Robust Benchmark Dose Estimation using an Infinite Family of Response Functions

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Aims

To provide

- **a method of estimating BMD robust to the assumed response functions.**
- **methods of finding BMDLs using a family of response functions.**
- **test the performance of the proposed method using real and simulated data.**

EXAMPLE

Table 1: Observed lung cancer incidence of rats exposed to 1-Bromopropane.

(Wheeler and Bailer 2012)

Dose levels (d_i)	Responses ($\bar{y}_i$)
0 ppm	1/50
62.5 ppm	9/50
125 ppm	8/50
250 ppm	14/50

Benchmark Dose

- Risk Function: $R(d) = P(Y = 1|d)$.

- Extra Risk Function: $R_E(d) = \frac{R(d) - p_0}{1 - p_0}$.

  (Simmons *et al.* (2015))

- Benchmark Dose: $R_E(BMD) = BMR$, $BMR \in [0.01, 0.1]$.

Response Functions

- Linear predictor: $\eta(d) = \mathbf{f}'(d)\beta$.
  ($\beta_0 + \beta_1 d$, $\beta_0 + \beta_1 d + \beta_2 d^2$, etc.)

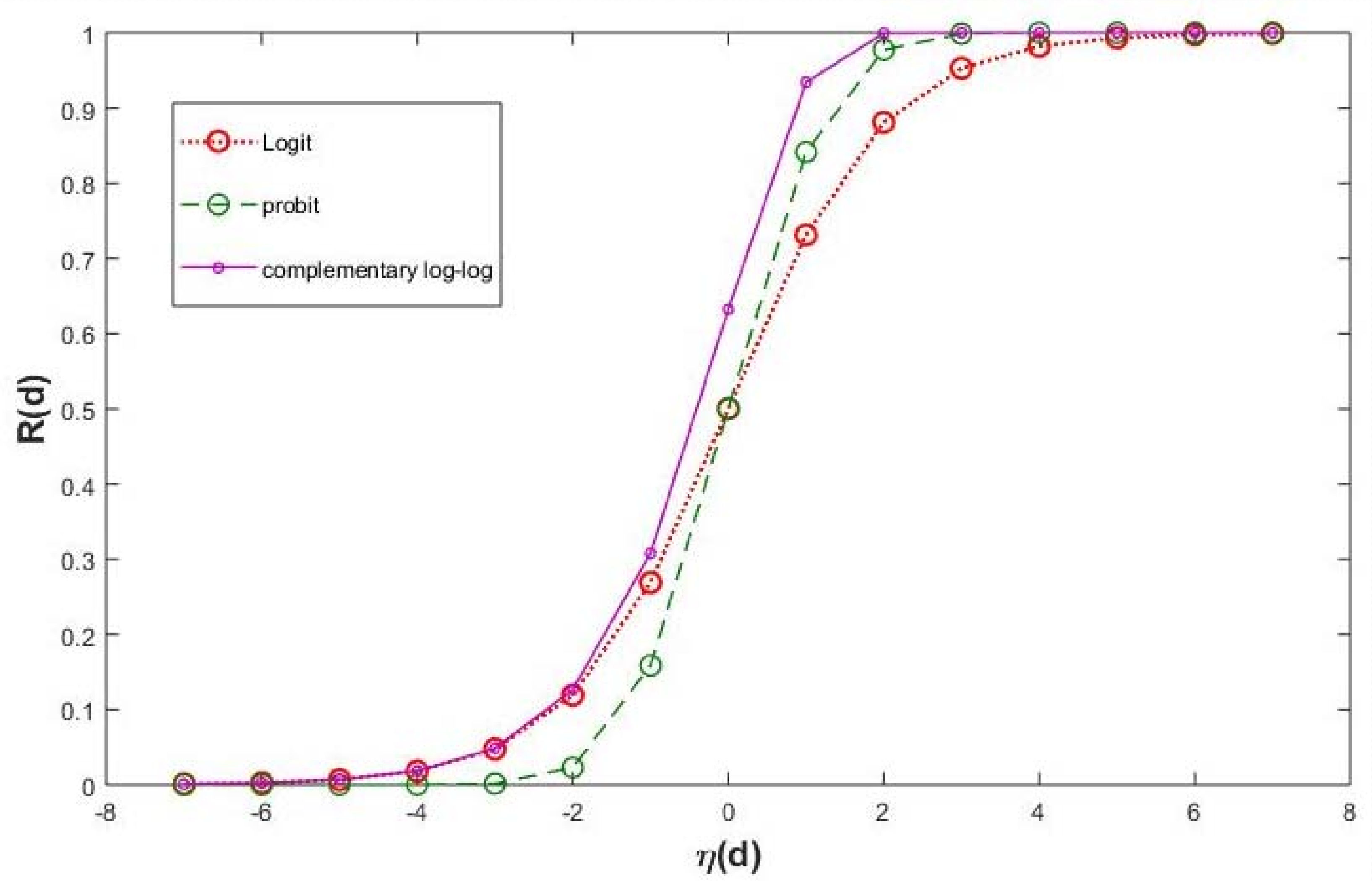
- Response Functions: $R(d) = h[\eta(d)]$

