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Incorporating Model Uncertainties along with Data Uncertainties in Microbial Risk Assessment[1]

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Much research on food safety has been conducted since the National Food Safety Initiative of 1997. Risk assessment plays an important role in food safety practices and programs, and various dose–response models for estimating microbial risks have been investigated. Several dose–response models can provide reasonably good fits to the data in the experimental dose range, but yield risk estimates that differ by orders of magnitude in the low-dose range. Hence, model uncertainty can be just important as data uncertainty (experimental variation) in risk assessment. Although it is common in risk assessment to account for data uncertainty, it is uncommon to account for model uncertainties. In this paper we incorporate data uncertainties with confidence limits and model uncertainties with a weighted average of an estimate from each of various models. A numerical tool to compute the maximum likelihood estimates and confidence limits is addressed. The proposed method for incorporating model uncertainties is illustrated with real data sets.

Key Words: **food safety; low-dose extrapolation; Akaike's information criterion; nonlinear programming; GAMS.**

1. INTRODUCTION

The incidence of foodborne illness continues to be a significant public health concern throughout the United States. Diseases caused by food are reported to cause an estimated 325,000 serious illness resulting in hospitalizations, 76 million cases of gastrointestinal illness, and 5000 deaths each year (Mead *et al.,* 1999). The National Food Safety Initiative of 1997 (FDA, USDA, EPA, CDCP, 1997) was the result of increasing concern about the safety of the nation's food supply. Its goal is to improve food safety, particularly in the area of surveillance, inspections, research, risk assessment and education.

Risk assessment is a valuable tool for helping to make public health decisions in food safety areas. It characterizes the likelihood of harm to the public, helps to define the uncertainties, and provides some level of comfort with the inferences that are made. Recently much research has been done in microbial risk assessment (Marks *et al.,* 1998; Haas *et al.,* 1999; Kodell *et al.,* 1999). Exposure to foodborne pathogens is at very low doses in most cases. In order to estimate risk at such low doses, experiments with voluntary human subjects are often conducted. The number of volunteers used in experiments is usually small and therefore high levels of dose are set to produce illness in an appreciable fraction (e.g., 10^{-1} or more) of volunteers. An important statistical problem is to use these high-dose data to estimate risk at low doses or estimate a dose level at which the risk of illness would exceed some specified low amount (e.g., 10^{-4}). This problem is commonly known as the low-dose extrapolation problem.

In the assessment of dose response, there might be a number of plausible dose–response models whose fits are consistent with the data, but they may have very different behaviors below the observed data range. In other words, the result of low-dose extrapolation procedures depends strongly on the dose–response relationship one assumes. Several dose–response models often provide reasonably good fits to the data in the experimental dose range, but yield risk estimates that differ by several orders of magnitude in the low-dose range. The primary purpose of this paper is to present a practically easy-to-use tool for incorporating model uncertainties along with data uncertainties into the risk assessment.

The paper is organized as follows. In section 2 we review existing dose–response models in microbial risk assessment, a way of fitting them to data, and confidence limits. In section 3 we review software to fit the models, conduct goodness-of-fit tests, and compute confidence limits. We also introduce the software GAMS.

[1] The opinions expressed in this article are solely those of the authors and not necessarily of the U.S. Food and Drug Administration.

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TABLE 1
Dose–Response Models Used in This Paper

Name	Dose–response models
Beta-Poisson	$P(d_i;\ \alpha,\ \beta) = 1 - (1 + d_i/\beta)^{-\alpha} \quad \alpha > 0,\ \beta > 0$
Log-Normal	$P(d_i;\ \alpha,\ \beta) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(\ln d_i - \alpha)/\beta} \exp\left(-\frac{1}{2} t^2\right) dt \quad -\infty < \alpha < \infty,\ \beta > 0$
Log-Logistic	$P(d_i;\ \alpha,\ \beta) = 1/(1 + \exp[-(\ln(d_i) - \alpha)/\beta]) \quad -\infty < \alpha < \infty,\ \beta > 0$
Extreme-Value	$P(d_i;\ \alpha,\ \beta) = 1 - \exp[-\exp(\alpha + \beta \ln d_i)] \quad -\infty < \alpha < \infty,\ \beta > 0$

In section 4 a method of incorporating model uncertainties is addressed with examples.

2. REVIEW OF STATISTICAL METHODS IN MICROBIAL RISK ASSESSMENT

A dose–response model is a mathematical function bounded by zero and one that takes as an argument a measure of dose and yields the probability of a particular adverse effect. For review of existing dose–response models in microbial risk assessment, see Haas *et al.* (1999) and Kodell *et al.* (1999). Some dose–response models used in this paper are summarized in Table 1.

