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Benchmark Dose Estimation Incorporating Multiple Data Sources

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With the increased availability of toxicological hazard information arising from multiple experimental sources, risk assessors are often confronted with the challenge of synthesizing all available scientific information into an analysis. This analysis is further complicated because significant between-source heterogeneity/lab-to-lab variability is often evident. We estimate benchmark doses using hierarchical models to account for the observed heterogeneity. These models are used to construct source-specific and population-average estimates of the benchmark dose (BMD). This is illustrated with an analysis of the U.S. EPA Region IX's reference toxicity database on the effects of sodium chloride on reproduction in *Ceriodaphnia dubia.* Results show that such models may effectively account for the lab-source heterogeneity while producing BMD estimates that more truly reflect the variability of the system under study. Failing to account for such heterogeneity may result in estimates having confidence intervals that are overly narrow.

KEY WORDS: Aquatic toxicology; Bayesian methods; generalized linear mixed models; hierarchical models; lab-to-lab variability; Poisson responses

1. INTRODUCTION

With environmental hazard information compiled from different sources, risk analysts are often confronted with the issue of combining data from these multiple sources to better inform the decision-making process. Although the benefits of such a meta-analysis are obvious, methodological considerations frequently prevent such a synthesis since data from multiple sources can contain source-specific variability. In this case, a simple pooled analysis is ill advised. Common risk assessment tools, often based upon generalized linear models, have no built-in structure to account for this data-source heterogeneity.

To illustrate this problem, consider a recent evaluation of the U.S. EPA Region IX's reference toxicity database, which included data from multiple labs conducted using the same organisms and the same toxicants.[1] One set of experiments considered the impact of sodium chloride exposures on reproduction of the cladoceran, *Ceriodaphnia dubia*. In this analysis, lab-to-lab heterogeneity was evident as analyses based upon individual labs yielded considerably different concentration-response curves. Further, lab-specific benchmark doses (BMDs) varied significantly. As these analyses show a large amount of heterogeneity between labs, the pooling of each lab source into a single dataset may result in an analysis that mischaracterizes the central estimate of the concentration-response curve. Alternative modeling frameworks, such as hierarchical models or generalized linear mixed-effects models (GLMM)[2] that include random effects for each lab, may provide a

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systematic structure that can readily account for the added lab/source variability.

A significant focus of previous work incorporating random effects in risk assessment has focused on developmental toxicity data and the heterogeneity often encountered between individual dams in relation to their litter size as well as fetal weight. Catalono and Ryan[3] and Dunson *et al.*[4] among others have proposed latent class models that take into account this correlative source structure into risk analysis. These studies, however, have focused primarily on the modeling aspect of the analysis, with little emphasis on the estimation of specific endpoints such as the BMD.

Other work estimating the BMD using mixed models has been described in the environmental literature. Piegorsch and Cox[5] reviewed generalized linear models with random effects in the estimation of the effective dose in ordinal and continuous regression. Simmons *et al.*[6] looked at modeling mutagenic potencies from different Salmonella strains, and Coull *et al.*[7] conducted a meta-analysis for methyl-mercury using a Bayesian hierarchical model to combine BMD point estimates from multiple studies. While these studies have focused on risk assessment, most have looked at continuous response regression, with less emphasis on nonnormal data.

We consider an extension of this work and suggest a general hierarchical framework that can be used by risk assessors to estimate the dose/concentration-response curve, as well as the BMD, for data assumed to be generated from the exponential family of distributions. We then use this framework to model the *C. dubia* concentration-response data, and then estimate the concentration associated with specified decrement in reproductive output, here number of young produced in three broods.

