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Inference for the existence of hormetic dose–response relationships in toxicology studies

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Summary

In toxicology studies hormesis refers to a dose–response relationship with a stimulatory response at low doses and an inhibitory response at high doses. In this manuscript, we particularly focus on a J-shaped dose–response relationship for binary cancer responses. We propose and examine two new flexible models for testing the hypothesis of hormesis in a Bayesian framework. The first model is parametric and enhances the flexibility of modeling a hormetic zone by using a non-linear predictor in a multistage model. The second model is non-parametric and allows multiple model specifications, weighting the contribution of each model via Bayesian model averaging (BMA). Simulation studies show that the non-parametric modeling approach with BMA provides robust sensitivity and specificity for detecting hormesis relative to the parametric approach, regardless of the shape of a hormetic zone.

Keywords: Bayesian model averaging; Hormesis; Hypothesis testing; Multistage models; Non-parametric models.

1. Introduction

In toxicology hormesis refers to a dose–response relationship with a stimulatory response at low doses and an inhibitory response at high doses (Calabrese and Baldwin, 2001; Mattson, 2009). Mathematically, a hormetic effect can be described as a non-monotonic dose–response curve with a sign change in the slope of the curve. In this manuscript, we focus on dichotomous cancer responses with a beneficial effect at low doses and a harmful effect at high doses that can be described as a J-shaped dose–response curve. The objective of this manuscript is to develop and assess flexible statistical models to test for hormesis in toxicology studies.

Hormesis has been extensively discussed in past literature. Calabrese and Baldwin applied *a priori* criteria to a large number of toxicology studies to determine whether each study provided sufficient evidence for hormesis (Calabrese and Baldwin, 1997; Calabrese, 2001). Later, additional studies evaluated hormetic effects in toxicant dose–response (Calabrese and Baldwin, 2003; Calabrese and Cook, 2005). Although

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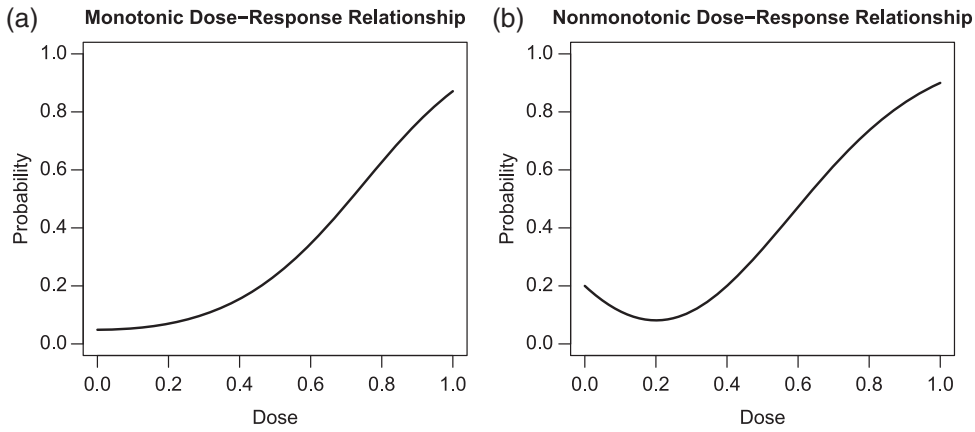

Fig. 1. Hypothetical dose–response curves. The figure on the left describes a monotonic dose–response relationship, and the figure on the right describes a hormetic dose–response relationship. (a) Monotonicity. (b) Hormesis.

these studies highlighted the potential importance of hormesis, other authors have expressed skepticism, pointing out a lack of formality in the hypothesis testing procedures, unknown specificity and sensitivity, and potential adverse consequences of incorporating hormetic models into policy decisions (Crump, 2001; Thayer *and others*, 2005; Mushak, 2009).

When attempting to distinguish hormesis from a monotonic dose–response relationship (see Figure 1), the importance of flexible dose–response modeling has been discussed (Sielken and Stevenson, 1998), and several dose–response models for testing monotonicity versus non-monotonicity have been proposed (Bowman *and others*, 1998; Hall and Heckman, 2000; Schabenberger and Birch, 2001; Hunt and Bowman, 2004; Hans and Dunson, 2005; Hunt and Rai, 2005; Belz and Piepho, 2012; Zhang *and others*, 2013; Kim *and others*, 2015). Among these existing models, the parametric model proposed by Hunt and Bowman (2004) classifies dose–response relationships into three classes: strictly increasing, threshold (i.e. flat below some threshold), and hormetic. This model was extended by Hunt and Rai (2005) to account for potential random effects due to litter affiliation when testing for hormetic and threshold effects in animal studies. The sample size they considered was relatively large, and therefore the method could be applied by relying on asymptotic results in a frequentist framework. Recently, Kim *and others* (2015) considered a multistage model that allows monotonicity and hormesis for the estimation of a benchmark dose defined by the Environmental Protection Agency (Environmental Protection Agency, 2012). The multistage model is a member of a class of well-known models included in the widely used EPA Benchmark Dose Software.

An important limitation of the aforementioned parametric models is that they assume symmetric hormetic zones. Our proposal in this manuscript is motivated by potential model misspecification when the true hormetic zone is not symmetric. To address the issue, we propose two alternative methods. The first is based on the multistage model with a non-linear predictor (i.e. non-linear multistage model). This parametric approach is able to fit an asymmetric hormetic zone with enhanced flexibility. The second is based on a weighted average of multiple non-parametric models using Bayesian model averaging (BMA) as proposed by Raftery *and others* (1997). This non-parametric approach quantifies the posterior probability of hormesis based on the BMA framework. In this manuscript, we mainly focus on hypothesis testing for monotonicity (the null hypothesis) versus hormesis (the alternative hypothesis).

The remainder of the manuscript is organized as follows: In Section 2, we briefly present a Bayesian formulation of the aforementioned Hunt–Bowman model (Hunt and Bowman, 2004) and propose a flexible

multistage model and a non-parametric BMA approach as novel alternatives for discriminating between hormetic and monotonic dose–response relationships. Section 3 presents the results of a simulation study to assess the performance of each approach in relatively sparse data settings that are commonly encountered in toxicology studies. In Section 4, we apply the proposed methods to data assessing the carcinogenic effect of cadmium compounds in male rats. Section 5 concludes the manuscript with a discussion of the approaches for detecting hormesis in toxicology studies and avenues for further research in the field.

