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Benchmark Dose Profiles for Joint-Action Quantal Data in Quantitative Risk Assessment

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Summary

Benchmark analysis is a widely used tool in public health risk analysis. Therein, estimation of minimum exposure levels, called Benchmark Doses (BMDs), that induce a pre-specified Benchmark Response (BMR) is well understood for the case of an adverse response to a single stimulus. For cases where two agents are studied in tandem, however, the benchmark approach is far less developed. This paper demonstrates how the benchmark modeling paradigm can be expanded from the single-dose setting to joint-action, two-agent studies. Focus is on response outcomes expressed as proportions. Extending the single-exposure setting, representations of risk are based on a joint-action dose-response model involving both agents. Based on such a model, the concept of a benchmark profile (BMP) – a two-dimensional analog of the single-dose BMD at which both agents achieve the specified BMR – is defined for use in quantitative risk characterization and assessment. The resulting, joint, low-dose guidelines can improve public health planning and risk regulation when dealing with low-level exposures to combinations of hazardous agents.

Keywords

Benchmark analysis; Joint-action model; Quantal response data; Quantitative risk assessment; Safety assessment; Simultaneous inference

1. Introduction: Benchmark Analysis

An important objective in quantitative risk assessment is the characterization of detrimental or adverse responses after exposure to chemical, environmental, biological, physical, or other hazardous agents (Stern, 2008). The adverse response could be cancer, mutation, birth defect, damage caused by environmental or ecological hazards, and so forth. In this context, the risk is quantified via a function $R(x)$, which is often the probability of exhibiting the adverse effect in a subject or object exposed to a particular dose level, x , of the hazardous agent.

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Supplementary Material

Web Appendices, Tables, and Figures referenced in Sections 3 and 5 are available with this paper at the *Biometrics* website on Wiley Online Library.

A major effort in risk analysis involves dose-response modeling, i.e., modeling of the risk function $R(x)$. Commonly, a statistical model for the relationship between exposure and response is fit to data from bioassays on small mammals or other biological systems, or from epidemiological analyses of human populations at risk. For many risk assessments the observations are in the form of proportions associated with a set of quantifiable exposure levels ('doses'). This is the *quantal response setting*, and is our focus here.

A popular statistical technique in risk assessment known as *Benchmark Analysis* (Crump, 1984) manipulates components of the dose-response model to yield the Benchmark Dose (BMD) of the agent necessary to induce a predetermined change in the adverse effect, relative to background levels. The pre-specified target change is called the benchmark response or benchmark risk (BMR). If the exposure is measured as a concentration, one refers to the exposure point as a Benchmark Concentration (BMC). Risk analysts use BMDs or BMCs for setting occupational exposure limits (OELs) or other so-called 'points of departure' (PODs) when assessing hazardous stimuli/exposures (Kodell, 2005).

Uncertainty in the estimation process is accounted for by constructing $100(1-\alpha)\%$ confidence limits on the BMD. Driven by public health considerations, only one-sided, lower limits are used, denoted as BMDLs (Crump, 1995). In this fashion, BMDs and BMDLs – or BMCs and BMCLs, etc. – are increasingly employed for risk characterization and management by a variety of Federal and state agencies, including the U.S. Environmental Protection Agency (EPA) or the U.S. Food and Drug Administration (FDA), as well as many private research laboratories and institutes.

Benchmark doses are widely used for studies involving only one hazardous agent (Piegorsch and Bailer, 2005, Sec. 4.3). For the case of two stimuli, however, the approach is far less developed. Consider the following example with the two agents dichlorodiphenyltrichloroethane (DDT) and titanium dioxide nanoparticles (nano-TiO₂). The data in Table 1 shows rates of cellular damage (as micronucleus formation) after human hepatic cells were exposed to various combinations of the two agents (Shi et al., 2010). As we discuss below, a critical issue with these data is whether a significant interactive effect ('synergy') is evident; however, from a risk assessment viewpoint it is also important to estimate which exposure combinations of the agents are likely to induce damage in the target cells, for use in further risk characterizations.

While substantial statistical and public health research has been directed at modeling this joint-action setting (e.g., Plackett and Hewlett, 1952; Piegorsch et al., 1988; Dawson et al., 2000; Stork et al., 2008), surprisingly little effort has supported benchmark analysis. For chemical mixture studies, Chen et al. (1990) and Auton (1991) computed BMDLs using a likelihood-ratio technique. These were obtained using information from each single chemical's observed dose response, however, and did not incorporate the effect of any joint exposure. This approach was further discussed by Kodell and Chen (1994), Kodell et al. (1995) and Hwang and Chen (1999). Zhu (2005) developed BMD estimators for two factors modeled in tandem, but where one of these factors was taken specifically as time and viewed as a secondary, nuisance variate. Hu et al. (2008) considered Bayesian models for inverse dose estimation based on two stimuli, but did not emphasize benchmark dose calculation.

Since no established definition has appeared in the literature for conducting full benchmark analysis with dual-exposure data, we describe here a new strategy for doing so in the two-stimulus, joint-action, quantal dose-response setting. We also study the operating characteristics of our approach, using both an analysis of the micronuclei data from Table 1 and a set of Monte Carlo evaluations. We conclude the paper with a brief discussion.