2. HIERARCHICAL MODELING FRAMEWORK

As in some of the previously cited work, we use a hierarchical model to estimate adverse effects of multiple-source toxicology data. Here, we assume that the mean response μ_c, at toxicant concentration c, can be represented as a linear function of the concentration through the link function $g(\mu_c)$, where $g(\mu_c)$ is a linear function of the ambient concentration, and the concentration effect is heterogeneous across sources (note that an internal dose can be substituted for the concentration). Given these assumptions, a multilevel hierarchical model can be specified allowing for the heterogeneity in response across multiple sources. For example, the multiple-source toxicology data described above can be modeled using a two-stage hierarchical model. Here, the first level explains the population mean response, given the jth lab, and is modeled as:

$$g(\mu_{jc}) = \theta_{0j} + \theta_{1j}c + \theta_{2j}c^2 + \cdots + \theta_{mj}c^m. \quad (1)$$

The second level models each lab's heterogeneity in response as:

$$\theta_{kj} = \beta_k + b_{kj}, \quad (2)$$

where $k = 0, 1, \ldots, m$, $\boldsymbol{\beta} = [\beta_0, \beta_1 \ldots \beta_m]$ represents the fixed effects, and $\mathbf{b_j} = [b_{0j}, b_{1j}, \ldots b_{mj}] \sim N_{m+1}(0, D)$. That is, $\mathbf{b_j}$ is a random vector for the jth lab, which is distributed multivariate normal with mean vector $\mathbf{0}$ and variance–covariance matrix $\mathbf{D} = \{\sigma_{rc}: r = 0, 1, \ldots, m; c = 0, 1, \ldots, m\}$. Note that while two levels are used in this formulation to represent the lab-source variability, additional levels could be introduced to model other source variability that may be present in the analysis. The hierarchical model can be rewritten into a single linear equation describing the mean by substituting Equation (2) into Equation (1), i.e.:

$$g(\mu_{jc}) = (\beta_0 + b_{0j}) + (\beta_1 + b_{1j})c + \cdots + (\beta_m + b_{mj})c^m.$$

Often $m \leq 2$ is sufficiently complex to model the aquatic toxicology data we consider. Under this formulation, the adverse response is assumed to have fixed effects associated with toxicant exposure with additional source heterogeneity accounted for by source-independent realizations of the specified random effect.

Given an estimate of μ_c, the BMD can be estimated. This endpoint is dependent upon the benchmark response (BMR) value p as well as the underlying data-generating mechanism. Crump[8] first discussed this quantity in terms of dichotomous dose-response data, Gaylor and Slikker,[9] among others, presented a formulation in terms of continuous dose response, and Bailer and Oris[10] presented a similar formulation for concentration-response studies where the underlying response was based upon count data. Regardless of the response distribution used to model the response, the *BMD(p)*, the benchmark dose specified at a specified BMR = p, is often of interest in risk assessment.

By definition, the estimation of the BMD requires all coefficients of the above model to be

specified, which implies that the estimate is source specific (i.e., it relies on a specific realization of the random variables $\mathbf{b}_j$). This source-specific dependence prohibits a single estimate, which includes the source heterogeneity; consequently, a population-average estimate (i.e., the expectation of the BMD across all realizations of the random effects) may be more useful when making scientific reasoning from combined sources.

From a Bayesian perspective in which the regression coefficients (β_k) and the variance components (σ_{rc}) are also random variables, the population-averaged estimate is an average BMD over all random variables impacting this endpoint, i.e.:

$$BMD_{pa} = \int BMD(p|\boldsymbol{\beta}, \mathbf{b}, \boldsymbol{\sigma})\pi(\boldsymbol{\beta}, \mathbf{b}, \boldsymbol{\sigma})d\boldsymbol{\beta}\, d\mathbf{b}\, d\boldsymbol{\sigma}, \quad (3)$$

where $\pi(\boldsymbol{\beta}, \mathbf{b}, \boldsymbol{\sigma})$ is the joint posterior distribution of these quantities. Thus, the population-average value integrates out the regression coefficients (βs), the lab-specific random effects (bs) and the variance components associated with the random effects (σ_{rc}).