2. Methods

In this section, we discuss three dose–response models that allow for both monotonicity and hormesis. The first model is the Hunt–Bowman model originally proposed by Hunt and Bowman (2004) in a frequentist framework, though we implement the model in a Bayesian framework to allow for potentially better performance in sparse data situations. The second model is a newly proposed multistage model with a non-linear predictor, which we refer to as the multistage model for the remainder of the manuscript. The third model is a novel BMA-based non-parametric approach that does not require any functional form for a dose–response relationship. Under each model, we consider hypothesis testing for strict monotonicity versus hormesis.

2.1 *Hunt–Bowman model*

2.1.1 *Parameterization.* Let $d \geqslant 0$ denote the experimental dose of a potentially toxic compound. The Hunt–Bowman model describes a dose–response relationship by

$$\pi_d(\vec{\theta}) = \begin{cases} \dfrac{1}{1+\mathrm{e}^{-\beta_0}} + \alpha d - \left(\dfrac{\alpha}{\tau}\right) d^2, & 0 \leqslant d \leqslant \tau, \\ \dfrac{1}{1+\mathrm{e}^{-\beta_0-\beta_1(d-\tau)}}, & d > \tau, \end{cases}$$

where $\pi_d(\vec{\theta})$ denotes the probability of a toxic event at dose d conditional upon model parameters $\vec{\theta} \equiv (\alpha, \beta_0, \beta_1, \tau)$. Let Θ_M and Θ_H be the parameter space for monotonicity and hormesis, respectively. Then, the test of H_0: $\vec{\theta} \in \Theta_M$ versus H_1: $\vec{\theta} \in \Theta_H$ simplifies to H_0: $\tau = 0$ versus H_1: $\tau > 0$.

2.1.2 *Prior.* To implement the Hunt–Bowman model in a Bayesian framework, we consider a spike and slab prior for τ (Ishwaran and Rao, 2005). We let $p_0 = P(\tau > 0) = P(H_1)$, the prior probability of hormesis. Then, the prior density function of τ is

$$f(\tau) = p_0 f^+(\tau) + (1 - p_0) I_{\tau=0}, \tag{2.1}$$

where $I_{\tau=0} = 1$ if $\tau = 0$ (zero otherwise) and $f^+(\tau)$ is a density function for $\tau > 0$.

For an interpretable prior specification on (β_0, β_1), we consider a conditional mean prior (Bedrick *et al.*, 1996). By choosing two arbitrary doses, say d_{-2} and d_{-1}, we independently model $\pi_{d_i} = (\mathrm{e}^{\beta_0+\beta_1 d_i}/(1+\mathrm{e}^{\beta_0+\beta_1 d_i})) \sim \mathrm{Beta}(r_i, s_i)$ using the logistic link. In other words, we impose the two independent Beta priors for the logistic link. Then, using Jacobian transformation,

$$f(\beta_0, \beta_1) = \prod_{i=-2}^{-1} \frac{\Gamma(r_i + s_i)}{\Gamma(r_i)\Gamma(s_i)} \left(\frac{\mathrm{e}^{\beta_0+\beta_1 d_i}}{1+\mathrm{e}^{\beta_0+\beta_1 d_i}}\right)^{r_i} \left(\frac{1}{1+\mathrm{e}^{\beta_0+\beta_1 d_i}}\right)^{s_i}. \tag{2.2}$$

If $\tau = 0$, we do not need to consider a prior distribution for α. Given $\tau > 0$ and $\beta_0 \in (-\infty, \infty)$, a hormetic effect can be quantified as $\pi_0(\vec{\theta}) - \pi_{0.5\tau}(\vec{\theta}) = -\alpha\tau/4$. To express large uncertainty for $-\alpha\tau/4$, we may consider the uniform distribution $-\alpha\tau/4 \mid \tau, \beta_0 \sim \text{Uniform}(0, 1/(1 + e^{-\beta_0}))$ so that

$$f(\alpha \mid \tau, \beta_0) = \frac{\tau(1 + e^{-\beta_0})}{4}, \quad -\frac{4}{\tau(1 + e^{-\beta_0})} < \alpha < 0. \tag{2.3}$$

From Equations (2.1–2.3), the joint prior density function of $\vec{\theta} = (\alpha, \beta_0, \beta_1, \tau)$ is

$$f(\vec{\theta}) = f(\alpha \mid \tau, \beta_0) f(\beta_0, \beta_1) f(\tau), \quad \vec{\theta} \in \Theta_M \cup \Theta_H. \tag{2.4}$$

2.1.3 *Posterior.* Let d_i denote experimental doses for $i = 0, 1, \ldots, I$ with $d_0 = 0$ being the control group and $0 < d_1 < \cdots < d_I$. Without loss of generality, we assume $d_I = 1$. Given n_i animals allocated at dose d_i, let $Y_i \sim \text{Binomial}(n_i, \pi_i)$ denote the number of toxic events with $\pi_i = \pi_{d_i}(\vec{\theta})$. The likelihood function is

$$f(\vec{y} \mid \vec{\theta}) = \prod_{i=0}^{I} \frac{n_i!}{y!(n_i - y_i)!} \{\pi_{d_i}(\vec{\theta})\}^{y_i} \{1 - \pi_{d_i}(\vec{\theta})\}^{n_i - y_i} \tag{2.5}$$

for given data $\vec{y} = (y_0, y_1, \ldots, y_n)$. By assuming $\tau \sim \text{Uniform}(d_0, d_I)$ in the presence of hormesis, from Equations (2.4) and (2.5), the joint posterior density function is

$$f(\vec{\theta} \mid \vec{y}) \propto \left\{ \frac{p_0 \tau (1 + e^{-\beta_0})}{4} I_{\tau > 0} + (1 - p_0) I_{\tau = 0} \right\} \prod_{i=-2}^{I} c_i \{\pi_{d_i}(\vec{\theta})\}^{y_i} \{1 - \pi_{d_i}(\vec{\theta})\}^{n_i - y_i},$$

for $\vec{\theta}$ respecting all constraints in the parameter space $\Theta_M \cup \Theta_H$, where c_i is the appropriate constant for $i = -2, \ldots, I$ and $y_i = r_i$ and $n_i = s_i + r_i$ are pseudo-observations for $i = -2, -1$. If data support H_1: $\tau > 0$, we expect to observe $P(H_1 \mid \vec{y}) > p_0 = P(H_1)$. If data support H_0: $\tau = 0$, we expect to observe $P(H_0 \mid \vec{y}) > 1 - p_0 = P(H_0)$.