2. Dual Risk Modeling

For dual-exposure quantal data as, e.g., in Table 1 we assume a binomial model:

$$Y_{ij} \stackrel{ind}{\sim} \text{Bin}(N_{ij}, \mathbf{R}(\mathbf{x}_{1i}, \mathbf{x}_{2j})) \quad (1)$$

where N_{ij} is the number of subjects tested and $\mathbf{R}(\mathbf{x}_{1i}, \mathbf{x}_{2j})$ is the joint dose-response function representing the probability that a subject will respond at dose (or log-dose; cf. Sec. 6

below) combination $\mathbf{x}_{1i}, \mathbf{x}_{2j}$ ($i = 1, \dots, n_1; j = 1, \dots, n_2$). We write $\eta_{ij} = \mathbf{x}_{ij}'\boldsymbol{\beta}$ as the linear predictor, where $\boldsymbol{\beta}$ is a vector of unknown parameters and $\mathbf{x}_{ij}$ is the corresponding vector of predictor variables. The linear predictor in its simplest 1st-order form with two dose regressors x_1 and x_2 would be

$$\eta(x_1, x_2; \boldsymbol{\beta}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2, \quad (2)$$

where $\mathbf{x}' = (1, x_1, x_2)$. However, we focus on the full 2nd-order ‘quadric’ surface

$$\eta(x_1, x_2; \boldsymbol{\beta}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1^2 + \beta_4 x_2^2 + \beta_5 x_1 x_2, \quad (3)$$

where $\mathbf{x}' = (1, x_1, x_2, x_1^2, x_2^2, x_1 x_2)$. This is clearly a form of generalized linear model (Dobson, 2002). Thus, we associate the linear predictor with $\boldsymbol{\pi} = \mathbf{R}(x_1, x_2)$ using a link function $g(\boldsymbol{\pi}) = \boldsymbol{\eta}$, which is assumed strictly monotone increasing in $\boldsymbol{\pi}$. The inverse link is $g^{-1}(\boldsymbol{\eta}) = \boldsymbol{\pi}$. In our notation this translates to $\mathbf{R}(x_1, x_2; \boldsymbol{\beta}) = g^{-1}(\boldsymbol{\eta}(x_1, x_2; \boldsymbol{\beta}))$.

Common link functions for quantal-response data include the logit link, $g(\boldsymbol{\pi}) = \log(\frac{\boldsymbol{\pi}}{1-\boldsymbol{\pi}})$, the probit link, $g(\boldsymbol{\pi}) = \Phi^{-1}(\boldsymbol{\pi})$, the complementary log-log link, $g(\boldsymbol{\pi}) = \log\{-\log(1-\boldsymbol{\pi})\}$ and the complementary log link, $g(\boldsymbol{\pi}) = -\log(1-\boldsymbol{\pi})$. The latter corresponds to the popular ‘multistage model’ in single-exposure cancer risk analysis (Guess and Crump, 1976; Hoel and Jennrich, 1979) and, coincidentally, to a useful form in joint-action quantal-response studies (Wahrendorf et al., 1981; Piegorsch et al., 1988). Given this fortuitous overlap, and the important attention the multistage model has received in benchmark risk assessment (Al-Saidy et al., 2003; Nitcheva et al., 2007), we will focus on the complementary log for modeling the link relationship. Other choices for the link function are possible, of course, and we comment briefly on this in the Discussion section.

Under our dual-exposure model (1) using the complementary log link and the 2nd-order linear predictor in (3), we must impose a constraint on the model to produce a valid quantal response; at a minimum, we require that

$$\eta(x_1, x_2; \boldsymbol{\beta}) > 0 \quad \forall x_1, x_2. \quad (4)$$

In a typical risk-analytic setting, however, it is generally expected that risk is an increasing function of exposure. Assuming similar relationships with dual risk, this translates into both $\mathbf{R}(x_1, 0)$ and $\mathbf{R}(0, x_2)$ being increasing functions in x_1 and x_2 , respectively. Enforcing this

constraint, we further require that $\frac{d}{dx_1} \mathbf{R}(x_1, 0) > 0$ and $\frac{d}{dx_2} \mathbf{R}(0, x_2) > 0$. These two inequalities produce the restrictions $\beta_1 > -2\beta_3 x_1$ and $\beta_2 > -2\beta_4 x_2$ for all $x_1, x_2 \geq 0$. Note however that this does not imply that $\mathbf{R}(x_1, x_2)$ is an increasing function in both x_1 and x_2 , since, e.g., a strong protective effect (corresponding to $\beta_5 < 0$) at certain levels of x_1 and x_2 could act to decrease the joint risk. Indeed, aside from the necessary regularity constraint in Equation (4), we impose no specific restrictions on the cross-product parameter β_5 .

Further, risk is usually studied over a constraint set, $\mathcal{X}$. This set represents the collection of (x_1, x_2) combinations pertinent to the risk-analytic scenario under investigation. A typical choice is the rectangle $\mathcal{X} = \{(x_1, x_2): A_1 \leq x_1 \leq \Omega_1, A_2 \leq x_2 \leq \Omega_2\}$ where $A_1 < \Omega_1$ and $A_2 < \Omega_2$ are known, non-negative, limits on the predictor variables. For the sort of dose-response modeling we consider here, $A_1 = A_2 = 0$ is a natural specification and this allows us to re-express the restrictions above as

$$\beta_1 > \max(-2\beta_3\Omega_1, 0) \quad \text{and} \quad \beta_2 > \max(-2\beta_4\Omega_2, 0). \quad (5)$$

3. Dual-Exposure Risk Analysis

3.1 Dual Extra Risk

In many biomedical and environmental applications of the benchmark approach, the risk function $R(x)$ is further refined into a form of excess risk, in order to adjust for background or spontaneous effects out of the control of the risk regulator (Piegorsch and Bailer, 2005, Sec. 4.2). For single exposures, a popular construct with quantal data is the extra risk

function $R_E(x) = \frac{R(x) - R(0)}{1 - R(0)}$, where we assume $0 \leq R(0) < 1$. For application to our dual-exposure setting, however, the concept requires modification. Unfortunately, no guidance exists in the literature on how to define an extra risk function or, for that matter, a benchmark ‘dose’ from two active exposure variates. As mentioned above, Zhu (2005) described risk specifications when the active dose x_1 is studied alongside a secondary variable x_2 such as a time marker. Following on his lead, a natural extension for the joint

extra risk is $R_E(x_1, x_2) = \frac{R(x_1, x_2) - R(0, 0)}{1 - R(0, 0)}$ where we assume $R(0, 0) < 1$. We will operate under this definition for extra risk when constructing benchmark quantities in our dual-exposure setting.