  - Logit: $R(d) = \frac{\exp[\eta(d)]}{1+\exp[\eta(d)]}$.

  - Probit: $R(d) = \Phi[\eta(d)]$.

  - Complementary log-log: $R(d) = 1 - \exp[-\exp\{\eta(d)\}]$.

Response Functions



Family of Response Functions

- A Family of Response Functions:

$$R(d) = h[\boldsymbol{\alpha}, \eta(d)] = \frac{\exp\{G(\boldsymbol{\alpha}, \eta)\}}{[1 + \exp\{G(\boldsymbol{\alpha}, \eta)\}]}.$$

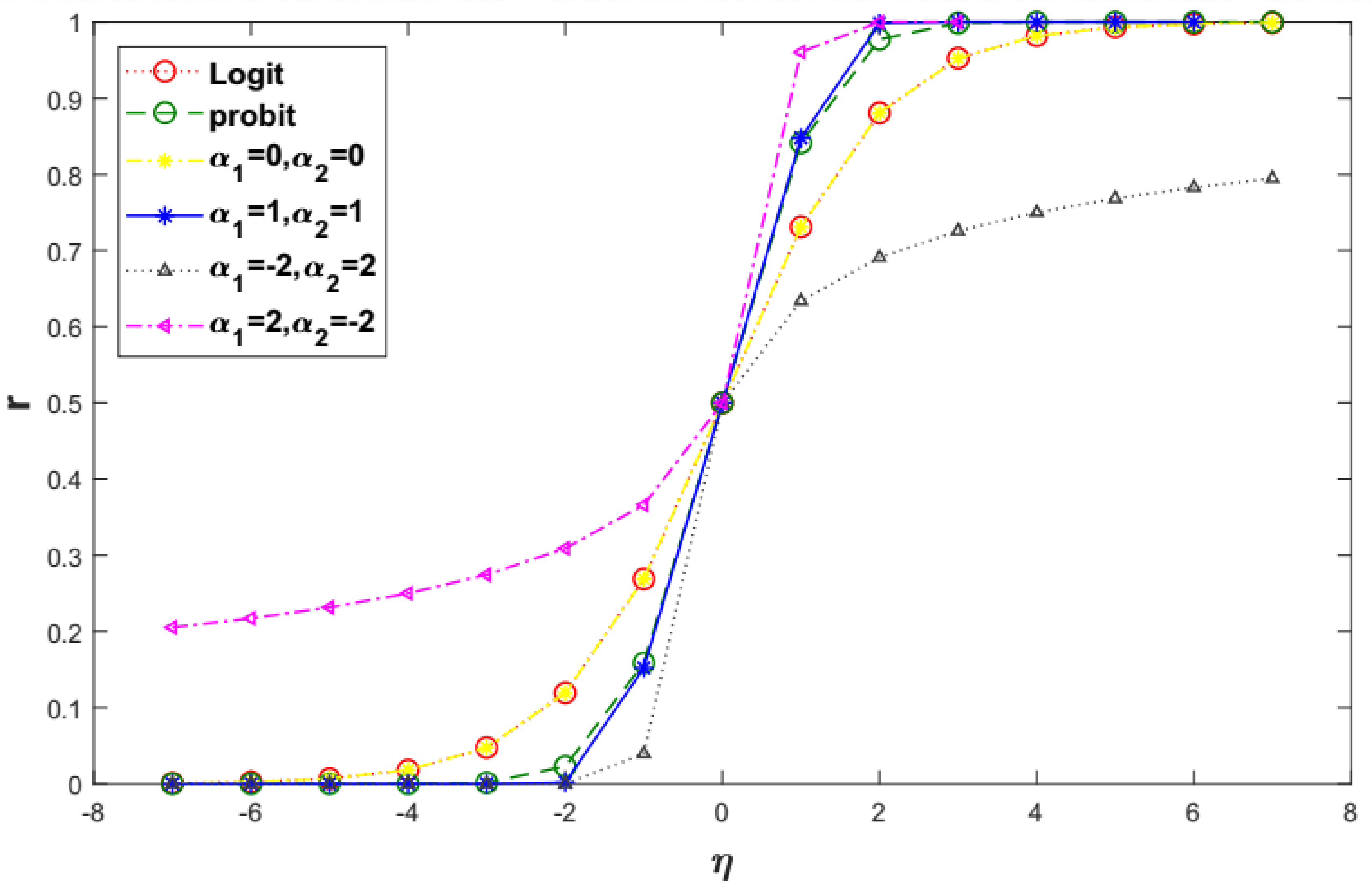
- A generating family proposed by Stukel(1988):
  if $\eta \geq 0$ (i.e., $r \geq \frac{1}{2}$),

$$G(\boldsymbol{\alpha}, \eta) = \begin{cases} \frac{\exp(\alpha_1 \eta) - 1}{\alpha_1}, & \alpha_1 > 0 \\ \eta, & \alpha_1 = 0 \\ -\frac{\log(1 - \alpha_1 \eta)}{\alpha_1}, & \alpha_1 < 0, \end{cases}$$

  and for $\eta < 0$ (i.e., $r < \frac{1}{2}$),

$$G(\boldsymbol{\alpha}, \eta) = \begin{cases} \frac{1 - \exp(-\alpha_2 \eta)}{\alpha_2}, & \alpha_2 > 0 \\ \eta, & \alpha_2 = 0 \\ \frac{\log(1 + \alpha_2 \eta)}{\alpha_2}, & \alpha_2 < 0. \end{cases}$$