2.2 *Multistage model*

2.2.1 *Parameterization.* The linearized multistage model describes a monotonic dose–response relationship by $\pi_d(\vec{\gamma}) = 1 - e^{-\sum_{m=0}^{M} \gamma_m d^m}$ with non-negative coefficients (Armitage, 1985; Crump, 1996). For the purpose of hormetic testing, we take $M = 2$ with an additional parameter γ_3 such that $\pi_d(\vec{\theta}) = 1 - e^{-\sum_{m=0}^{2} \gamma_m d^{m\gamma_3}}$, and allow $\gamma_1 < 0$ to model a hormetic effect at low dose. By the non-linear predictor, we are able to model an asymmetric hormetic zone with a smooth transition from a hormetic zone to a monotonic zone. This characteristic is an important distinction from the Hunt–Bowman model which only allows a symmetric hormetic zone and has discontinuity with respect to the first derivative at the transition point.

We can partition the 4D parameter space for $\vec{\gamma} = (\gamma_0, \gamma_1, \gamma_2, \gamma_3)$ into the monotonic parameter space $\Gamma_M = \{\vec{\gamma} : \gamma_0 > 0, \gamma_1 \geqslant 0, \gamma_2 > 0, \gamma_3 > 0\}$, and the hormetic parameter space $\Gamma_H = \{\vec{\gamma} : \gamma_0 > 0, \gamma_1 < 0, \gamma_2 > 0, \gamma_3 > 0, \gamma_1^2 < 4\gamma_0\gamma_2\}$. The last inequality in Γ_H guarantees $\pi_{d^*} > 0$, where

$$d^* = d^*(\vec{\gamma}) = \left(-\frac{\gamma_1}{2\gamma_2} \right)^{1/\gamma_3} \tag{2.6}$$

is the nadir of the dose–response curve (i.e. the most beneficial dose). The sufficient condition for $\pi_d(\vec{\gamma}) > 0$ for all $d \geqslant 0$ is $\sum_{m=0}^{2} \gamma_m (d^*)^{m\gamma_3} > 0$. Under this model, the length of the hormetic zone is

$$d^{**} = d^{**}(\vec{\gamma}) = \left(-\frac{\gamma_1}{\gamma_2}\right)^{1/\gamma_3}, \tag{2.7}$$

where $\pi_0(\vec{\gamma}) = \pi_{d^{**}}(\vec{\gamma})$ and $\pi_d(\vec{\gamma}) < \pi_0(\vec{\gamma})$ for all $d \in (0, d^{**})$.

Another distinction from the Hunt–Bowman model is that all four parameters are present in both the monotonic case and hormetic case. However, the non-linear predictor may cause over-fitting, particularly when the number of experimental doses is small. To avoid fitting a hormetic curve to monotonic empirical points, we may impose some restrictions on Γ_H. In particular, we may be reluctant to allow $d^* < d_1$ and $d^{**} < d_2$. In addition, we may not be practically interested in extremely small hormetic effects. For example, if we measure a hormetic effect by the odds ratio comparing the odds of toxicity at doses $d = 0$ and $d = d^*$,

$$\eta(\vec{\gamma}) = \frac{\pi_0(\vec{\gamma})}{1 - \pi_0(\vec{\gamma})} \frac{1 - \pi_{d^*}(\vec{\gamma})}{\pi_{d^*}(\vec{\gamma})}, \tag{2.8}$$

we may only be interested in hormetic cases, where $\eta(\vec{\gamma})$ exceeds some threshold. To this end, we define a restricted hormetic parameter space as $\Gamma_H^{(R)} = \{\vec{\gamma} \in \Gamma_H : d^*(\vec{\gamma}) \geqslant d_L^*, d^{**}(\vec{\gamma}) \geqslant d_L^{**}, \eta(\vec{\gamma}) \geqslant \eta_L\}$ for some $d_L^* \geqslant d_1, d_L^{**} \geqslant d_2$, and $\eta_L > 1$. In other words, $\Gamma_H^{(R)}$ is the hormetic parameter space of practical importance, and $\Gamma_H - \Gamma_H^{(R)}$ becomes the hormetic parameter space of indifference.

Whether we restrict the hormetic parameter space or not, a test of the hypothesis $H_0 : \vec{\gamma} \in \Gamma_M$ versus $H_1 : \vec{\gamma} \in \Gamma_H$ (or $\Gamma_H^{(R)}$) simplifies to a test of H_0: $\gamma_1 \geqslant 0$ versus H_1: $\gamma_1 < 0$ for $\vec{\gamma} \in \Gamma_M \cup \Gamma_H$.

2.2.2 *Prior.* Unlike the prior specification for the Hunt–Bowman model, we do not need a spike and slab prior under the multistage model. Instead, we specify a conditional joint prior distribution for $(\gamma_0, \gamma_1, \gamma_2)$ given γ_3 using a conditional mean prior. Operationally, we can arbitrarily select three doses, say $d_{-3} < d_{-2} < d_{-1}$, and specify three independent Beta priors as $\pi_{d_i} = 1 - \mathrm{e}^{-\sum_{m=0}^{2} \gamma_m d_i^{m\gamma_3}} \sim \text{Beta}(t_i, u_i)$ for $i = -3, -2, -1$. In other words, we impose the three independent Beta priors for the link function. To transform from the three independent Beta distributions to the conditional joint distribution of $(\gamma_0, \gamma_1, \gamma_2)$ given γ_3, it can be shown that the determinant of the Jacobian matrix is $\det(J) = (c_{-1,0} - c_{-2,0} + c_{-2,-1}) \prod_{i=-3}^{-1} \{1 - \pi_{d_i}(\vec{\gamma})\}$, where $c_{j,k} = (d_j d_k)^{\gamma_3}(d_k - d_j)$. Letting $c(\gamma_3) = |c_{-1,0} - c_{-2,0} + c_{-2,-1}|$ the conditional joint prior density function of $(\gamma_0, \gamma_1, \gamma_2)$ given γ_3 is

$$f(\gamma_0, \gamma_1, \gamma_2 \mid \gamma_3) = c(\gamma_3) \prod_{i=-3}^{-1} \frac{\Gamma(t_i + u_i)}{\Gamma(t_i)\Gamma(u_i)} \left(1 - \mathrm{e}^{-\sum_{m=0}^{2} \gamma_m d_i^{m\gamma_3}}\right)^{t_i - 1} \left(\mathrm{e}^{-\sum_{m=0}^{2} \gamma_m d_i^{m\gamma_3}}\right)^{u_i}. \tag{2.9}$$

Then, the joint prior density function is $f(\vec{\gamma}) = f(\gamma_3) f(\gamma_0, \gamma_1, \gamma_2 \mid \gamma_3)$, where $f(\gamma_3)$ is the prior distribution for $\gamma_3 > 0$. Similar to the prior specification described in Section 2.1.2, we consider $t_i - 1 = y_i$ and $u_i = n_i - y_i$ as pseudo-observations at the fixed dose d_i for $i = -3, -2, -1$.