3.2 The Benchmark Profile

For single-exposure risk assessments, the BMD is defined as the smallest positive dose at which the extra risk achieves a specified BMR $\in (0, 1)$. Applying this concept in a dual-exposure risk assessment leads, at least generically, to a *collection* of benchmark points, each point satisfying $R_E(x_1, x_2) = \text{BMR}$. We define this as the *Benchmark Profile*: $\text{BMP} = \{(x_1, x_2): R_E(x_1, x_2) = \text{BMR}\}$. Following Zhu (2005), it is convenient to view the BMP at a fixed value of BMR in terms of the relationship it defines between x_1 and x_2 in the (x_1, x_2) -plane; i.e., how values of x_1 change as a (possibly nonlinear) function of x_2 , say, $x_1(x_2; \beta)$. For clarity, we use the notation $\text{BMP}_1(x_2; \beta)$. To also explicate the dependence on BMR we write $\text{BMP}_{\text{BMR},1}(x_2; \beta)$, where necessary. For the linear predictor in Equation (3) and any general link function $g(\pi)$, with inverse link $g^{-1}(\eta)$, this gives

$$\text{BMP}_{\text{BMR},1}(x_2; \beta) = -\frac{(\beta_1 + \beta_5 x_2)}{2\beta_3} + \frac{\sqrt{(\beta_1 + \beta_5 x_2)^2 - 4\beta_3(c(\text{BMR}, \beta_0) + \beta_2 x_2 + \beta_4 x_2^2)}}{2\beta_3} \quad (6)$$

for $x_2 \geq 0$, where $c(\text{BMR}, \beta_0) = \beta_0 - g(\text{BMR} \cdot (1 - g^{-1}(\beta_0)) + g^{-1}(\beta_0))$ and we require $R(x_1, x_2; \beta)$ to be increasing in x_1 for small positive values of x_1 and x_2 (a likely circumstance for the kinds of models we consider. In particular, for the complementary log link we have $c(\text{BMR}, \beta_0) = \log(1 - \text{BMR})$. Thus the BMP may be written as

$$\text{BMP}_{\text{BMR},1}(x_2; \beta) = -\frac{(\beta_1 + \beta_5 x_2)}{2\beta_3} + \frac{\sqrt{(\beta_1 + \beta_5 x_2)^2 - 4\beta_3(\log(1 - \text{BMR}) + \beta_2 x_2 + \beta_4 x_2^2)}}{2\beta_3} \quad (7)$$

for $x_2 = 0$. As above we require the β_k s and their corresponding estimates to satisfy the restrictions from equations (4) and (5). If desired, this construction can be easily manipulated to instead write x_2 as a function of x_1 , producing $\text{BMP}_2(x_1; \beta)$, etc. (For more details on the BMP see Web Appendices A and B.)

4. Benchmark Profile Estimation

Once the two-predictor model is specified, we fit it via maximum likelihood (ML) to the observed data to produce ML estimates (MLEs), $\hat{\beta}$, of the unknown parameters. Substituting these into the pertinent expressions leads to MLEs of the dual risk, $\hat{R}_E(x_1, x_2)$, the dual extra risk, $\hat{R}_E(x_1, x_2)$ and the benchmark profile, $\widehat{\text{BMP}}_{\text{BMR},1}(x_2) = \text{BMP}_{\text{BMR},1}(x_2; \hat{\beta})$. In analogous fashion to the single-exposure setting, public health concerns direct attention to only upper, one-sided, confidence limits on R_E , and hence lower confidence limits on the BMP. Due to the profile's multivariable nature, however, finding lower confidence limits on exposure is tantamount to constructing a lower confidence band, the BMPL, on the BMP.

Given sufficiently large sample sizes, construction of BMPLs can make use of the asymptotic features of $\hat{\beta}$ (Deutsch et al., 2010). For instance, we can expand on a strategy proposed by Al-Saidy et al. (2003) and find BMPLs by inverting upper, simultaneous, confidence surfaces on $R_E(x_1, x_2)$. Our application of Al-Saidy et al.'s approach hinges on the observation that under a complementary log link, the extra risk is a monotone function of the reduced linear predictor $\lambda(x_1, x_2; \beta) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1^2 + \beta_4 x_2^2 + \beta_5 x_1 x_2$. Therefore, any confidence statement on $\lambda(x_1, x_2; \beta)$ can be manipulated directly into a confidence statement on the extra risk. But $\lambda(x_1, x_2; \beta)$ is linear in the parameters, β , and so confidence bands for it can employ well-established methods from linear model theory.

To construct such a band, we could take an *ad hoc* approach and use only the upper component from a standard large-sample $100(1 - 2\alpha)\%$ Working-Hotelling-Scheffé (WHS) band (Working and Hotelling, 1929; Scheffé, 1953) on $\lambda(x_1, x_2; \beta)$. Alternatively, we could employ the dedicated, one-sided, $100(1 - \alpha)\%$ WHS-style band given by Hochberg and Quade (1975). In both cases, however, the bands cover the linear predictor for all $(x_1, x_2) \in \mathbb{R}^2$ and thus consider a far wider range of predictor values than necessary in a typical dose-response risk assessment. This leads to overly conservative inferences on the BMP.

Instead, we construct a targeted, one-sided, confidence surface on $\lambda(x_1, x_2; \beta)$ over the rectangle $\mathcal{X} = \{(x_1, x_2): 0 \leq x_1 \leq \Omega_1, 0 \leq x_2 \leq \Omega_2\}$. Liu (2010, Sec. 3.2) presents a simulation-based method for computing one-sided critical points for WHS-style confidence bands on a multiple linear predictor over such rectangular constraint regions. Via this algorithm, we can simulate random variates that produce a critical point w_α to approximate

