A Bayesian Approach to Arrhenius Prediction of Shelf-Life

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The use of a bayesian method for estimating the shelf-life of pharmaceutical formulations is evaluated and compared with classical linear regression. Using three real data sets, the greater flexibility provided by the bayesian approach is demonstrated. In particular, the bayesian approach enabled the consideration of cases when the error distribution is non-normal. However much more computation is required with the bayesian method.

KEY WORDS: stability-testing; shelf-life; bayesian methods.

INTRODUCTION

Whenever a new pharmaceutical formulation is introduced, there is a need to assign its shelf-life under normal storage conditions. Usually, at the time of product licensing, the shelf-life is assigned tentatively on the basis of accelerated stability data. This predicted shelf-life is updated once data on the product, stored under normal ambient conditions, become available. Acceptable protocols have been defined recently by the International Committee on Harmonisation (1).

When predicting shelf-life from accelerated storage data, a reaction order is assigned or determined and the rate constants obtained at elevated temperatures are used to predict the rate constant at ambient temperature. Form this, the shelf-life is estimated. To date, the emphasis in regulatory work is usually on point values with little reference to confidence intervals although the US Food and Drug Administration does give guidelines on defining confidence intervals for shelf-life estimates. Recently several authors, including ourselves, (2–5) have undertaken simulation work to show that the confidence intervals associated with point estimates derived from typical experimental data can be very broad. In this report, we investigate this issue further using a bayesian approach proposed by Box and Tiao (6).

THEORETICAL AND METHODS

The assumption in this work is that the decomposition being studied follows zero order kinetics under isothermal conditions. Many pharmaceutical systems behave in this manner and in any case, with low extents of decomposition typical of most formulations, this kinetic order provides satisfactory approximation to systems following different kinetic orders (7). The drug content C at time t can be described by equation (1) under such conditions

$$C = C_o - kt \tag{1}$$

k is the rate constant, C_o the initial drug content and T is the isothermal storage temperature. The room temperature rate constant can be estimated using the Arrhenius equation and two or more pairs of k and T data. Equation (2) expresses the Arrhenius equation in its linear form

$$\ln k' = \ln A - \frac{Ea}{R}\frac{1}{T} \tag{2}$$

where A is the pre-exponential factor, Ea, the activation energy and R the gas constant.

Generalization to the Linear Model

Let variable Y represent ln k and variable X represent 1/T of equation (2). Then in vector notation the relationship can be written as

$$Y = X\Theta + \underline{\epsilon} \tag{3}$$

where

$$Y = [y_1, y_2, \ldots, y_n]^T$$

$$X = \begin{bmatrix} 1 & 1 & \ldots & 1 \\ x_1 & x_2 & \ldots & x_n \end{bmatrix}^T$$

$$\Theta = [\theta_1, \theta_2]^T = [\ln A, Ea/R]^T$$

and

$$\underline{\epsilon} = [\epsilon_1, \epsilon_2, \ldots, \epsilon_n]^T$$

the vector of random errors with each element of $\underline{\epsilon}$ being independent and having an exponential power distribution

$$p(\epsilon|\sigma,\beta) = \omega(\beta)\,\sigma^{-1}\exp\left[-c(\beta)\left|\frac{\epsilon}{\sigma}\right|^{2/(1+\beta)}\right]$$

$$-\infty < \epsilon < \infty,\ \sigma > 0,\ -1 < \beta \leq 1 \tag{4}$$

where

$$c(\beta) = \left\{\frac{\Gamma\left[\frac{3}{2}(1+\beta)\right]}{\Gamma\left[\frac{1}{2}(1+\beta)\right]}\right\}^{1/(1+\beta)}$$

$$\omega(\beta) = \frac{\left\{\Gamma\left[\frac{3}{2}(1+\beta)\right]\right\}^{1/2}}{(1+\beta)\left\{\Gamma\left[\frac{1}{2}(1+\beta)\right]\right\}^{3/2}}$$

The parameter β may be regarded as a measure of kurtosis. The likelihood function of (Θ,σ,β) is defined by

$$l(\Theta,\sigma,\beta|Y) \propto [\omega(\beta)]^n\,\sigma^{-n}$$

$$\exp\left[-c(\beta)\,\Sigma\left|\frac{y_i - \theta_1 + \theta_2 x_i}{\sigma}\right|^{2/(1+\beta)}\right] \tag{5}$$