Let there be I independent dose groups ($i = 1, \ldots, I$) with n_i independent subjects per group. Let X_i denote the number of infected subjects in dose group i, with observed value x_i. Assuming that the X_i are distributed Binomial (n_i, $P(d_i; \boldsymbol{\theta})$), $\boldsymbol{\theta} = (\alpha, \beta)$, the log-likelihood function differs only by a constant from

$$L(\theta) = \sum_{i=1}^{I} [X_i \ln P(d_i; \boldsymbol{\theta}) + (n_i - X_i)\ln(1 - P(d_i; \boldsymbol{\theta}))].$$

The maximum likelihood estimates of $\boldsymbol{\theta}$ are obtained by finding the values of $\boldsymbol{\theta}$ to maximize $L(\boldsymbol{\theta})$. Goodness-of-fit is tested by comparing each fitted model's log-likelihood value to that of the saturated model, i.e., the model giving the observed probabilities x_i/n_i for each group. The significance of twice the difference in log-likelihoods is assessed by comparison to $\chi^2(I - \dim(\boldsymbol{\theta}))$, with $\dim(\theta)$ being the dimension of the parameter vector $\boldsymbol{\theta}$.

In a particular family of dose–response models such as the Beta-Poisson models, different values of the parameters may describe dose–response data reasonably well and predict divergent risks at low doses. This uncertainty can be expressed roughly as the range of risks consistent with the data within a particular parameter family and generally quantified with the use of statistical confidence limits. Crump and Howe (1985) provide a nice review of approaches for setting confidence limits. In this paper we employ the confidence limits based on the asymptotic distribution of the likelihood ratio. According to the approach, the 95% upper confidence limit on risk at a dose d_0 (denoted by R_U^*) is determined from solving the equation

$$R_U^* = \text{Maximum of } P(d; \boldsymbol{\theta})$$

$$\text{subject to } d = d_0 \quad 2[L(\hat{\boldsymbol{\theta}}) - L(\boldsymbol{\theta})] = (1.64485)^2,$$

where $\hat{\boldsymbol{\theta}}$ is the unconstrained maximum likelihood estimate of $\boldsymbol{\theta}$. Similarly, the 95% lower confidence limit on risk (denoted by R_L^*) is found by minimizing $P(d; \boldsymbol{\theta})$ subject to the constraint. The 95% lower limit of dose at risk R_0 (denoted by d_L^*) is determined from solving the equation

$$d_L^* = \text{Minimum of } d$$

$$\text{subject to } P(d; \boldsymbol{\theta}) = R_0 \quad 2[L(\hat{\boldsymbol{\theta}}) - L(\boldsymbol{\theta})] = (1.64485)^2.$$

3. NUMERICAL TOOLS TO CONDUCT STATISTICAL ANALYSES

Haas *et al.* (1999) obtain the maximum likelihood estimates of the Beta-Poisson model using the SOLVER in EXCEL. The performance of the SOLVER in EXCEL is not always satisfactory, although it gives the right answer in some cases. As an example we consider a human dose–response study of *Salmonella typhi* (Hornick *et al.*, 1970) summarized in Table 2.

The SOLVER in EXCEL fails to produce the right answer with several candidates of initial values of the unknown parameters. The FORTRAN IMSL subroutine NCONF also failed to give the right answer. Crystall Ball Pro gives the right answer after running ap-

TABLE 2
Human Dose–Response Study of *Salmonella typhi* (Hornick *et al.*, 1970)

Dose:	10^3	10^5	10^7	10^8	10^9
Total	14	116	32	9	42
Ill	0	32	16	8	40

proximately 10 min on 400-MHz IBM-PC, but it is not suitable for computing confidence limits described in the previous section. Therefore, it is desirable to find an easier and more reliable way of computing the maximum likelihood estimates of dose–response models. Another issue is to compute the upper confidence limits on risk at a dose d and lower confidence limits for the dose corresponding to a risk R. To compute confidence limits from the likelihood approach is much more difficult than obtaining the maximum likelihood estimates of dose–response parameters.

To obtain the maximum likelihood estimates can be viewed as a nonlinear programming problem. The nonlinear programming problem is defined by maximizing a nonlinear objective function subject to linear and nonlinear constraints (Mangasarian, 1994). Therefore, finding an upper (lower) confidence limit is also a nonlinear programming problem. To solve the problem numerically, we use GAMS (Brooke *et al.*, 1988; GAMS Development Corporation, Washington, DC), a high-level language for solving nonlinear programming problems. GAMS finds a local minimum point by checking the Karush–Khun–Tucker necessary optimality conditions (e.g., Han and Mangasarian, 1979, p. 257). The restricted free-trial version of GAMS can be downloaded from its homepage (http://www.gams.com).