$P(\lambda(x_1, x_2; \beta) \leq \lambda(x_1, x_2; \hat{\beta}) + w_\alpha \cdot \widehat{SE}(\lambda(x_1, x_2; \hat{\beta}))) = 1 - \alpha$, where $\widehat{SE}(\lambda(x_1, x_2; \hat{\beta}))$ is the usual large-sample standard error of $\lambda(x_1, x_2; \hat{\beta})$; i.e., $\widehat{SE}^2(\lambda(x_1, x_2; \hat{\beta})) = x_1^2 \text{Var}(\hat{\beta}_1) + x_2^2 \text{Var}(\hat{\beta}_2) + 2x_1 x_2 \text{Cov}(\hat{\beta}_1, \hat{\beta}_2) + \dots + 2x_1^2 x_2^2 \text{Cov}(\hat{\beta}_3, \hat{\beta}_4) + x_1^2 x_2^2 \text{Var}(\hat{\beta}_5)$. Given w_α , an upper $100(1 - \alpha)\%$ simultaneous confidence surface on the extra risk is then

$$\overline{R_E}(x_1, x_2) = 1 - \exp\{\lambda(x_1, x_2; \hat{\beta}) + w_\alpha \cdot \widehat{SE}(\lambda(x_1, x_2; \hat{\beta}))\}. \quad (8)$$

Although the critical point w_α is calculated via Monte Carlo approximation, Liu notes that the precision available to the analyst can approach exact levels by increasing the number of simulations used to perform the Monte Carlo calculations. We give further detail on the calculation of w_α in supplementary online material; see Sec. 8.

Setting the upper surface in (8) equal to BMR and inverting produces a simultaneous $100(1-\alpha)\%$ BMPL at that BMR: $\text{BMPL}_{\text{BMR}} = \{(x_1, x_2): \text{BMR} = \overline{R}_E(x_1, x_2)\}$. Indeed, because the extra risk confidence surface involves a simultaneous construction, multiple choices for BMR can be applied, and the resulting BMPLs will still retain minimal simultaneous $1-\alpha$ coverage. This holds even if the BMR(s) are chosen in a *post hoc* fashion, after the data have been analyzed (Al-Saidy et al., 2003).

As an alternative to confidence band inversion we also consider an approach by Cox and Ma (1995), who combined a simultaneous Scheffé confidence region with the delta method (Piegorsch and Bailer, 2005, Sec. A.6) to obtain two-sided confidence statements on nonlinear functions of any model's unknown parameters. Exploiting this approach for use with (7), an *ad hoc* $100(1-\alpha)\%$ BMPL for our setting can be obtained by constructing an approximate $100(1-2\alpha)\%$ confidence region on $\text{BMP}_1(x_2; \beta)$ and disregarding the upper bound. The construction is similar in strategy and form to the WHS approach noted earlier, except that the lower bound is now based on the complete expression for the BMP. Since this involves a non-linear function of the unknown parameters, a delta-method approximation is used to build the standard error of the point estimator. We find

$$\text{BMPL}_1(x_2) = \text{BMP}_1(x_2; \hat{\beta}) - \sqrt{\chi_{2\alpha}^2(p) \cdot \widehat{SE}(\text{BMP}_1(x_2; \hat{\beta}))}, \quad (9)$$

where p is the number of model parameters and $\widehat{SE}(\text{BMP}_1(x_2; \hat{\beta}))$ is the delta-method standard error. This latter quantity is found from the inverse of the Fisher information

matrix, $\mathcal{Q}^{-1}(\beta)$, as $\widehat{SE}(\text{BMP}_1(x_2; \hat{\beta})) = \left[\left(\frac{\partial}{\partial \beta} \text{BMP}_1(x_2; \beta) \right)' \mathcal{Q}^{-1}(\beta) \left(\frac{\partial}{\partial \beta} \text{BMP}_1(x_2; \beta) \right) \right]^{0.5} \Big|_{\beta=\hat{\beta}}$. Notice that (9) can produce a negative BMPL, which has no practical interpretation. If this occurs, simply truncate the lower bound at zero.

5. BMPL Performance Evaluation

Since we appeal to the asymptotic normality of the MLEs in $\hat{\beta}$ (Dobson, 2002, Sec. 5.3), all the BMPL confidence statements constructed above hold in the limit as $N_{ij} \rightarrow \infty$ and $N_{ij}/N \rightarrow \kappa \in (0, 1)$ for $N = \sum_i \sum_j N_{ij}$. In finite samples, however, the inferences are only approximate. To examine the performance of the profiles based on (8) and (9) in both small- and large-sample settings we conducted a series of Monte Carlo evaluations. We studied BMPL coverage at the commonly seen values of BMR = 0.01, 0.05, and 0.10. To do so, we simulated quantal data via (1) with a complementary log link and the linear predictors in (2) and (3). The specific parameterizations chosen for the simulation models are summarized in Table 2: for both x_1 and x_2 levels were taken to vary over 0, 0.25, 0.5, 1, a common single-exposure design in cancer risk experimentation (Portier, 1994). The parameterizations for β were then determined by specifying response rates at the points $(x_1, x_2) = (0,0), (0,1), (1,0)$

for (2) and $(x_1, x_2) = (0,0), (0, \frac{1}{2}), (0,1), (\frac{1}{2}, 0), (1,0), (1,1)$ for (3); see the upper portions of each sub-table. These represent a variety of response surfaces combined from single-regressor risk models given previously by Bailer and Smith (1994) and Buckley and Piegorsch (2008). All parameterizations were studied over the same constraint region $\mathcal{X}$ with the upper limits equal to the largest dose on each scale: $\Omega_1 = \Omega_2 = 1$.

Simulating from these models, Monte Carlo coverage probabilities for the BMPLs were calculated using equi-replicated sample sizes $N_{jj} = N$ ranging from $N = 20$ to $N = 3000$. The simulated data were fit via ML to the model from which they were generated; corresponding standard errors and other pertinent quantities were calculated using these ML values. All simulations and computations were conducted in the R programming environment, version 2.11 (R Development Core Team, 2005).

For inversion of Liu's confidence surfaces on R_E , we first determined the critical points w_α at each sample size under study by generating a random sample of 320,000 pseudo-random variates as outlined in Liu (2010, Appendices A and B). Since all parameterizations are studied over the same constraint region $\mathcal{X}$ it is sufficient to run the Liu-algorithm prior to the actual simulation study. This was the only computational demand we encountered: calculation of the Liu critical point w_α from 320,000 variates took roughly 25 minutes on a desktop computer running Windows XP with a 2.5GHz CPU and 3.5 GB of RAM. Obviously, this runtime can be substantially reduced by generating fewer pseudo-random variates, but at the cost of a less accurate computation; for details, see Liu (2010, Sec. A.2). No other single calculation we describe here took more than 1 second on the same machine.