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Table I. The Effect of Various Choices of β on the Estimates of θ_1, θ_2 and Shelf-life (t_{90}) at 25°C of Vitamin A Decomposition (9)

β	Estimated parameters[a] $\hat{\theta}_1$	$\hat{\theta}_2$	Lower 95%[b] CI of $\hat{\theta}_1$	Upper 95% CI of $\hat{\theta}_2$	MSE[c] $\Sigma(y_i - \hat{y}_i)^2/n$	MAE[d] $\Sigma\lvert y_i - \hat{y}_i\rvert/n$	t_{90} (day)	Lower 95% CI of t_{90}	Upper 95% CI of t_{90}
−0.90	30.975	9.742	8.581	11.056	0.00243	0.04538	55.64	1.13	4574.51
−0.75	31.073	9.768	8.568	11.068	0.00245	0.04553	55.04	0.98	4317.89
−0.50	31.117	9.794	8.546	11.088	0.00211	0.04523	57.48	0.87	4418.86
−0.25	31.127	9.797	8.524	11.104	0.00210	0.04522	57.48	0.80	4616.21
0.00	31.141	9.802	8.507	11.109	0.00210	0.04521	57.63	0.75	4629.05
0.25	31.164	9.810	8.497	11.105	0.00210	0.04519	57.86	0.71	4463.50
0.50	31.211	9.825	8.493	11.095	0.00211	0.04515	58.05	0.66	4118.03
0.75	31.351	9.871	8.495	11.084	0.00215	0.04501	58.89	0.58	3450.29
1.00	32.448	10.226	8.500	11.072	0.00423	0.04401	64.72	0.20	1106.49

[a] $\hat{\theta}_1 = \ln A$; $\hat{\theta}_2 = Ea/1000R$.
[b] The 95% confidence interval for $\hat{\theta}_2$ is calculated by integrating posterior distribution of parameter θ_2 within appropriate limits. The 95% confidence interval for $\hat{\theta}_2$ using standard linear regression is 8.462 − 11.142 for β = 0.0.
[c] Mean square error.
[d] Mean absolute error.

If Θ and ln σ are supposed to be approximately independent and locally uniform, then for a given β, the joint posterior distribution of Θ and σ is described by

$$p(\Theta,\sigma|\beta,Y) \propto \sigma^{-(n+1)} \exp\left[-c(\beta)\,\Sigma\left|\frac{y_i - \theta_1 + \theta_2 x_i}{\sigma}\right|^{2/(1+\beta)}\right]$$
$$\sigma > 0,\ -\infty < \theta_j < \infty,\ j = 1,2 \qquad (6)$$

On integrating out σ, we obtain the conditional posterior distribution Θ in the following simple form

$$p(\Theta|\beta,Y) = J(\beta)^{-1}\,[M(\Theta)]^{-n(1+\beta)/2} \qquad (7)$$

where

$$M(\Theta) = \Sigma|y_i - \theta_1 + \theta_2 x_i|^{2/(1+\beta)} \qquad (8)$$

and the appropriate normalizing constant J(β) is given by

$$J(\beta) = \int_R [M(\Theta)]^{-n(1+\beta)/2}\,d\Theta \qquad (9)$$

R: $(-\infty < \theta_j, < \infty, j = 1,2)$.

Thus, for any fixed β, $p(\Theta|\beta,Y)$ is simply proportional to a power of $M(\Theta)/n$.

From equation (7), the posterior distribution of either parameter, conditional on β, can be obtained by integrating out the other

$$p(\theta_j|\beta,Y) = \int_{-\infty}^{\infty} (\theta_1,\theta_2|\beta,Y)\,d\theta_|$$
$$-\infty < \theta_j < \infty\ j = 1,2,\ | = 1,2, \text{ and } j \neq |. \qquad (10)$$

Because the conditional posterior distribution is a function of β, equation (8) may be used to study how sensitive to β inferences about Θ are. Similarly the effect of β on marginal distributions of θ_1 and θ_2 can be investigated using the equation (10).

Numerical Computation

Unconstrained minimization (NAG® FORTRAN (8)) was used to estimate the parameters of the models. The confidence intervals for θ_1 and θ_2 for different values of β were calculated by numerical integration. At β = 0.00 the error distribution is then normal. For classical linear regression, the package Minitab® (9) was used. All computations were carried out on a VAX computer in double precision.