2.2.3 *Posterior.* Using the same form of the likelihood function in Equation (2.5), the joint posterior density function of $\vec{\gamma}$ is given by

$$f(\vec{\gamma} \mid \vec{y}) \propto f(\gamma_3) c(\gamma_3) \prod_{i=-3}^{I} \left(1 - \mathrm{e}^{-\sum_{m=0}^{2} \gamma_m d_i^{m\gamma_3}}\right)^{y_i} \left(\mathrm{e}^{-\sum_{m=0}^{2} \gamma_m d_i^{m\gamma_3}}\right)^{n_i - y_i}$$

for $\vec{\gamma} \in \Gamma_M \cup \Gamma_H$, the unrestricted hormetic zone, or $\vec{\gamma} \in \Gamma_M \cup \Gamma_H^{(R)}$, the restricted hormetic zone.

2.3 *Non-parametric models with BMA*

2.3.1 *Parameterization.* Suppose we have $I+1$ experimental doses $d_0 < d_1 < \cdots < d_I$, where $d_0 = 0$ is the control group. We let M_j denote the jth dose–response model and $\pi_{ij} = \pi_{d_i, j}$ denote the probability of a toxic event at dose d_i under M_j for $i = 0, 1, \ldots, I$. We do not introduce any mathematical relationship between d_i and π_{ij}. Instead, we consider I non-parametric models, say $M_0, \ldots, M_{I-1}$. Without loss of generosity, let M_j denote a model such that $\min(\pi_{0j}, \pi_{1j}, \ldots, \pi_{Ij}) = \pi_{jj}$ for $j = 0, 1, \ldots, I-1$. With a restriction such that the dose–response has a positive slope once it passes its nadir (i.e. $\pi_{jj} < \pi_{j+1,j} < \cdots < \pi_{Ij}$), $M_1, \ldots, M_{I-1}$ represent hormetic models with nadirs at $d_1, \ldots, d_{I-1}$, respectively, and M_0 represents a strictly monotonic model. In this non-parametric setting, hypothesis testing for monotonicity versus hormesis is then equivalent to H_0: M_0 versus H_1: $\bigcup_{j=1}^{I-1} M_j$.

2.3.2 *Prior.* We let $\vec{\pi}_j = (\pi_{0j}, \pi_{1j}, \ldots, \pi_{Ij})$ denote the vector of parameters under M_j for $j = 0, 1, \ldots, I-1$. For a joint prior distribution of $\vec{\pi}_j$, we consider a series of conditional truncated Beta distributions. We say $\pi \sim \mathrm{TB}(a, b, l, r)$ if the density function is $f(\pi) = g(\pi)/\int_l^r g(\pi)\,\mathrm{d}\pi$, where $g(\pi) = (\Gamma(a+b)/\Gamma(a)\Gamma(b))\pi^{a-1}(1-\pi)^{b-1}$ for $\pi \in (l, r)$ and $g(\pi) = 0$ for $\pi \notin (l, r)$. For the control dose group, we assume a Beta distribution which is equivalent to $\pi_{0j} \sim \mathrm{TB}(a_{0j}, b_{0j}, 0, 1)$, and this prior distribution may be constant over M_j based on the prior knowledge regarding the prevalence of a toxic event in the absence of the toxin. If $\pi_{i+1,j}$ shall be $> \pi_{ij}$, we assume $\pi_{i+1,j} \mid \pi_{ij} \sim \mathrm{TB}(a_{ij}, b_{ij}, \pi_{ij}, r_{ij})$ for some $r_{ij} \in (\pi_{ij}, 1)$. If $\pi_{i+1,j}$ shall be smaller than π_{ij}, we assume $\pi_{i+1,j} \mid \pi_{ij} \sim \mathrm{TB}(a_{ij}, b_{ij}, l_{ij}, \pi_{ij})$ for some $l_{ij} \in (0, \pi_{ij})$. To allow for a wide range of dose–response curves, we may let $l_{ij} = 0$ and $r_{ij} = 1$. By the multiplication rule, the joint prior density function of $\vec{\pi}_j$ under M_j is $f(\vec{\pi}_j \mid M_j) = f(\pi_{0j}) \prod_{i=1}^{I} f(\pi_{ij} \mid \pi_{i-1,j})$ for $j = 0, 1, \ldots, I-1$.

In addition to the prior specification on each $\vec{\pi}_j$, we assign the prior model probability $P(M_j) > 0$ such that $\sum_{j=0}^{I-1} P(M_j) = 1$. This probability assignment should reflect the prior plausibility of each hypothesis as $P(H_0) = P(M_0)$ and $P(H_1) = \sum_{j=1}^{I-1} P(M_j)$. For example, $P(M_0) = 1/2$ and $P(M_j) = 1/(I-1)$ for $j = 1, \ldots, I-1$ reflects the same degree of prior belief for monotonicity and hormesis, and also reflects the same degree of prior belief for each nadir conditioning on hormesis.

2.3.3 *Posterior.* We are interested in $P(H_0 \mid \vec{y}) = P(M_0 \mid \vec{y})$ and $P(H_1 \mid \vec{y}) = \sum_{j=1}^{I-1} P(M_j \mid \vec{y})$. Appealing to BMA, each posterior model probability is $P(M_j \mid \vec{y}) = f(\vec{y} \mid M_j)P(M_j)/\sum_{j=0}^{I-1} f(\vec{y} \mid M_j)P(M_j)$, where $f(\vec{y} \mid M_j)$ is the marginal likelihood function under M_j.

3. SIMULATION

In this section, we investigate sensitivity and specificity of the Hunt–Bowman model, the multistage model, and the BMA-based non-parametric method in the context of hypothesis testing.