We set the desired confidence level to $1 - \alpha = 0.95$, thus the critical point $w_{0.05}$ was chosen as the 95th percentile of this generated sample. To invert each upper confidence surface on R_E , we constructed the contour of the surface at the given BMR. We next projected the contour on to the (x_1, x_2) -plane on a fine grid of points, and connected these via cubic spline interpolation (method `fmm` in the R `splinefun` function) to yield the BMPL.

We checked coverage of the resulting BMPLs by comparing them to the true-model BMPs on a fine grid of values in the constraint rectangle $\mathcal{X}$ if the BMPL rested below and to the left – i.e., closer to the origin – of the true BMP over all grid values within $\mathcal{X}$ we viewed this as coverage for that particular simulated data set. We simulated 2000 data sets for each parameterization in Table 2; empirical coverage rates were taken as the proportion of times coverage was achieved among the 2000 data sets. Notice then that the approximate standard error of each estimated coverage rate is $\sqrt{(0.05)(0.95)/2000} = 0.005$. The Cox & Ma-BMPLs were constructed using Equation (9), and coverage probabilities were assessed by again comparing the resulting BMPLs to the true-model BMPs on a fine grid (for full details see Web Appendices C and D).

Results of the simulation studies for BMR = 0.01 and 0.10 are displayed in Table 3 (results at BMR = 0.05 were roughly intermediate between these two values; see Web Appendix E). From the Monte Carlo evaluations, we see that coverage for both the Liu- and the Cox & Ma-BMPLs largely depends on the number of model parameters. For the three-parameter models, the coverage probabilities exhibit similar behavior for both BMR levels. When N is small the coverage ranges between approximately 90% to almost 100%, and it tends to grow closer between the two methods as N increases. The coverage generally becomes conservative for large N .

For the six-parameter models, the BMPLs again appear very conservative, especially for $N = 100$ and with BMR = 0.01. At BMR = 0.10, the BMPLs for some models (2C and 2D) are not as conservative when using the Liu method. For models with low background response rates and relatively shallow response surfaces (2A and 2B), the coverage probabilities rest closer to the nominal 95% level at smaller sample sizes, dropping as low as 0.92 at $N = 20$. At larger sample sizes the empirical coverage rises to near 98–100% for all models.

Comparing the two methods, the Cox & Ma-BMPLs are generally more conservative than the Liu-BMPLs. This difference is most pronounced for lower sample sizes: for models 1A

and 1B, the Cox & Ma-BMPL seems to be the preferred method when using $N = 20$. For all other cases, the Liu-BMPLs appear as or more advantageous. The coverage probabilities for the Liu-BMPLs are also more model dependent (i.e., variable) at higher sample sizes than the generally very conservative Cox & Ma-BMPLs. Note that despite the possibility that the Cox & Ma-BMPL can produce negative lower limits, as noted in Sec. 4, we did not encounter any instances of such in these simulations.

The conservatism seen with both forms of BMPLs is, upon reflection, not unexpected; we attribute it to a series of factors. For the Cox-Ma BMPLs, a primary driver is the fact that the underlying construction is valid for all x_1 and x_2 , and does not adjust for constrained interest over only $\mathcal{X} = \{(x_1, x_2): 0 \leq x_1 \leq \Omega_1, 0 \leq x_2 \leq \Omega_2\}$. The simultaneous Liu bands improve upon this by adjusting for these constraints; however, their simultaneity also makes them valid for all choices of $\text{BMR} \in (0, 1)$. Although our simulations did examine simultaneous BMPL coverage for all $(x_1, x_2) \in \mathcal{X}$ we only assessed the coverage at a single, ‘pointwise’ BMR. While the bands’ ability to account for multiple, even *post hoc* BMRs is an important feature, it apparently also comes with broad conservatism for a single BMR. A similar effect for single-agent BMDLs was observed by Nitcheva et al. (2005).

Although not a focus of our Monte Carlo evaluations, we also used the results to study selected characteristics of the $\widehat{\text{BMP}}$, concentrating on the estimator’s bias. We found it convenient to consider deviations between $\widehat{\text{BMP}}$ and the true BMP along rays emanating from the origin in the first quadrant of (x_1, x_2) space. These deviations are best expressed in terms of the angle, θ , the ray makes with the x_1 -axis, creating a so-called bias profile over

$\theta \in (0, \frac{\pi}{2})$. We computed the deviation, $b_{\text{BMR}}(\theta)$, as the distance from the (x_1, x_2) pair comprising $\widehat{\text{BMP}}_{\text{BMR}}$ to that comprising the true BMP_{BMR} along the ray at a fixed θ . Negative values of $b_{\text{BMR}}(\theta)$ correspond to $\widehat{\text{BMP}}_{\text{BMR}}$ s closer to the origin than the true BMP_{BMR} ; positive values correspond to $\widehat{\text{BMP}}_{\text{BMR}}$ s farther out along that ray. To characterize the bias, we average the computed $b_{\text{BMR}}(\theta)$ values at a given θ among all 2000 simulated data sets for each of the model parameterizations in Table 2, then report that model’s profile over $\theta \in (0, \frac{\pi}{2})$.