Table II. The Effect of Various Choices of β on Estimates of θ_1, θ_2 and Shelf-life (t_{90}) at 85°C of Lithium Sulphate Monohydrate (10)

β	Estimated parameters $\hat{\theta}_1$	$\hat{\theta}_2$	Lower 95%[a] CI of $\hat{\theta}_1$	Upper 95% CI of $\hat{\theta}_2$	MSE $\Sigma(y_i - \hat{y}_i)^2/n$	MAE $\Sigma\lvert y_i - \hat{y}_i\rvert/n$	t_{90} (minute)	Lower 95% CI of t_{90}	Upper 95% CI of t_{90}
−0.85	21.922	10.216	8.943	11.820	0.03999	0.17256	1.31	0.04	115.67
−0.75	22.069	10.273	8.898	11.970	0.03909	0.16988	1.33	0.03	151.78
−0.50	22.273	10.354	8.810	12.210	0.03759	0.16441	1.36	0.02	241.99
−0.25	22.456	10.428	8.820	12.275	0.03666	0.16018	1.39	0.02	241.60
0.00	22.852	10.580	8.880	12.282	0.03637	0.15649	1.43	0.01	166.07
0.25	23.119	10.681	8.957	12.282	0.03647	0.15619	1.45	0.01	127.16
0.50	23.356	10.770	9.040	12.278	0.03666	0.15599	1.47	0.01	98.91
0.75	23.866	10.959	9.120	12.275	0.03711	0.15557	1.49	0.01	58.99
1.00	24.615	11.239	8.898	11.970	0.03862	0.15496	1.55	0.00	11.90

[a] The 95% confidence interval for $\hat{\theta}_2$, using standard linear regression, is 8.878 − 12.282 for β = 0.0. Abbreviations used are as in Table 1.

Table III. The Effect of Various Choices of β on Estimates of θ_1, θ_2 and Shelf-life (t_{90}) at 25°C of Indomethacin (11)

β	Estimated parameters $\hat{\theta}_1$	Estimated parameters $\hat{\theta}_2$	Lower 95%[a] CI of $\hat{\theta}_2$	Upper 95% CI of $\hat{\theta}_2$	MSE $\Sigma(y_i - \hat{y}_i)^2/n$	MAE $\Sigma\lvert y_i - \hat{y}_i\rvert/n$	t_{90} (minute)	Lower 95% CI of t_{90}	Upper 95% CI of t_{90}
−0.90	21.379	8.051	7.910	8.508	0.00059	0.02055	29.57	18.45	137.26
−0.75	21.391	8.058	7.909	8.512	0.00050	0.01949	29.93	18.15	137.33
−0.50	21.830	8.194	7.908	8.522	0.00031	0.01650	30.47	11.67	91.57
−0.25	21.897	8.216	7.912	8.527	0.00027	0.01377	30.72	11.06	87.12
0.00	21.915	8.223	7.921	8.526	0.00026	0.01188	30.86	11.20	85.28
0.25	21.895	8.218	7.933	8.522	0.00027	0.01128	30.89	11.89	85.81
0.50	21.864	8.208	7.945	8.515	0.00028	0.01095	30.89	12.77	86.47
0.75	21.836	8.200	7.957	8.507	0.00031	0.01060	30.91	13.67	86.60
1.00	21.839	8.201	7.968	8.499	0.00031	0.01058	30.91	14.15	84.06

[a] The 95% confidence interval for $\hat{\theta}_2$, using standard linear regression, is 7.920 − 8.525 for β = 0.0. Abbreviations used are as in Table I.

Data Sets

Three data sets are used in this study. The first data set on Vitamin A decomposition (Table 1) is from Yoshioka et al. (10). The second data set (Table 2) is from a study of the thermal dehydration of lithium sulphate monohydrate as reported by Brown et al. (11). The third data set (Table 3) concerns the hydrolysis of indomethacin (12).

RESULTS AND DISCUSSION

Tables 1–3 list the estimates for θ_1, θ_2 and the corresponding predicted shelf-lives (t_{90}) at 25°C for vitamin A and indomethacin and at 85°C for lithium sulphate monohydrate. The higher temperature was chosen for the latter since dehydration at 25°C is not meaningful for the monohydrate. Also shown are the associated 95% confidence intervals for θ_1, θ_2 and t_{90} and the mean square error and the mean absolute error in the unconstrained minimization.