Multiple methods for estimating the BMD_{pa} could be considered. While it is possible to estimate the above model parameters using maximum likelihood methods, computing the BMD_{pa} and subsequent lower bound calculations may be difficult as the above formulation does not easily yield to computationally simple methods. A bootstrap-based analysis[11] could be used to determine this lower bound; since each fit of a GLMM may take several minutes on larger problems, an adequate number of bootstrap replications may be computationally intractable. A Bayesian formulation of the problem may be a more natural choice. In this setting the BMD_{pa} is a quantity that can be readily sampled through the use of the Markov chain Monte Carlo (MCMC) algorithms.[12] Consequently, we formulate the rest of the discussion in the Bayesian setting.

3. *CERIODAPHNIA* BMD MODELING

We return to the *C. dubia* water toxicity tests conducted by the U.S. EPA Region IX between July 18, 1989 and June 16, 1993, and analyze this dataset using a hierarchical model/GLMM in a Bayesian framework. The data were obtained from a series of experiments conducted in seven labs with multiple replicate experiments per lab, ranging from 8 to 46 experiments in a given lab. For a given experiment, different ambient concentrations of the reference toxicant, sodium chloride, was introduced, and the number of young from three broods was recorded as the measured response. The testing procedure used in all labs is fully described by the U.S. EPA.[13] Bailer *et al.*[1] studied this database and concluded that experiments exhibited significant lab-to-lab heterogeneity. Their analysis suggests that any model based upon the combined data from the seven labs should account for this interlaboratory variability; consequently, we use the hierarchical model implied by Equations (1) and (2) to account for this lab-source heterogeneity.

In this analysis, let Y_{jnc} represent the observed number of young given the jth lab, nth experiment, at the concentration c. Following Bailer *et al.*,[1] we assume that that $Y_{jnc} \sim \mathrm{Poisson}(\mu_{jc})$ having a logarithmic link function that relates the mean response to a quadratic polynomial of the fixed and random effects, i.e.:

$$\log(\mu_{jc}) = (\beta_0 + b_{0j}) + (\beta_1 + b_{1j})c + (\beta_2 + b_{2j})c^2, \quad (4)$$

where b_{kj} is modeled as in Equation (2). Model (4) extends the model of Bailer *et al.*[1] by adding a lab random effect to the background, linear, and quadratic terms of the equation. The model can be thought of as having some central tendency represented by the βs with each lab having a slightly different background, as well as an unaccounted for concentration effect in the concentration-response curve, represented by the bs.

Given the concentration-response curve (Equation (4)) or the equivalent formulation of Equations (1) and (2), the lab-specific BMD(p) is defined as the concentration that decreases the expected brood size, below background levels (i.e., concentration = 0), by some proportion p for that lab. This value is defined as the concentration c that satisfies the equation $\mu_{jc} = (1 - p)\mu_{j0}$. This concentration is found by taking the largest positive root of the equation $(\beta_1 + b_{j1})c + (\beta_2 + b_{j2})c^2 = \ln(1 - p)$. The RIp estimator defined by Bailer and Oris[10] is a BMD estimator defined for a BMR corresponding to inhibition in reproduction relative to control-group mean response. This is a lab-specific estimator and does not take into account the observed heterogeneity between labs. The population-average (Equation (3)) estimator, which is the average of all lab-source estimates, may be preferred for risk management purposes.

Table I. Posterior Mean for the Population-Average Parameters of Equation (5) (i.e., β_ks), as Well as the Mean and Median Estimates of the Lab Effect Variance

		95% Credible Interval				
Fixed Reg. Effect	Mean	2.5%	97.5%	Variance Component	Mean	Median
β_0	3.06	2.89	3.23	$\sigma_0^2 = \sigma_{00}$	0.05	0.04
β_1	0.24	−0.31	0.82	$\sigma_1^2 = \sigma_{11}$	0.51	0.38
β_2	−0.81	−1.09	−0.55	$\sigma_2^2 = \sigma_{22}$	0.12	0.09

Note: A large portion of the variability, in the concentrations of interest, is accounted for in the linear random effect term.