In general, bias profiles for the three-parameter models (1A–1H) exhibited slight overestimation (i.e., positive bias): $b_{\text{BMR}}(\theta)$ was roughly at over most values of θ but sometimes increased sharply as $\theta \rightarrow 0$. As N grew large the bias decreased considerably and became negligible for $N = 500$. Figure 1 displays representative examples using models 1B and 1D at $\text{BMR} = 0.01$. We observed roughly similar bias profiles with those six-parameter models whose BMPs were comparable in shape to the three-parameter BMPs (namely, 2B, 2C, 2D and 2F, with BMPs exhibiting limited curvature and lying closer to the x_1 axis). Their bias profiles were generally flat and positive, although the bias now dropped below zero as $\theta \rightarrow 0$. Again, see Figure 1. (Note that for any given quantal data set, the $\widehat{\text{BMP}}_{\text{BMR}}$

may not necessarily extend to all values of θ near 0 or $\frac{\pi}{2}$ resulting in no contribution for calculating the empirical bias at that θ . The corresponding average for $b_{\text{BMR}}(\theta)$ was then based on fewer than 2000 replications.) For the other six-parameter models, the bias profiles were more diverse: we observed centralized patterns of underestimation (i.e., negative bias) for models 2A, 2E and 2G, with contrasting positive bias as θ approached its extremes at 0 and $\frac{\pi}{2}$. Figure 1 displays a representative example with model 2E at $\text{BMR} = 0.01$. Model 2H was perhaps the most particular of all: it exhibited consistent underestimation for all values of θ . In all other cases, the absolute bias dampened to zero as N increased. (For details and results see Web Appendix F.)

It is worth remarking that in general our Monte Carlo evaluations uncovered fewer instances of negative bias than of positive bias with the ML-based $\widehat{\text{BMP}}$. In terms of how this affects the corresponding BMPLs, we would expect consistent negative bias to drive the coverage rates higher while positive bias would have a more-ambiguous effect. The empirical coverage results in Table 3 do indicate conservative coverage; however, at least for the parameterizations studied here, it is unclear if bias in the point estimator provides a contributing factor.

6. Micronuclei Example Revisited

To illustrate application of the BMPL in practice, consider again the micronuclei data from Table 1. The first agent, dichlorodiphenyltrichloroethane (DDT), was a heavily used organochlorine pesticide and is a known animal carcinogen and a suspected human carcinogen. To expedite degradation of DDT, some nations employ titanium dioxide (TiO_2) as a photocatalysis aid. While on a micron-level scale TiO_2 toxicity is considered low, nano- TiO_2 particles are strong oxidizing reagents, capable of reacting with a wide range of organic molecules. This led Shi et al. (2010) to study via the data in Table 1 the joint cellular toxicity between nano- TiO_2 and DDT in human hepatic cells.

We fitted the quantal-response model from (1) to the data in Table 1 using the quadric linear predictor in (3) and the complementary log link. We took x_1 to represent DDT exposure and x_2 to represent nano- TiO_2 exposure. Since the two exposure regimes are geometrically spaced, we applied logarithmic transforms and set $x_1 = \log_{10}(\text{DDT}) + 4$ and $x_2 = \log_{10}(\text{TiO}_2) + 3$. For the control levels we applied consecutive-dose average spacing (Piegorsch and Bailer, 2005, Sec. 1.1), producing $x_1 = 0$ at the DDT control and $x_2 = 0$ at the nano- TiO_2 control. Notice that by moving to these logarithmic scales, estimates and inferences for the BMP are guaranteed to be positive when reverse-transformed to the original scale(s). This is a desirable consequence, since we expect the ‘dose’ of a toxic agent to be non-negative.

To enforce the restrictions in (5), we set the upper predictor bounds to the corresponding, transformed high doses: $\Omega_1 = \Omega_2 = 3$. Standard analysis of deviance for these data (not shown) indicated that all the higher-order terms were insignificant: the likelihood ratio test for $H_0: \beta_3 = \beta_4 = \beta_5 = 0$ yielded a test statistic of $X^2 = 2.316$ ($P = 0.51$, referenced against $\chi^2(3)$). We note in particular that the insignificance of β_5 implies a lack of interactive ‘synergy’ between the two agents. Nonetheless, it is still of interest to characterize the risk of cellular damage across the joint-exposure levels. To do so, we re-applied the complementary log link with the reduced, no-interaction, first-order model in (2). This gave constrained MLEs of $\hat{\beta}_0 = 0.0192$, $\hat{\beta}_1 = 0.0045$, and $\hat{\beta}_2 = 0.0016$. Figure 2 displays the corresponding, fitted extra risk surface using the complementary log link, as well as the BMP obtained at $\text{BMR} = 0.01$. (This smaller, more protective BMR can be employed when sufficient data are available to support inferences at extreme low doses. With these data, the large sample sizes and small observed proportions provide for reasonably accurate determination of the dose response at very low response levels.) We represent BMP here as a function of x_1 . Under the no-interaction, first-order model in (2), we find $\text{BMP}_{\text{BMR},2}(x_1, \beta_1, \beta_2) = \{-\log(1-\text{BMR}) - \beta_1 x_1\} / \beta_2 (x_1 - 0)$. The corresponding MLE at $\text{BMR} = 0.01$ with these data is $\widehat{\text{BMP}}_{0.01,2}(x_1) = \{-\log(0.99) - 0.0045 x_1\} / 0.0016 (x_1 \geq 0)$, also plotted in Figure 2.

In addition, we calculated 95% BMPLs at $\text{BMR} = 0.01$, using both the Liu- and the Cox & Ma-based approaches. For the Liu-based BMPL, we determined the critical point over the rectangle $\mathcal{X} = \{(x_1, x_2): 0 \leq x_1 \leq 3, 0 \leq x_2 \leq 3\}$ to be $w_{0.05} = 2.4488$ (again using a random sample of 320,000 pseudo-random variates). Figure 2 displays the resulting curve obtained via inversion of $\overline{R}_E(x_1, x_2)$ on to the (x_1, x_2) plane, along with the Cox & Ma BMPL. We see