Posterior Distributions for θ_1 and θ_2

The posterior probability densities for θ_1 and θ_2 associated with various values of β are shown in Figures 1–3. From the plots, it is quite clear that inferences about θ_1 and

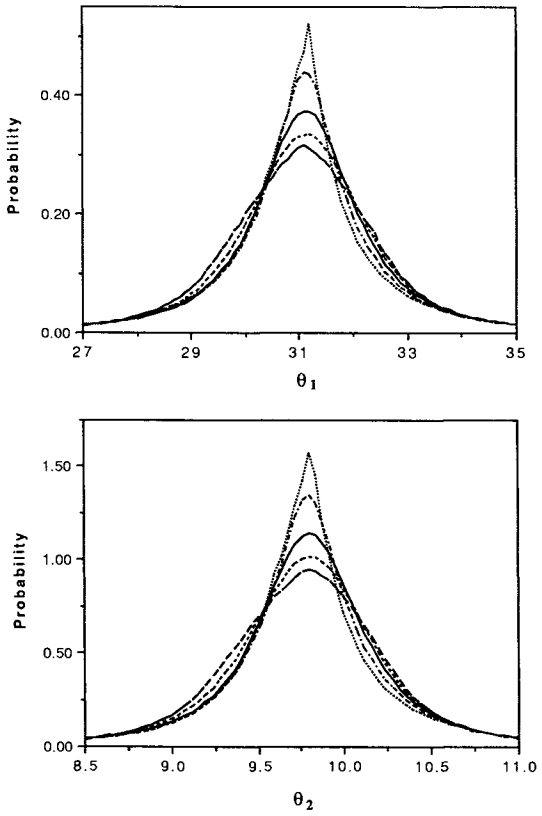

Fig. 1. Posterior distributions of θ_1 and θ_2, conditional on β. Vitamin A decomposition data.
····· β = −0.9 -·-·-· β = −0.5 ——— β = 0.0
------- β = 0.5 ------ β = 1.0

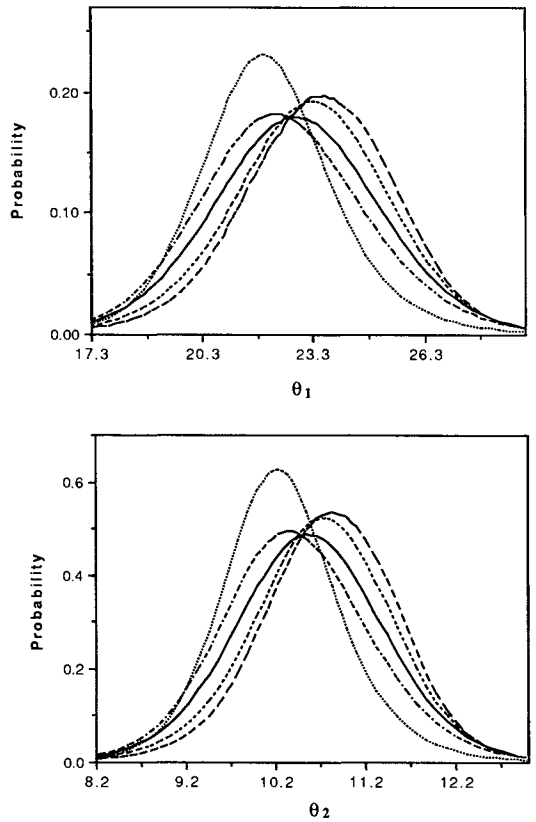

Fig. 2. Posterior distributions of θ_1 and θ_2, conditional on β. Lithium sulphate monohydrate data.
····· β = −0.85 -·-·-· β = −0.50 ——— β = 0.00
------- β = 0.50 ------ β = 1.00