3.1 *Scenarios*

We consider two monotonic scenarios and seven hormetic scenarios with various hormetic zone shapes. Scenario 1 is a threshold case which is generated under the Hunt–Bowman model with $\vec{\theta} = (\alpha, \beta_0, \beta_1, \tau) = (0, -1.386, 4, 0.125)$. Scenario 2 is a strictly monotonic case which is generated under the multistage model with $\vec{\gamma} = (\gamma_0, \gamma_1, \gamma_2, \gamma_3) = (0.223, 0, 1.5, 2)$. The two monotonic scenarios are presented in

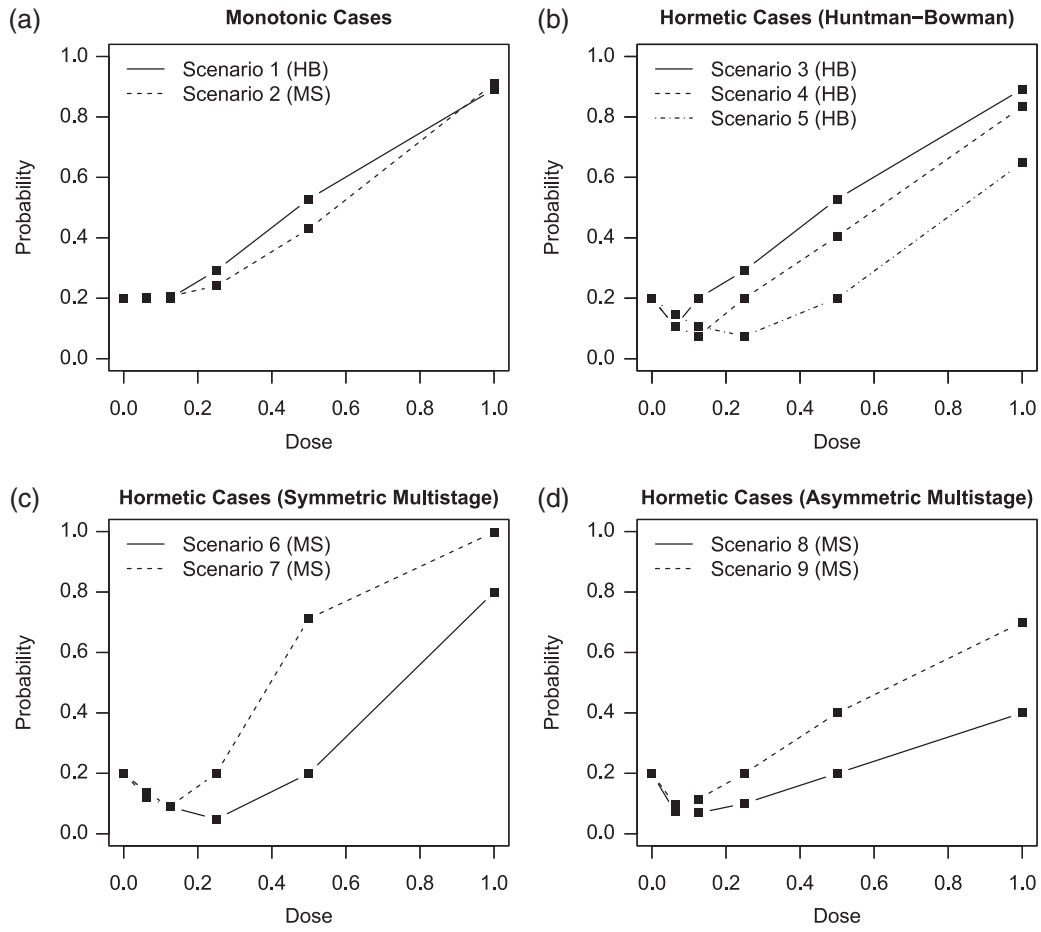

Fig. 2. Simulation scenarios. Scenarios 1 and 2 are monotonic cases generated by Hunt–Bowman model and multistage model, respectively. Scenarios 3–5 are hormetic cases generated by the Hunt–Bowman models. Scenarios 6 and 7 are hormetic cases generated by the multistage models with symmetric hormetic zones. Scenarios 8 and 9 are hormetic cases generated by the multistage models with asymmetric hormetic zones. The different line types connecting the six dots distinguish scenarios in each subfigure. (a) Scenarios 1 and 2. (b) Scenarios 3–5. (c) Scenarios 6 and 7. (d) Scenarios 8 and 9.

Figure 2(a). Scenarios 1 and 2 serve as references when we evaluate specificity (i.e. concluding H_0 when H_0 is true).

Scenarios 3–5 are hormetic cases generated under the Hunt–Bowman model. The respective true parameters are $\vec{\theta} = (-3, -1.386, 4, 0.125)$, $\vec{\theta} = (-2, -1.386, 4, 0.25)$, and $\vec{\theta} = (-1, -1.386, 4, 0.5)$ so that the hormetic zone is shortest in Scenario 3 and longest in Scenario 5 among the three scenarios. All three hormetic zones are symmetric as shown in Figure 2(b). Scenarios 6 and 7 are hormetic cases generated under the multistage model. The respective parameter values are $\vec{\gamma} = (0.223, -1.386, 2.773, 1)$ and $\vec{\gamma} = (0.223, -2.045, 8.180, 1)$. By fixing $\gamma_3 = 1$, the hormetic zones are symmetric, and the hormetic zone in Scenario 6 is shorter than the hormetic zone in Scenario 7 as shown in Figure 2(c). Scenarios 8 and 9 are hormetic cases also generated under a multistage model, but with an asymmetric hormetic zone ($\gamma_3 \neq 1$)

as shown in Figure 2(d). Scenarios 3–9 serve as references when we evaluate sensitivity (i.e. concluding H_1 when H_1 is true) in the context of hypothesis testing.

For each scenario, six experimental doses are geometrically spaced at $d_0 = 0$, $d_1 = 1/16$, $d_2 = 1/8$, $d_3 = 1/4$, $d_4 = 1/2$, and $d_5 = 1$, and $n_i = 50$ animals are allocated at each experimental dose which sum to the sample size of $\sum_{i=0}^{5} n_i = 300$.

3.2 *Models compared*

We compare five different models with respect to the performance of hypothesis testing for hormesis. The first model is the Hunt–Bowman denoted by HB. The second model is the multistage model with the unrestricted parameter space $\Gamma_M \cup \Gamma_H$ denoted by MS, and the third model is the multistage model with the restricted parameter space $\Gamma_M \cup \Gamma_H^{(R)}$ denoted by MSR. The MSR model rules out negligible hormetic effects by setting the lower bounds $d_L^* = d_1 = 1/16$, $\eta_L^* = d_2 = 1/8$, and $\gamma_L = 1.2$ in Equation (2.8). The fourth and fifth models are based on the non-parametric approach with BMA. We place vague priors in the fourth model and denote it by BMA_V, and we elicit relatively strong priors in the fifth model and denote it by BMA_S (see Section 3.3 for detail explanation).