that the Cox-Ma profile is more conservative – i.e., closer to the origin – than the Liu profile. This is not surprising, given the more-conservative coverage the Cox-Ma BMPL exhibited in our Monte Carlo evaluations from Sec. 5. Since both profiles possess asymptotic 95% coverage, one would typically choose the Liu profile for practical use here. Indeed, the Liu-based BMPL provides a valid set of dual benchmark values with these data, allowing for integrated risk estimation and coordinated determination of acceptable levels of exposure between the two toxic agents. For example, in combination with a DDT concentration of $0.001 \mu\text{mol/L}$ (i.e., $x_1 = 1$) a nano-TiO₂ concentration of $0.036 \mu\text{g/L}$ (i.e., $x_2 = 1.56$ from the Liu BMPL in Figure 2) represents a two-dimensional ‘point of departure’ at $\text{BMR} = 0.01$ for further risk-analytic calculations on joint DDT/TiO₂ cellular toxicity. By comparison, suppose we ignore DDT exposure and analyze the marginal nano-TiO₂ dose response via the complementary log model in (2) with $\beta_1 = 0$. A pointwise 95% Wald-type BMDL_{01} for nano-TiO₂ is then $0.085 \mu\text{g/L}$ (corresponding to $x_2 = 1.93$ on the transformed scale). Referring to Figure 2, we see that for high DDT exposures – past approximately $x_1 = 0.75$ – reporting a single (transformed) nano-TiO₂ exposure of $x_2 = 1.93$ as a safe lower limit is misleading: as indicated by the Liu BMPL, joint DDT toxicity drives nano-TiO₂ benchmark limits far below 1.93 on the transformed scale as x_1 rises. Failure to compensate for the joint action could lead to dangerous, possibly unsafe conclusions in any consequent risk assessment.

7. Discussion

Herein, we consider a joint-action dose-response model for estimating benchmark points in quantitative risk analysis. Placing emphasis on toxicological risk assessment, we introduce an approach for estimating a joint benchmark profile (BMP) of points past which dual exposure to a pair of toxic agents may produce unacceptable risk of adverse events. Conceptually, the BMP can be extended to more than the two agents we focus on here; however, we imagine that barriers to such applications may exist in practice. These include (a) an increase in the computing demands if employing the Liu profile, since the calculational complexity for finding the Liu critical point and determining the BMPL will increase greatly as the number of dimensions rises; and (b) the likely need to collect rather large numbers of subjects at each jointly-studied, multi-dimensional, exposure combination in order for the asymptotic approximations for BMPL coverage to take hold. Of course, as the technology advances over time, these issues may mitigate somewhat.

In our example we worked exclusively with the complementary log link to produce the joint-action fit and the $\widehat{\text{BMP}}$. However, other forms such as the popular logit or probit links are available for use in (6) under our general paradigm. Indeed, when we fit either of these links with the no-interaction linear predictor in (2) to the data in Table 1, we find the corresponding AICs to be slightly lower and hence more informative than that for the complementary log link: $\text{AIC}_{\text{logit}} = 109.743$ and $\text{AIC}_{\text{probit}} = 109.750$, while $\text{AIC}_{\text{clog}} = 110.623$. These are differences of less than 1%, however, and do not imply a substantive loss in information or degradation of fit across the various link functions. Nonetheless, additional study is required to determine whether our methods can translate effectively to other link functions for joint-action quantal-response models. Indeed, application of the strategy to joint-action ordinal data (e.g., malformation severity), joint-action continuous data (e.g., birth weights), or cases where the exposures occur in ordered sequence (i.e., one before the other) are all questions open for further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Bias profiles at BMR = 0.01 for four selected models from Table 2. Solid curves indicate that average bias at the respective angle is based on all 2000 Monte Carlo samples, whereas dashed curves indicates that fewer than 2000 replicates were available for the bias calculation.

Figure 2.

Benchmark profile at $BMR=0.01$ for the data from Table 1. The darker surface represents the estimated extra risk, the light horizontal plane represents the BMR. The $\widehat{BMP}$ is obtained by projecting the intersection of these two surfaces on to the joint, dual-predictor plane. Also displayed are the 95% Liu BMPL based on a Liu critical point of $w_{0.05} = 2.4488$ and the 95% Cox & Ma BMPL.

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Proportions of human hepatic cells exhibiting micronuclei after exposure to DDT and nano-TiO₂ (adapted from Shi et al., 2010)

Table 1

		nano-TiO ₂ conc. (µg/L)			
		0	0.01	0.1	1.0
DDT conc. (µmol/L)	0	59/3000	65/3000	70/3000	67/3000
	0.001	67/3000	75/3000	83/3000	84/3000
	0.01	76/3000	87/3000	96/3000	83/3000
	0.1	94/3000	107/3000	110/3000	117/3000

Table 2
Two-Regressor Simulation Models Using Equations (2) and (3): Formulation and Parameterizations

Model:	1A	1B	1C	1D	1E	1F	1G	1H
$RY = 1 x_1 = 0.0, x_2 = 0.0)$	0.01	0.01	0.01	0.05	0.10	0.10	0.10	0.30
$RY = 1 x_1 = 1.0, x_2 = 0.0)$	0.10	0.10	0.20	0.30	0.30	0.50	0.50	0.75
$RY = 1 x_1 = 0.0, x_2 = 1.0)$	0.20	0.50	0.50	0.50	0.90	0.75	0.90	0.90
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Comp. log params.	β_0	0.0101	0.0101	0.0101	0.0513	0.1054	0.1054	0.3567
	β_1	0.0953	0.0953	0.2131	0.3054	0.2513	0.5878	1.0296
	β_2	0.2131	0.6831	0.6831	0.6419	2.1972	2.1972	1.9459
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Model:	2A	2B	2C	2D	2E	2F	2G	2H
$RY = 1 x_1 = 0.0, x_2 = 0.0)$	0.01	0.01	0.01	0.05	0.10	0.10	0.10	0.30
$RY = 1 x_1 = 0.5, x_2 = 0.0)$	0.04	0.04	0.07	0.17	0.17	0.30	0.30	0.52
$RY = 1 x_1 = 1.0, x_2 = 0.0)$	0.10	0.10	0.20	0.30	0.30	0.50	0.50	0.75
$RY = 1 x_1 = 0.0, x_2 = 0.5)$	0.07	0.30	0.30	0.30	0.50	0.52	0.50	0.50
$RY = 1 x_1 = 0.0, x_2 = 1.0)$	0.20	0.50	0.50	0.50	0.90	0.75	0.90	0.90
$RY = 1 x_1 = 1.0, x_2 = 1.0)$	0.30	0.55	0.60	0.60	0.95	0.80	0.95	0.99
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Comp. log params.	β_0	0.0101	0.0101	0.0101	0.0513	0.1054	0.1054	0.3567
	β_1	0.0278	0.0278	0.0370	0.2348	0.0726	0.4175	0.4796
	β_2	0.0370	0.7034	0.7034	0.5797	0.1539	1.2335	-0.6000
	β_3	0.0675	0.0675	0.1761	0.0706	0.1788	0.1703	0.5501
	β_4	0.1761	-0.0203	-0.0203	0.0622	2.0433	0.0474	2.5459
	β_5	0.0382	0.0101	0.0101	-0.0822	0.4418	-0.3646	1.2730

Table 3

Empirical coverage probabilities for the Liu-based and the Cox & Ma (CM) BMPLs under the models from Table 2, as related to per-dose sample size N.