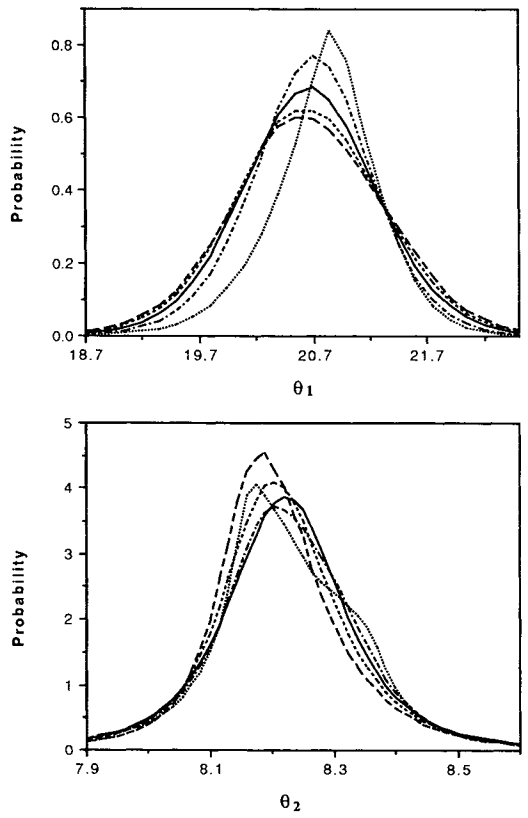

Fig. 3. Posterior distributions of θ_1 and θ_2, conditional on β. Indomethacin data.
····· $\beta = -0.9$ -·-·-· $\beta = -0.5$ ——— $\beta = 0.0$
------ $\beta = 0.5$ ——— $\beta = 1.0$

θ_2 are affected by the probability distributions being assumed for the parameters concerned.

The greater the scatter in the data, the larger the effect of β on the estimates of θ_1 and θ_2 will be. This is seen in Figures 4–6 which show the Arrhenius plots for all three data sets. The indomethacin data showed close adherence to the Arrhenius equation (Figure 6) with little scatter and the lines corresponding to various values of β are virtually su-

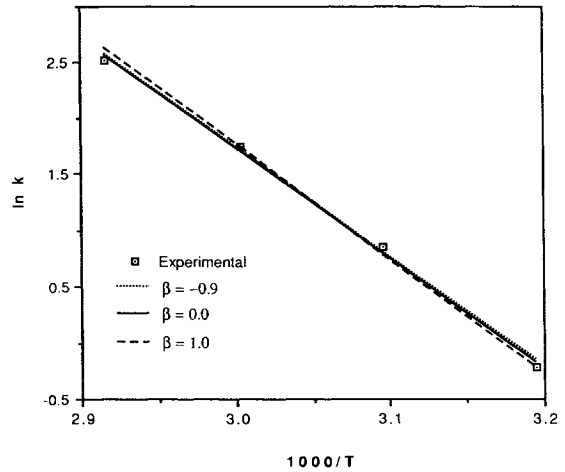

Fig. 4. Comparison of fitted Arrhenius lines for various values of β. Vitamin A decomposition data.

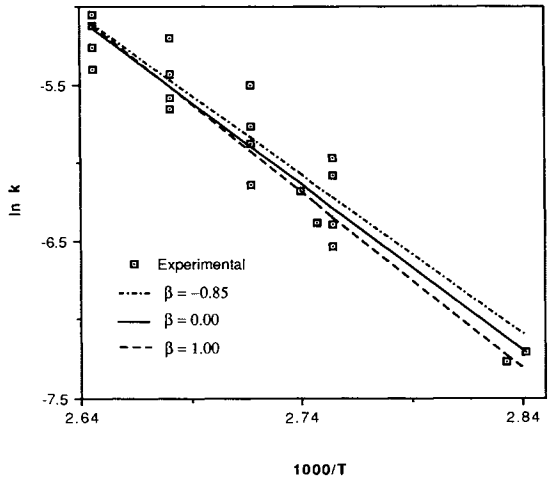

Fig. 5. Comparison of fitted Arrhenius lines for various values of β. Lithium sulphate monohydrate data.

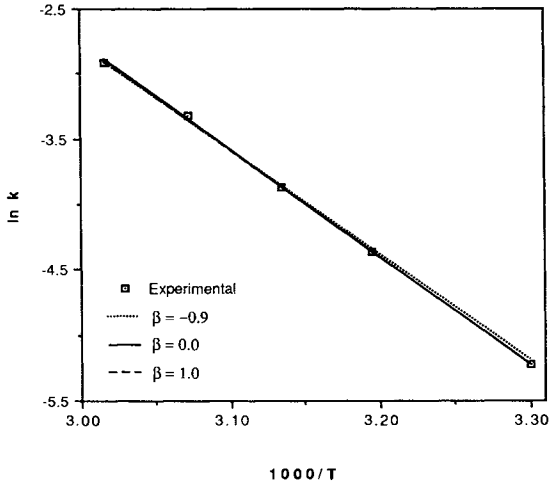

Fig. 6. Comparison of fitted Arrhenius lines for various values of β. Indomethacin data.