For the human dose–response study of *S. typhi* (Hornick *et al.*, 1970), GAMS succeeds to find the (unconstrained) maximum likelihood estimate ($\hat{\alpha} = 0.203$, $\hat{\beta} = 29{,}173$) in the first trial. It is also ascertained that $\hat{\alpha} = 0.203$, $\hat{\beta} = 29{,}173$ is the right answer from the complete grid search.

The 95% upper confidence limit on risk (denoted by R_U^*) at a dose $d = 1$ based on the Beta-Poisson model is computed by GAMS as $R_U^* = 1.59 \times 10^{-5}$. The 95% lower limit for the dose d corresponding to an risk of 10^{-4} (denoted by d_L^*) is also computed by GAMS, and $d_L^* = 6.125$. The GAMS programs to compute the upper confidence limits on risk and the lower confidence limit for the dose d are available from the authors upon request.

4. INCORPORATING MODEL UNCERTAINTY IN MICROBIAL RISK ASSESSMENT

When experimental results are extrapolated to very low doses to obtain an accurate estimate of risk due to daily exposure, many functional forms for describing dose response may provide adequate statistical fits for the experimental data. The important factors in model selection are the consistency of the model assumptions with the underlying biology of the system and the plausibility of extrapolating the model that has been derived from data in the high-dose region to the low-dose region. Unfortunately, explicit details of the biological mechanisms of colonization and infection are not well known, even with high-dose challenges. Another difficulty with extrapolation procedures is that the estimates of risk at low doses depend highly on the selected model. Diverse models could provide good fits to the observed data, but give very different estimates of low-dose risks. Therefore, model selection uncertainty should be fully incorporated into statistical inference.

In this study in order to incorporate model uncertainty into a parameter estimate we will follow the approach of Buckland *et al.* (1997) as reviewed by Pinsky (1999). Suppose that we have K contending models, M_i, $i = 1, \ldots, K$. We assume that the parameter of interest θ is common to all models. Let $\hat{\theta}_i$ be the estimate of θ under the model M_i. We take a weighted average of $\hat{\theta}_i$ as the estimate of θ.

$$\hat{\theta} = \sum_{i=1}^{K} w_i \hat{\theta}_i,$$

where w_i is the weight for the model M_i and $\sum_{i=1}^{K} w_i = 1$. The theory still holds for any theoretical quantity associated with the model such as the 95% upper confidence limit on risk. We compute the weights w_i's by using Akaike's information criterion AIC (Akaike, 1973; Burnham and Anderson, 1992).

$$I = -2L + 2h,$$

where L is the log-likelihood function, evaluated by substituting the maximum likelihood estimates of the parameters and h is the number of parameters. The philosophy underlying AIC is that the true model is high-dimensional, requiring many (possibly infinitely many) parameters to describe it. Sakamoto *et al.* (1986) note that AIC is not a criterion for the estimation of the true order but the one for the best model fit. That is, we seek the best approximate model.

We consider $I_i = -2L_i + 2h_i$ for K contending models. The model with the smallest value for I is the best model in the sense of AIC. A plausible choice for weight w_i is

$$w_i = \frac{\exp(-I_i/2)}{\sum_{j=1}^{K} \exp(-I_j/2)}, \quad i = 1, \ldots, K.$$

Note that in some cases dose–response models are nested. For example, the exponential model is a special case of the Beta-Poisson model, while the Log-Logistic and Beta-Poisson models are submodels of the Weibull–Gamma model, which is a three-parameter model. Since the method of Buckland *et al.* (1997) assumes that the fitted models are in some sense a random sample from an infinite set of possible models, in

TABLE 3
Human Dose–Response Study of *Shigella dysenteriae 1* Strain M131 (Levine *et al.*, 1973)

Dose:	10	200	2000	10000
Total	10	4	10	6
Ill	1	2	7	5

TABLE 5
Human Dose–Response Study of *Shigella paradysenteriae* (Shaughnessy *et al.*, 1946)

Dose:	10^8	10^9	10^{10}
Total	4	4	8
Infected	1	4	8

the following examples we consider a set of models in which a model is not a submodel of the others.