4. HIERARCHICAL MODELING OF THE SODIUM CHLORIDE TOXICITY DATABASE

Given Equation (1) with $m = 2$ and the *C. dubia* experimental data recorded from the seven EPA Region IX testing facilities, the posterior distribution of the model parameters was obtained using MCMC algorithms implemented in WinBugs version 1.4.[14] In this implementation, all parameters in Equations (1) and (2) were assumed to have relatively flat prior information with the following priors being used:

$$\theta_j \sim N_3(\beta, D), \tag{5}$$

where

$$\mathbf{D} = \begin{bmatrix} \sigma_{00} & 0 & 0 \\ 0 & \sigma_{11} & 0 \\ 0 & 0 & \sigma_{22} \end{bmatrix}$$

or, more simply, $\theta_{kj} \sim N(\beta_k, \sigma_{kk})$ for $k = 0, 1, 2$ with uncertainty in these parameters reflected by $\beta_k \sim N(0, 10^6)$, and $\sigma_{kk} \sim$ InvGamma (0.001, 0.001).

A full listing of the WinBugs code used to estimate the model is described in the Appendix. In all, 10,000 burn-in samples were used on three separate chains, and convergence was monitored. Once convergence was achieved, 20,000 additional samples were taken from the posterior distribution for the $\boldsymbol{\theta}$, $\boldsymbol{\beta}$, and $\boldsymbol{\sigma}$ (i.e., entries from $\mathbf{D}$) vectors.

Posterior mean estimates for the $\boldsymbol{\beta}$ and $\boldsymbol{\sigma}$ parameters, as well as a 95% credible interval for the $\boldsymbol{\beta}$ vector, are presented in Table I. Here, the population-averaged concentration-response curve, the curve defined by the posterior mean values of $(\beta_0, \beta_1, \beta_2)$, suggests an increased response associated with sodium chloride at low concentrations (i.e., the expectation of the linear term is positive but the 95% credible intervals contain 0), where at higher concentrations the deleterious effect of sodium chloride becomes evident (i.e., the expectation of the quadratic term is negative). Further, the linear lab-source effect shows the highest variability. This reflects the observation that any amount of sodium chloride may lead to a reduction in brood size in some labs while an increased brood size is observed at low NaCl concentrations in other labs. The concentration-response patterns for the different labs are displayed in Fig. 1. Here the solid curve represents the population-averaged concentration-response curve and the dashed lines represent the expected lab-specific responses.

Table II presents the BMD/RIp calculations for $p = 0.25$ and 0.5, for the lab-specific and population-average estimates. (Note that in the original papers describing these data and potency endpoints, the relative inhibition estimator/RIp was defined and estimated. This quantity corresponds to a BMD for a particular definition of the BMR. Thus, we refer to the RIp and BMD interchangeably.) From this table, it is clear that there is a significant lab-to-lab variability in these estimates, with lab-specific RI25 posterior means differing by a factor of 5 and RI50

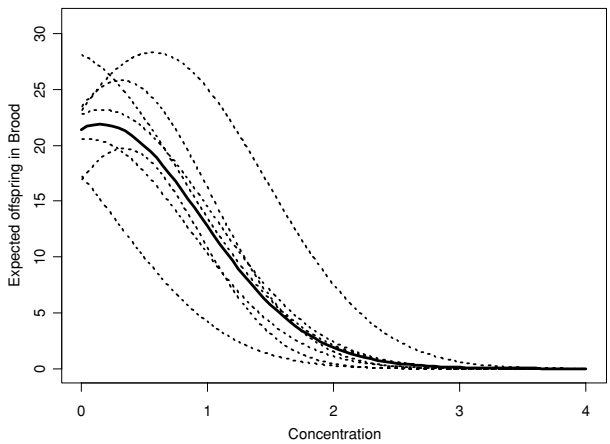

Fig. 1. Posterior means of the expected number of offspring given the lab-source variability. The solid line represents the population-average expected response, whereas the dotted lines represent the expected response, given an individual lab.