		BMR = 0.01										BMR = 0.10									
		N										N									
Model		20	50	100	2450	2.450	0.967	0.977	0.987	0.986	0.995	0.910	0.967	0.978	0.987	0.994	0.993	0.996	0.997	0.998	0.999
<i>w_{0.05}</i>																					
1A	Liu CM	0.921	0.967	0.977	0.987	0.986	0.995	0.910	0.967	0.978	0.987	0.994	0.993	0.996	0.997	0.998	0.999	1.000	0.999	0.998	0.997
1B	Liu CM	0.888	0.967	0.967	0.982	0.987	0.991	0.890	0.964	0.975	0.984	0.992	0.991	0.992	0.994	0.997	0.998	0.999	1.000	0.999	0.998
1C	Liu CM	0.930	0.990	0.994	0.991	0.997	0.994	0.918	0.982	0.992	0.995	0.996	0.997	0.998	0.999	1.000	0.999	0.998	0.997	0.996	0.995
1D	Liu CM	0.952	0.972	0.978	0.982	0.987	0.991	0.951	0.974	0.984	0.989	0.993	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994
1E	Liu CM	0.980	0.990	0.990	0.994	0.994	0.992	0.986	0.989	0.994	0.998	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994	0.994
1F	Liu CM	0.980	0.975	0.979	0.980	0.992	0.996	0.976	0.976	0.978	0.985	0.991	0.991	0.992	0.992	0.992	0.992	0.992	0.992	0.992	0.992
1G	Liu CM	0.960	0.978	0.980	0.975	0.980	0.977	0.955	0.976	0.976	0.982	0.992	0.992	0.992	0.992	0.992	0.992	0.992	0.992	0.992	0.992
1H	Liu CM	0.969	0.998	0.998	0.992	0.990	0.993	0.970	0.998	0.996	0.994	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993
2A	Liu CM	0.979	0.976	0.978	0.988	0.989	0.996	0.974	0.979	0.985	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993
2B	Liu CM	0.998	0.994	0.993	0.994	0.997	0.992	0.996	0.994	0.990	0.995	0.996	0.996	0.996	0.996	0.996	0.996	0.996	0.996	0.996	0.996
2C	Liu CM	0.968	0.972	0.986	0.980	0.970	0.975	0.974	0.977	0.976	0.983	0.981	0.985	0.985	0.985	0.985	0.985	0.985	0.985	0.985	0.985
2D	Liu CM	0.996	0.994	0.990	0.988	0.987	0.989	0.998	0.994	0.988	0.992	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993	0.993
2E	Liu CM	0.974	0.978	0.982	0.953	0.943	0.965	0.973	0.974	0.969	0.938	0.948	0.960	0.960	0.960	0.960	0.960	0.960	0.960	0.960	0.960
2F	Liu CM	0.999	0.996	0.996	0.954	0.956	0.972	0.997	0.997	0.994	0.968	0.977	0.997	0.997	0.997	0.997	0.997	0.997	0.997	0.997	0.997
2G	Liu CM	0.987	1.000	1.000	1.000	1.000	0.999	0.999	0.948	0.992	0.997	0.999	0.995	0.995	0.995	0.995	0.995	0.995	0.995	0.995	0.995
2H	Liu CM	1.000	1.000	1.000	1.000	1.000	0.999	0.999	0.964	0.991	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998
2I	Liu CM	0.963	0.996	0.996	0.999	1.000	0.999	0.999	0.931	0.994	0.965	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998	0.998
2J	Liu CM	0.999	1.000	1.000	1.000	1.000	1.000	1.000	0.919	0.988	0.997	1.000	0.998	0.997	1.000	0.998	0.994	0.994	0.994	0.994	0.994
2K	Liu CM	0.995	0.989	0.983	0.990	0.988	0.983	0.997	0.999	0.982	0.981	0.987	0.984	0.984	0.984	0.984	0.984	0.984	0.984	0.984	0.984
2L	Liu CM	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.994	0.996	0.998	0.997	0.996	0.997	0.997	0.997	0.997	0.997	0.997	0.997	0.997
2M	Liu CM	0.999	0.999	0.999	0.997	0.999	0.999	0.999	0.995	0.991	0.988	0.981	0.981	0.981	0.981	0.981	0.981	0.981	0.981	0.981	0.981
2N	Liu CM	0.994	0.997	0.996	0.991	0.994	0.995	0.995	0.995	0.995	0.995	0.997	0.996	0.997	0.997	0.997	0.997	0.997	0.997	0.997	0.997

		BMR = 0.01										BMR = 0.10									
		N										N									
Model		20	50	100	500	1000	3000	20	50	100	500	1000	3000	20	50	100	500	1000	3000		
2E	Liu	1.000	1.000	1.000	1.000	1.000	0.999	1.000	1.000	1.000	1.000	1.000	0.998	1.000	1.000	1.000	1.000	1.000	0.998		
	CM	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.999		
2F	Liu	1.000	1.000	0.999	0.999	0.999	0.999	1.000	1.000	0.998	1.000	1.000	0.999	1.000	0.999	0.998	1.000	0.998	0.999		
	CM	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		
2G	Liu	1.000	1.000	1.000	0.999	0.999	0.999	1.000	1.000	1.000	0.999	0.999	0.999	1.000	1.000	1.000	0.999	1.000	0.999		
	CM	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		
2H	Liu	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		
	CM	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		