In the first example, the four 2-parameter models of section 2 are selected. The data are from a human dose–response study of *Shigella dysenteriae 1* strain M131 (Levine *et al.*, 1973) summarized in Table 3. Four 2-parameter models are fitted and the results are summarized in Table 4. After the incorporation of model uncertainty, the maximum likelihood estimates and the 95% upper confidence limit on risk at a dose $d = 1$ are obtained by

$$0.033 = 0.275 \times 0.0127 + 0.256 \times 0.0261 + 0.253 \times 0.0374 + 0.216 \times 0.0618$$

$$0.177 = 0.275 \times 0.102 + 0.256 \times 0.191 + 0.253 \times 0.197 + 0.216 \times 0.234,$$

respectively.

In the second example, the data are the human dose–response study of *Shigella paradysenteriae* (Shaughnessy *et al.*, 1946) summarized in Table 5. Four 2-parameter models are fitted and the results are summarized in Table 6. After the incorporation of model uncertainty, the maximum likelihood estimate and the 95% lower confidence limit of dose at risk 10^{-4} are 13,276,616 and 7095, respectively. We would like to emphasize that the study of *S. paradysenteriae* (Shaughnessy *et al.*, 1946) is not typical among the 25 data sets in Teunis *et al.* (1996) in the sense that the maximum likelihood estimate of dose at risk 10^{-4} with the Log-Logistic model is greater than one. For 15 data sets of 25, the maximum likelihood estimate of dose at risk 10^{-4} is less than one, which implies that the lower confidence limit is obviously less than one. It means that even one microorganism is not allowed if a risk of 10^{-4} is to be achieved. A feature of the other 10 data sets is that they may have zero responses in the first (and sometimes second) dose so that a dose–response curve does not *take off* much at the low doses. In such cases a huge amount of model uncertainty exists as shown in Table 6.

5. DISCUSSION

Often times high doses such as 10^9 and 10^{10} cause numerical problems in running GAMS. In order to get around the problems we rescale the original doses by dividing by a big constant C (for example, 10^9). After rescaling, the risk at the original dose d is evaluated at the rescaled dose $d^{(r)} = d/C$.

The inverse function of a dose–response model is used in the computation of the 95% lower confidence limit of dose at a given risk. However, the GAMS does not support the inverse function of the standard normal distribution function. Iteration is used for the Log-Normal model. Several doses are tried, so that a dose can be finally selected to yield a given risk.

A background risk is often assumed in the models of chemical risk assessment. It seems that more discussion will be needed for a background risk in microbial risk assessment. All models in Table 1 have zero background risk, while only the Exponential–Exponential model (Kodell *et al.*, 1999) has nonzero background risk. However, the Exponential–Exponential model gives one of the poorest fitting models for the 25 data sets examined (Kodell *et al.*, 1999).

In this paper incorporating model uncertainties is achieved using a simple weighting method, where the weights are obtained from Akaike's information crite-

TABLE 4
Results of Model Fitting and Confidence Limits for *Shigella dysenteriae 1* Strain M131

Model	$L(\boldsymbol{\theta})$	w_i	R^*_U at $d = 1$	MLE of risk at $d = 1$
Beta-Poisson	−14.851	0.275	0.102	0.0127
Log-Normal	−14.920	0.256	0.191	0.0261
Log-Logistic	−14.932	0.253	0.197	0.0374
Extreme-Value	−15.093	0.216	0.234	0.0618

TABLE 6
Results of Model Fitting and Confidence Limits for *Shigella paradysenteriae*

Model	$L(\boldsymbol{\theta})$	w_i	d^*_L at risk 10^{-4}	MLE of dose at risk 10^{-4}
Beta-Poisson	−2.443	0.234	5,699.0	25,117.2
Log-Normal	−2.276	0.277	19,295.0	10,569,762.4
Log-Logistic	−2.249	0.285	1,463.8	36,287,569.1
Extreme-Value	−2.584	0.204	2.13×10^{-4}	4,693.3

rion. The method is simply chosen because it is easy to use for the applied statisticians. There are different methods and philosophies for incorporating model uncertainties into inference (Burnham and Anderson, 1998). It might be interesting in future studies to investigate the performance of the simple weighting method and compare it with the other methods.

The main reason to account for model uncertainty in risk prediction is to reduce dependence on individual models. Combining estimates from different plausible models will not necessarily reduce model uncertainty. However, it will reduce dependence on individual models, i.e., model bias. The current practice in risk assessment, whether for chemicals or microbes, is to use a single dose–response model. Hence, the results are highly dependent on the particular model chosen. The approach applies to risk assessment in general, not just to microbial risk assessment. It could be used in chemical risk assessment as well.

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