Table II. Posterior Mean and Standard Deviation Estimates for the Lab- and Population-Average RIp Distribution

		RI25				RI50			
				95% Credible Interval				95% Credible Interval	
EPA Lab		Mean	*SD*	2.5%	97.5%	Mean	*SD*	2.5%	97.5%
Lab-specific estimates	CAAQS	0.58	0.01	0.56	0.61	0.97	0.01	0.95	0.99
	CAMEC	0.91	0.02	0.87	0.95	1.13	0.02	1.10	1.16
	CAMEC1	0.30	0.02	0.27	0.33	0.60	0.02	0.56	0.64
	CAOEE	0.67	0.02	0.64	0.70	1.01	0.01	0.98	1.03
	CASRH	0.84	0.02	0.81	0.88	1.20	0.01	1.17	1.22
	CAUCD	1.45	0.02	1.41	1.49	1.75	0.02	1.72	1.79
	MNEPAD	0.94	0.02	0.91	0.98	1.21	0.01	1.18	1.24
Lab-average estimates		0.80	0.37	0.43	1.36	1.12	0.38	0.74	1.67

Note: Here, for the RI25 and RI50 distribution, p represents a 25% or 50% decrement in expected response in relation to control group responses.

Table III. Comparison of the Posterior Estimates of the β_ks and the RIp Estimates for the Pooled-Data/Fixed and Hierarchical/Mixed Effects Generalized Linear Model Analyses

	Pooled-Data/Fixed Effects Analysis			Hierarchical/Mixed Model Analysis		
	95% Credible Interval			95% Credible Interval		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%
β_0	3.12	3.11	3.13	3.06	2.89	3.23
β_1	0.16	0.14	0.19	0.24	-0.31	0.82
β_2	−0.68	−0.70	−0.66	−0.81	−1.09	−0.55
RIp25	0.78	0.77	0.80	0.80	0.43	1.36
RIp50	1.14	1.13	1.15	1.12	0.74	1.67
DIC			96800			87766

Note: The DIC estimate is shown as a method of Bayesian model comparison; here smaller is better.

posterior means differing by a factor of 3. Individual credible intervals are tight around the posterior mean in each lab, suggesting a RIp posterior distribution that is quite narrow for a given lab; however, these RIp distributions were quite different among labs. This suggests that inference from any one lab may not be generalizable to the population as a whole, and may be unsuitable for risk management purposes. The table further shows that the population-averaged RIp/BMD$_{pa}$ estimates, based upon Equation (2), tend to have much larger credible intervals as they explicitly incorporate the lab-to-lab heterogeneity.

One can look at the effect of modeling the lab heterogeneity on the posterior parameter estimates, by comparing Equation (5) to a model that does not include random effects, i.e., essentially pool all lab-specific data into a single dataset and then fit a model with only fixed effects. Here, the posterior distribution of the parameters for model

$$\log(\mu_i) = \beta_0 + \beta_1 c + \beta_2 c^2$$

was sampled using WinBugs version 1.4 with all parameters being given the following diffuse priors: $\beta_k \sim N(0,\ \sigma^2 = 10^6)$. Table III highlights this comparison and shows how an analysis that ignores the lab-source heterogeneity may improperly quantify the level of precision in the analysis. Although the central estimates/posterior means are similar for all β_k parameters, the credible intervals are much wider for the hierarchical/mixed model estimates. Employing such naïve/pooled approaches might lead to risk estimates that underestimate the true nature of the hazard involved or that report a false level of precision for the estimate of the BMD. The hierarchical model is superior to the pooled fixed-effects-only analysis in terms of describing the experimental data as indicated by a smaller deviance information criterion,[15] adding support for the use of a hierarchical model.

5. DISCUSSION

The BMD based on a hierarchical model allows the risk analyst to gain further insight into the system being studied by incorporating data source variability into the estimation of a potency endpoint. In the example described above, the model's linear term showed the highest degree of variability among labs. This variability may simply indicate differences in lab conditions. For example, this might indicate differences in the lab populations of *C. dubia* used by the different labs. It may be that particular labs are using subpopulations that are more sensitive to NaCl exposure. Such research questions are interesting in their own right, and this analysis might help identify labs for additional investigation.