Table IV. Comparison of Confidence Intervals Obtained for θ_2 at $\beta = 0.0$ using Numerical Integration and Linear Least Squares Estimation Followed by Use of Tabulated z Values

Data set	Point estimate of θ_2	95% Confidence interval	
		Numerical integration	Least-square
Vitamin A	9.802	8.507 – 11.109	8.462 – 11.142
Lithium sulphate monohydrate	10.580	8.880 – 12.282	8.878 – 12.282
Indomethacin	8.223	7.921 – 8.526	7.920 – 8.526

Table V. Comparison of 95% Confidence Limits of t_{95} Obtained at $\beta = 0.0$ Using Confidence Intervals of $\hat{\theta}_2$ and of Predicted $\hat{y}$

	t_{90} and its 95% confidence limits			
	Based on $\hat{\theta}_2$		Based on $\hat{y}$	
Data sets	Numerical integration	Least-squares		Units
Vitamin A	57.63 (0.75 – 4629.05)	57.63 (0.64 – 5171.13)	57.63 (35.07 – 94.68)	days
Lithium sulphate monohydrate	1.43 (0.01 – 166.07)	1.43 (0.01 – 165.78)	1.43 (1.22 – 1.67)	minutes
Indomethacin	30.86 (11.20 – 85.28)	30.86 (11.16 – 84.98)	30.86 (28.73 – 33.15)	minutes

perimposable. The lithium sulphate monohydrate data on the other hand showed much greater scatter and asymmetry in the assumed probability distribution had a much larger effect on the regression line. While the slopes do not appear very different (Figure 5), the estimates are widely divergent (Table 2).

Confidence Intervals

Equation (11) was used to calculate the shelf-life of Vitamin A as the reaction followed zero order kinetics. For indomethacin the changes observed were first order and equation (12) was used for predicting their shelf-lives. For lithium monohydrate equation (13) was used.

$$t_{90} = \frac{0.1C_o}{A} \exp\left(\frac{Ea}{298R}\right) \quad (11)$$

$$t_{90} = \frac{0.1054}{A} \exp\left(\frac{Ea}{298R}\right) \quad (12)$$

$$t_{90} = \frac{0.1054}{A} \exp\left(\frac{Ea}{358R}\right) \quad (13)$$

The confidence intervals obtained are surprisingly wide (Table 1–3) thus stressing the importance of obtaining reliable data in the first instance, particularly when the data set is sparse. The lithium sulphate monohydrate data (Table 2) illustrates the difficulties in obtaining good data. With hydrolytic reactions, such as the hydrolysis of indomethacin, more precise data can be collected (Table 3). Even then the limits of the 95% confidence interval show a three fold discrepancy on either side of the point estimate.

With β taking the value zero, the underlying probability distribution is normal. Therefore the estimates for θ_1, θ_2 and t_{90} derived using unconstrained minimization as discussed, coincide with those obtained using standard least square estimation at this point. The associated 95% confidence interval derived using numerical integration should be symmetrical at $\beta = 0.00$ and the interval should be concordant with that obtained using linear least squares. Table 4 shows that the estimates and intervals are approximately, as predicted.

Examination of the confidence intervals obtained with the different values of β (Table 1–3), indicates clearly that the narrowest confidence interval at a given significance level, is seen when $\beta = 1.0$. However, the point estimates were furthest from that obtained assuming a normal error distribution ($\beta = 0.0$). The discrepancies in point estimates and widths of confidence intervals are smaller the better the data, as shown by comparing Tables 2 and 3. There is little deviation from the predicted line in the indomethacin data compared to the lithium sulphate monohydrate data. In a recent report (4) we showed that non-linear estimation and Monte-carlo estimations gave narrower confidence intervals than the least squares method.

The data in Table 5, comparing predicted shelf-lives based on estimates of θ_2 and extrapolated ln k shows that the point values are essentially coincident. However, the confidence intervals obtained with the extrapolated ln k values were much narrower.

The clear conclusion is intuitive. To get the best estimates, obtain the best possible data in the first instance. Failing that, the best method to use is then one based on risk assessment. The more insight one has on the probability distribution of the errors, the better will the estimate be.

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