4	2.9	21
coronaviridae	79	3	5.3	7	96	3	11	12	17	3	13	76
rhabdoviridae	59	4	4.2	7	66	4	6.4	10	8.2	4	2.9	36
herpesviridae	76	3	14	18	90	3	22	25	10	3	2.5	26
poxviridae	62	3	2.5	4	69	3	5.1	7	8.1	3	3.0	37
paramyxoviridae	74	2	13	18	89	2	23	26	14	2	5.6	40
enveloped viruses	70	5	8.9	13	82	5	13	16	11	5	3.8	33

RSD, relative standard deviations; SD, standard deviations; *z*, temperature causing a 1 $\log_{10}$ change in decimal reduction value.

Table 3: Intra-family and inter-family comparison of viral heat inactivation characteristics.

Figure 2: Intra-species and inter-species comparisons of heat inactivation characteristics for two caliciviruses. Mean ± standard deviation ($n = 5$ determinations for MNV, $n = 4$ determinations for FeCV, see Table 1) for (A) the temperature causing a 1 $\log_{10}$ decrease in infectivity in 30 s; and (B) z value (temperature causing a 1 $\log_{10}$ change in decimal reduction value [D]) for the caliciviruses murine norovirus (MNV) and feline calicivirus (FeCV). The mean values for the two caliciviruses are not significantly different from each other ($P = 1.00$ for panel A and $P = 0.80$ for panel B, by ANOVA).

and inactivation temperature [37] has been presented. The review has enabled us to conduct for the first time quantitative inter-family and intra-family comparisons for various heat inactivation characteristics for viruses, including z value or temperature in °C for 1 $\log_{10}$ or 4 $\log_{10}$ inactivation in 30 seconds. The parvoviridae family was confirmed to be the most heat resistant of the various virus families for which data were analyzed. The heat inactivation parameters for two caliciviruses (murine norovirus and feline calicivirus) that are commonly used as surrogates for human norovirus were found to be equivalent.

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For the z value, the relative standard deviation values ranged from 22% for caliciviruses to 94% for picornaviruses. In most cases, the variability around z values appeared to be substantially higher than the variability around the modeled inactivation parameters (Table 3). The overall z value for non-enveloped viruses (four families) was $14 \pm 2.9°C$ (relative standard deviations=21%), compared to $11 \pm 3.8°C$ (relative standard deviations=33%) for enveloped viruses (five families). The overall z value for non-enveloped viruses was not significantly different from that for enveloped viruses ($P=0.30$ by ANOVA).

Of the four families of non-enveloped viruses and the eight families of enveloped viruses for which heat inactivation data were identified and analyzed (Tables 1-3), the modeling results indicate that the parvovirus family is by far the most resistant to heat inactivation. The most susceptible virus families appear to be the rhabdoviruses, retroviruses, and orthomyxoviruses, although conclusions on the relative susceptibilities of the latter two families should be considered tentative, as only a single species has been represented in the data set for these.

Conclusions

A systematic review of the viral heat inactivation literature for data compatible with modeling using the D/z approach [38] as well as a new approach based on the power function relationship between D

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