3.3 *Priors*

To place large uncertainty under the HB model, we specify $f^+(\tau) = 1$ for $\tau \in (0, 1)$ and $p_0 = 0.5$ in Equation (2.1). In other words, we express $P(H_0) = P(H_1)$ and the length of hormetic zone can be anywhere within the experimental range before observing data. Then, we specify $(d_{-2}, r_{-2}, s_{-2}) = (0.2, 1.01, 1.10)$ and $(d_{-1}, r_{-1}, s_{-1}) = (0.8, 1.10, 1.01)$ in Equation (2.2). This specification adds small numbers of pseudo-observations at $d_{-2} = 0.2$ and $d_{-1} = 0.8$.

Similarly, to place large uncertainty under the MS and MSR models, we *a priori* assume $(d_j, t_j, u_j) = (0.2, 1.01, 1.10), (0.5, 1.05, 1.05), (0.8, 1.10, 1.01)$ for $j = -3, -2, -1$ in Equation (2.9). This specification also adds small numbers of pseudo-observations at the three chosen doses. We then place a nearly flat prior on γ_3 using the $\Gamma(0.001, 0.001)$ prior.

For the BMA_V model (V stands for "vague"), we specify $(a_{ij}, b_{ij}) = (1.01, 1.10)$ for $i = 0, 1, 2, 3$, $(a_{4j}, b_{4j}) = (1.05, 1.05)$, and $(a_{5j}, b_{5j}) = (1.10, 1.01)$. This vague prior is comparable to the prior specifications in the parametric models with large uncertainty. For the BMA_S model (S stands for "strong"), we specify $(a_{ij}, b_{ij}) = (2.64, 7.55)$ for $i = 0, 1, 2, 3$, $(a_{4j}, b_{4j}) = (1.53, 1.53)$, and $(a_{5j}, b_{5j}) = (5.38, 1.49)$. This strong prior reasonably well assumes the trajectory of the dose–response curves in all scenarios. For both BMA_V and BMA_S, we have one monotonic model M_0 and four hormetic models M_i with the nadirs at d_i for $i = 1, 2, 3, 4$. For prior model probabilities we let $P(H_0) = P(H_1) = 1/2$ and $P(M_i) = 1/8$ for $i = 1, 2, 3, 4$. When $\pi_{i+1,j} > \pi_{ij}$, we let $\pi_{i+1,j} \in (\pi_{ij}, 1)$ under the truncated Beta distribution. When $\pi_{i+1,j} < \pi_{ij}$, we let $\pi_{i+1,j} \in (0, \pi_{ij})$.

3.4 *A receiver operating characteristic curve in the context of hypothesis testing*

Suppose we conclude H_1 when $P(H_1 \mid \vec{y}) \geqslant q$ for some q. By repeating simulated trials and computing $P(H_1 \mid \vec{y})$ under a null scenario and an alternative scenario, we can plot one minus specificity on the x-axis and sensitivity on the y-axis by varying the decision threshold q from zero to one. In our setting, sensitivity is the probability of concluding H_1 under an alternative scenario (Scenarios 3–9), and specificity is the probability of concluding H_0 under a null scenario (Scenarios 1 or 2). This plot is known as a receiver operating characteristic (ROC) curve in the context of hypothesis testing, and a large area under the curve indicates a plausible operating characteristic. Since we have two null scenarios, we obtain two areas under ROC curves for each hormetic scenario. When Scenario 1 serves as the reference (which is generated under

Table 1. *Simulation results in Scenarios* 3–7 (*symmetric hormetic zones*). *In Scenario* 1, $E[P(H_1 \mid \vec{y})] = 0.708, 0.334, 0.167, 0.816,$ *and* 0.768 *for HB*, *MS*, *MSR*, BMA_V, *and* BMA_S, *respectively. In Scenario* 2, *the respective results are* 0.860, 0.348, 0.201, 0.846, *and* 0.813. *In the table*, A_1 *and* A_2 *denote the area under the ROC curve relative to the HB model and the MS model*, *respectively*

Scenario	Truth	Length of hormetic zone	Model	$E[P(H_1 \mid \vec{y})]$	A_1 (relative to HB)	A_2 (relative) to MS)
3	HB	1/8	HB	0.809	0.633	0.375
			MS	0.434	0.609	0.580
			MSR	0.229	0.501	0.458
			BMA_V	0.914	0.650	0.579
			BMA_S	0.883	0.656	0.572
4	HB	1/4	HB	0.943	0.860	0.653
			MS	0.668	0.850	0.842
			MSR	0.575	0.818	0.827
			BMA_V	0.994	0.926	0.887
			BMA_S	0.994	0.957	0.925
5	HB	1/2	HB	0.989	0.966	0.881
			MS	0.832	0.962	0.968
			MSR	0.792	0.922	0.959
			BMA_V	0.999	0.968	0.943
			BMA_S	1.000	0.987	0.971
6	MS	1/4	HB	0.998	0.992	0.967
			MS	0.876	0.972	0.978
			MSR	0.850	0.933	0.971
			BMA_V	1.000	0.974	0.952
			BMA_S	1.000	0.988	0.973
7	MS	1/2	HB	0.987	0.960	0.866
			MS	0.610	0.783	0.771
			MSR	0.545	0.795	0.799
			BMA_V	0.988	0.905	0.862
			BMA_S	0.989	0.934	0.892

HB), the area is denoted by A_1. When Scenario 2 is serves as the reference (which is generated under MS), the area is denoted by A_2.

3.5 *Results*

The simulation results are summarized in Tables 1 and 2. In the tables, $E[P(H_1 \mid \vec{y}_n)]$ denotes the average posterior probability for hormesis, and A_1 and A_2 denote the area under the ROC curve in each hormetic scenario when Scenario 1 and Scenario 2 served as the reference for a monotonic scenario, respectively. In the two monotonic scenarios, the HB model, BMA_V model, and BMA_S model tended to yield relatively large values of $P(H_1 \mid \vec{y})$ on average when compared with the MS and MSR models. In Scenario 1 (the threshold HB model), we obtained $E[P(H_1 \mid \vec{y}_n)] = 0.708, 0.334, 0.167, 0.816,$ and 0.768 in the HB, MS, MSR, BMA_V, and BMA_S models, respectively. In Scenario 2 (the strictly monotonic MS model), the respective results were 0.860, 0.348, 0.201, 0.846, and 0.813. Due to the restricted hormetic zone, the MSR model yielded smaller $P(H_1 \mid \vec{y}_n)$ than the MS model on average in both monotonic scenarios.