For example, one may define a lab or its *C. dubia* as "sensitive" when its linear term shows no beneficial effect (i.e., those in the population whose $\beta_1 + b_1 \leq 0$), and seek to estimate the RIp from this group. This calculation can be readily incorporated in a Bayesian framework since each MCMC iteration produces a sample from the posterior distribution of the parameters. The RIp calculation could then be restricted to those samples having $\beta_1 + b_1 \leq 0$ (and $\beta_2 + b_2 \leq 0$). If this is done, then the subpopulation's RI25 posterior mean is estimated at 0.51 with symmetric 95% credible interval being (0.32, 0.67). The RI50 posterior mean is estimated to be 0.84 with a symmetric 95% credible interval being (0.61, 1.05). Not surprisingly, the RIp mean estimates are lower in this analysis than the previously derived population-average values, as they represent RIp estimates from lab sources whose *C. dubia* populations show no low-concentration increases in response to the exposure of sodium chloride. Alternatively, an investigation into labs where $\beta_1 + b_1 > 0$ might be of interest since these labs exhibit some increase in mean response at low concentrations.

Arguably a subpopulation analysis should only be used if there is reasonable scientific evidence that such a population exists. Further, the motivation for this additional analysis will come from risk managers, who may want to consider how these analyses support or influence a risk management decision. This analysis was intended to highlight and illustrate other questions that might be explored in the context of the modeling framework under discussion. The hierarchical structure allows such broad questions to be asked, whereas the standard modeling framework may force risk managers to make a decision based upon one single lab.

6. CONCLUSIONS

The hierarchical modeling framework describes and illustrates an analytic framework for modeling experimental data from multiple sources and deriving BMD estimates that reflect this lab-to-lab variability. This reflects an integration of more scientific knowledge into the decision process and formally incorporates an important source of variability into potency estimation. Regardless of how the hierarchical model is fit, this strategy may more realistically represent the true system by capturing lab source variation explicitly. While the framework was demonstrated by estimating the BMD based upon concentration (Poisson)-response data, it is easily generalized given a suitable definition of the BMD for other responses. Finally, we note that the aforementioned methods assume the link function that is a linear function of the parameters. In practice, this may not be the case as one might be interested in a nonlinear function of the parameters. In such cases, minimal suitable modifications can be made to the above framework, and the estimation would proceed as specified above.

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APPENDIX: WINBUGS CODE

Full listing of the WinBugs code used to obtain posterior estimates from Equation (5) is given below. The dataset, which is too large to include in the Appendix, is specified by the variables totyoung[], conc[], conc2[], dlines, and labid[]. Further note that the RIp estimates were calculated from the sampled parameter values in the Microsoft Excel spreadsheet package.

```
model{
       ##set up all of the random effects
       for (j in 1:7){
       ###################################
       #specify the random effects
       #for individual labs
       ###################################
                    lab.int[j]~dnorm(lab.mu.int, l.tau.int)
                    lab.bone[j]~dnorm(lab.mu.one, l.tau.one)
                     lab.btwo[j]~dnorm(lab.mu.two, l.tau.two)
       }
       ########################################################
       #Specify the likelihood
       ########################################################
       for (i in 1:dlines){
                   totyoung[i]~dpois(mu[i])
                   ################################################
                   #specify the fixed effects models
                   ################################################
                   log(mu[i])<- lab.int[labid[i]] + conc[i]*lab.bone[labid[i]]
                       + conc2[i]*lab.btwo[labid[i]]
       }
       l.tau.one~dgamma(0.001,0.001)
       l.tau.two~dgamma(0.001,0.001)
       l.tau.int~dgamma(0.001,0.001)
       s.one <- 1/l.tau.one
       s.two <- 1/l.tau.two
       s.int <- 1/l.tau.int
       lab.mu.int~dnorm(0,1.0E-6)
       lab.mu.one~dnorm(0,1.0E-6)
       lab.mu.two~dnorm(0,1.0E-6)
}
```

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