Table 2. *Simulation results in Scenarios* 8 *and* 9 (*asymmetric hormetic zones*). *In Scenario* 1, $E[P(H_1 \mid \vec{y})] = 0.708, 0.334, 0.167, 0.816,$ *and* 0.768 *for HB*, *MS*, *MSR*, BMA_V, *and* BMA_S, *respectively. In Scenario* 2, *the respective results are* 0.860, 0.348, 0.201, 0.846, *and* 0.813. *In the table*, A_1 *and* A_2 *denote the area under the ROC curve relative to the HB model and the MS model*, *respectively*

Scenario	Truth	Length of hormetic zone	Model	$E[P(H_1 \mid \vec{y})]$	A_1 (relative to HB)	A_2 (relative to MS)
8	MS	1/2	HB	0.973	0.913	0.715
			MS	0.877	0.975	0.981
			MSR	0.831	0.928	0.964
			BMA_V	0.999	0.970	0.946
			BMA_S	1.000	0.988	0.974
9	MS	1/4	HB	0.902	0.777	0.521
			MS	0.694	0.880	0.877
			MSR	0.520	0.781	0.784
			BMA_V	0.985	0.878	0.828
			BMA_S	0.986	0.922	0.876

In the three hormetic scenarios generated by the HB model (Scenarios 3 to 5), the BMA_V and BMA_S models outperformed the three parametric methods based on both A_1 and A_2. Despite the fact that true model was the HB model, the performances of MS and MSR methods were comparable to the HB method (see Table 1).

In the next two hormetic scenarios generated by the MS model with symmetric hormetic zones (Scenarios 6 and 7), the performances of BMA_S and BMA_V were robust yielding fairly large A_1 and A_2. Again, the outperformance was regardless of the amount of prior information we considered. The areas, A_1 and A_2, in the HB methods were comparable to the areas in the BMA_S model, and the HB method performed better than the MS and MSR methods in Scenario 7. MS and MSR did not yield the largest A_1 and A_2 among the five methods despite generating Scenarios 6 and 7 under the MS model (see Table 1).

In the last two hormetic scenarios generated by the MS model with asymmetric hormetic zones (Scenarios 8 and 9), the performances of BMA_S and BMA_V were also shown to be robust with respect to both A_1 and A_2. On the other hand, the HB method showed the impact of model misspecification in these asymmetric cases. The areas A_1 and A_2 were consistently smallest among the five methods in these two scenarios. The MS method exhibited good results, but it was not substantially superior to the non-parametric methods despite the scenarios belonged to its own parameterization (see Table 2).

In summary, the BMA method imposes few restrictions on the shape of the dose–response curve and showed robust results across all scenarios considered. The HB and MS methods perform similarly well when the true hormetic zone is symmetric. The HB method well-tolerated model misspecification as long as the hormetic zone was symmetric (Scenarios 6 and 7), but it did not perform well under an asymmetric hormetic zone (Scenarios 8 and 9).

We repeated the same set of scenarios with the smaller sample size of $n_i = 30$ for each dose group. The estimated areas A_1 and A_2 were generally smaller due to the reduced amount of data, but the relative operating characteristics were preserved. We tested prior sensitivity by varying the values of hyperparameters. For MS, we tried $(t_{-3}, u_{-3}) = \{(1, 3), (2, 2), (3, 2)\}$, $(t_{-2}, u_{-2}) = \{(2, 6), (4, 4), (6, 2)\}$, and $(t_{-1}, u_{-1}) = \{(5, 5), (5, 5), (5, 5)\}$, and the operating characteristics were generally preserved. For HB, when we considered $\tau \mid \tau > 0 \sim \text{Beta}(2, 8)$ and $\text{Beta}(8, 2)$, the areas A_1 and A_2 were below 0.5 in Scenarios 3, 8, and 9. Within the observed degrees of sensitivity, the relative performances were preserved

in each scenario, and the non-parametric BMA approach continued to yield robust results. For the vague priors, we also tested additional monotonic scenarios serving as the reference for a monotonic scenario, and BMA was still more robust than HB and MS. The results have been added to an online supplementary document (see supplementary material available at *Biostatistics* online).

4. Application

Cadmium compounds have been known to be associated with human prostate and renal cancers. Waalkes *and others* (1998) studied cadmium carcinogenesis by injecting one of seven experimental doses into male rates. The seven dose groups were (0, 1, 2.5, 5, 10, 20, 40) in μmol/kg. By dividing each dose by the maximum dose 40 μmol/kg, the experimental doses transform to (0, 0.025, 0.0625, 0.125, 0.25, 0.5, 1), respectively. These experimental doses are similar to Scenarios 8 and 9 in Section 3 with the additional dose $d_1 = 0.025$ between $d_0 = 0$ and $d_2 = 0.0625$. We focus on the development of testicular tumors as an outcome of interest among multiple toxic outcomes measured in the study. The respective sample sizes and observed numbers of events at the experimental doses were (45, 30, 29, 30, 30, 29, 29) and (8, 1, 3, 3, 4, 21, 24), respectively. The respective observed proportions of events were (0.178, 0.033, 0.103, 0.100, 0.133, 0.724, 0.828). Based on this empirical trend, the possibility of hormesis was extensively discussed in Zapponi and Marcello (2006).

For the BMA model, we used vague priors similar to those used for the BMA_V model in Section 3.3. We specified $P(H_0) = P(H_1)$ with uniform $P(M_j)$ for $j = 1, \ldots, 5$. For hyper-parameters in the truncated Beta distributions, we chose $(a_{ij}, b_{ij}) = (1.01, 1.10)$ for $i = 0, \ldots, 4$, $(a_{5j}, b_{5j}) = (1.05, 1.05)$, and $(a_{6j}, b_{6j}) = (1.10, 1.01)$ to express large uncertainty under all M_j. Given the data, we estimated $P(H_1 \mid \vec{y}) \approx 1$. When we altered the hyper-parameters to $(a_{ij}, b_{ij}) = (2.64, 7.55)$ for $i = 0, \ldots, 4$, $(a_{5j}, b_{5j}) = (1.53, 1.53)$, and $(a_{6j}, b_{6j}) = (5.38, 1.49)$, we obtained $P(H_1 \mid \vec{y}) = 0.998$. We attempted various strong priors, and they altered the posterior probabilities to various degrees while they continued to yield values of $P(H_1 \mid \vec{y})$ close to one.

For the three parametric models, HB, MS, and MSR, we used the same priors as described in Section 3.3. The fitted dose–response curves are presented in Figure 3. Figure 3(a) presents the fitted curves conditioning on monotonicity, and Figure 3(b) presents the fitted curves conditioning on hormesis. The posterior probability for hormesis was 0.877, 0.821, and 0.851 under HB, MS, and MSR, respectively. We did not observe relevant changes in $P(H_1 \mid \vec{y})$ from various priors we attempted in a reasonable range.

For additional analyses using the parametric models, we estimated the length of the hormetic zone, denoted by τ under the HB model and d^{**} under the MS and MSR models as defined in Equation (2.7). The posterior mean of the hormetic zone length was 0.122 with 95% credible interval (CI) of (0.030, 0.272) under HB, 0.183 with 95% CI of (0.042, 0.315) under MS, and 0.200 with 95% CI of (0.103, 0.319) under MSR. The estimated hormetic zone was the shortest under the HB model potentially due to model misspecification. The empirically shown hormetic zone in Figure 3(b) does not appear to be symmetric. The difference in the estimation under MS and MSR was small, but the estimated hormetic zone was slightly longer under MSR by disregarding too short of a hormetic zone and use of a minimal hormetic effect in $\Gamma_H^{(R)}$. In addition, the posterior interval was shorter under MSR than under MS. When we compare the estimated hormetic zone length to the empirical points where the observed proportion at $d_4 = 0.25$ (0.133) is still smaller than the observed proportion at the control dose $d_0 = 0$ (0.178), the three model-specific posterior means all appear to underestimate the length of hormetic zone. However, the 95% CI from each does cover $d_4 = 0.25$.

To test prior sensitivity under the parametric models, we changed the prior distribution of τ for HB and the values of (t_i, u_i) for MS and MSR (fixing $d_j = 0.2, 0.5, 0.8$). When we considered $\tau \mid \tau > 0 \sim$ Beta(5, 5), Beta(2, 8), and Beta(8, 2), we observed $P(H_1 \mid \vec{y}) =$ 0.966, 0.969, and 0.938, respectively,

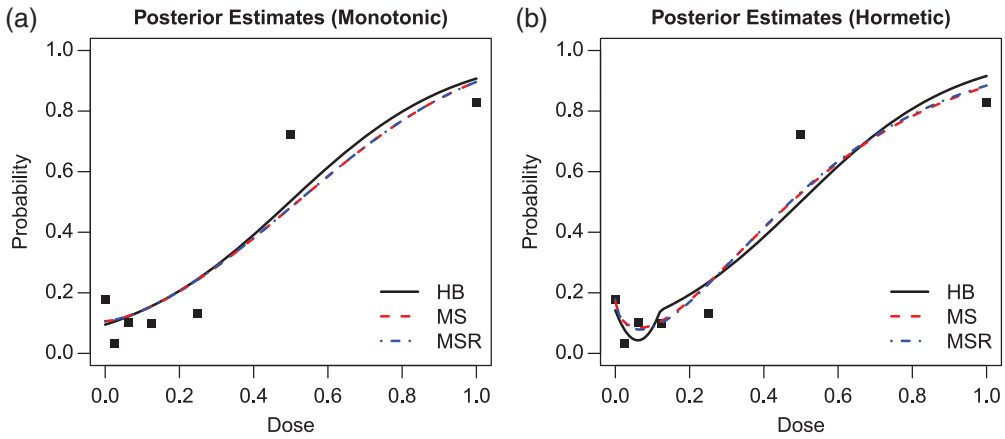

Fig. 3. Estimated dose–response curves using the posterior means of parameters under the HB, MS, and MSR models. The solid curve is from the HB model, and the dotted curves are from the MS and MSR models which are nearly identical. (a) Monotonic. (b) Hormetic.

with $E(\tau \mid \tau > 0, \vec{y}) = 0.258$, 0.092, and 0.363, respectively. When we tested various values of (t_i, u_i) for $2 \leqslant t_i + u_i \leqslant 10$ for each $i = -3, -2, -1$, we observed $0.700 \leqslant P(H_1 \mid \vec{y}) \leqslant 0.865$ for MS and $0.479 \leqslant P(H_1 \mid \vec{y}) \leqslant 0.957$ for MSR. The estimation of hormetic zone showed little sensitivity for both MS and MSR. The non-parametric BMA method showed little sensitivity for various values of the hyper-parameters with $P(H_1 \mid \vec{y})$ close to one. Based on the sensitivity analyses in both simulation studies and the applied example, the BMA method showed robustness with respect to $P(H_1 \mid \vec{y})$, thus it would be our primary choice. For the estimation for the length of hormetic zone under a parametric model (conditioning on H_1), MS provides a less restrictive approach when compared with HB, resulting in relatively mild sensitivity.

5. SUMMARY

We proposed two new flexible models for discriminating between hormetic and monotonic dose–response relationships in toxicology studies and compared them to an existing parametric approach originally developed by Hunt and Bowman (2004) under a frequentist inferential framework. The Hunt–Bowman model was observed to be inflexible in the sense that it cannot model an asymmetric hormetic zone, but it is flexible in that it can fit a hormetic zone and a monotonic zone separately. The newly proposed multistage model is flexible in that it can approximate various shapes of hormetic zone, but it is inflexible in that it needs to model the two zones simultaneously. Finally, the proposed non-parametric approach using BMA is more flexible than the parametric models we examined, and tends to perform well under a variety of scenarios.

When we considered simulation results with 50 animals per dose level to results with 30 animals per dose level (six dose groups total), the BMA-based non-parametric approach seems most appealing among the models considered. However, if the BMA method is adopted, we still recommend to carefully choose a joint prior distribution because the marginal likelihood can be sensitive to prior specification. Further, one may gain efficiency by imposing further restrictions on unreasonable prior dose–response paths based on available prior knowledge.

Though we could not exhaust all possible dose–response curves in the simulation studies, we could determine that the parametric approaches considered here may not be reliable, particularly under poorly

designed studies. The parametric approaches tend to be heavily influenced by leverage points. As such, experimental designs with high leverage points (multiple observations at the highest range of the dose space) may be an issue for detecting hormesis under a parametric model. While it may be possible to create a scenario with an asymmetric hormetic zone such that the MS model performs poorer than the HB model, such scenarios appear to be limited.

Future work is needed to consider optimal experimental designs when discriminating between hormetic and dose–response relationships is of primary interest in toxicology studies. To this end, Dette *and others* (2011) proposed optimal experimental designs for hormesis studies under specific parametric models. However, when the BMA method is used we recommend sensitivity analysis and especially careful selection of the joint prior distribution because the marginal likelihood can be sensitive to prior specification. In order to reduce the impact of model misspecification in the parametric modeling approach and to gain more efficiency under non-parametric approaches, an efficient experimental design in a non-parametric framework remains a focus of our future research. In addition, point and interval estimation for dose–response curve and hormesis parameters (e.g. the hormetic zone, the most beneficial dose and the minimum risk) are often important in toxicology and biomedical studies. This topic is another focus of our ongoing research.

Supplementary material

Supplementary material is available at http://biostatistics.oxfordjournals.org.

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