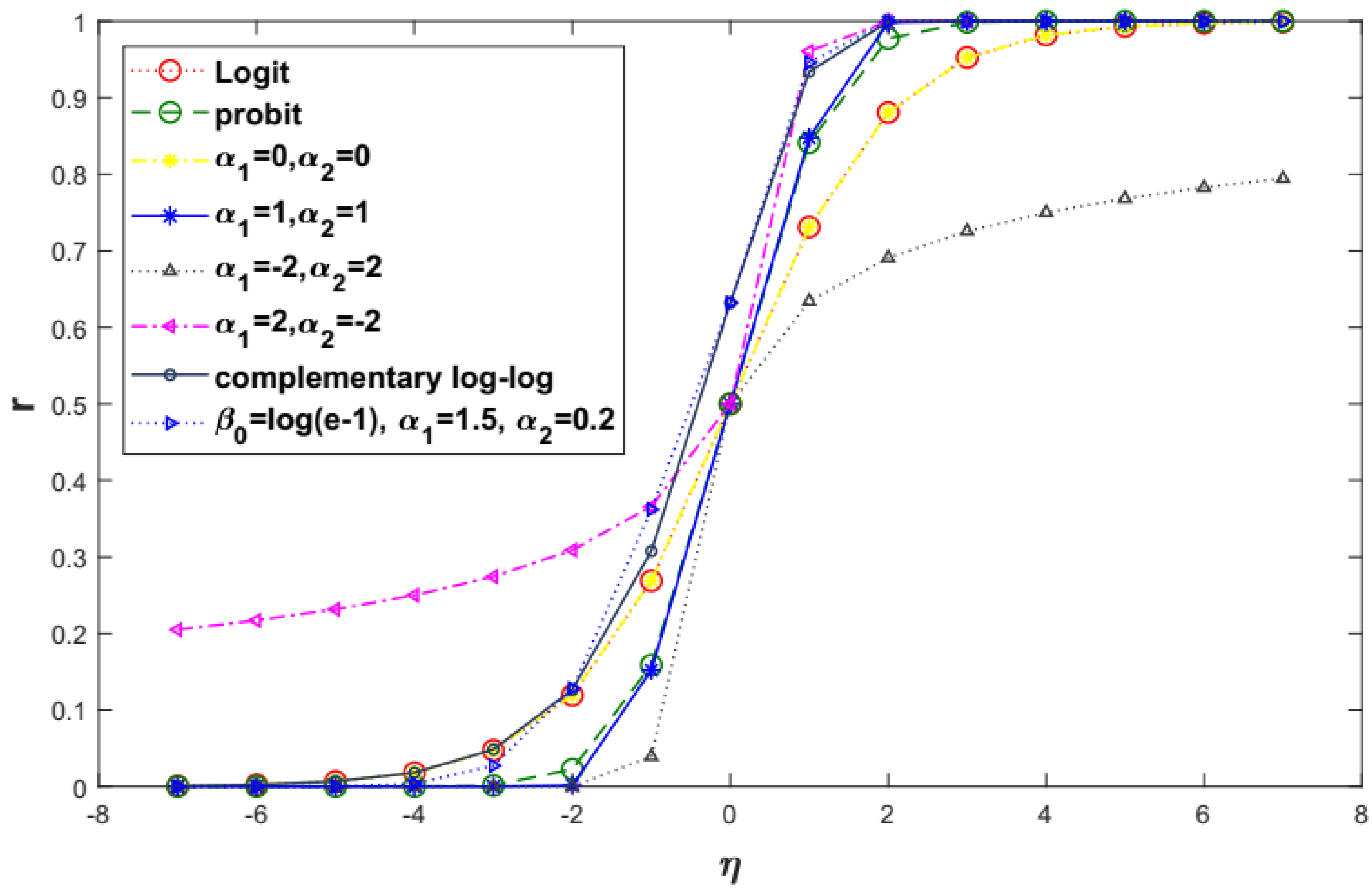
Family Response Functions



Complementary log-log

- Note that $r = 0.5$ at $\eta = 0$ for all response functions above.
- Complementary log-log: $r = 1 - \exp[-\exp(\eta)] \Rightarrow r = \frac{e-1}{e}$ at $\eta = 0$.
- Complementary log-log response functions can not be approximated by any members of the above family.
- We need to take a transformation $G_0(\boldsymbol{\alpha}, \eta) = \beta_0 + G(\boldsymbol{\alpha}, \eta)$.

Family of Response Functions



Standardized Generating Family

if $\eta_c \geq 0$ $[logit(r) \geq \beta_0]$, (Czado 1997)

$$G_c(\boldsymbol{\alpha}, \eta) = \beta_0 + \begin{cases} \frac{\exp(\alpha_1 \eta_c) - 1}{\alpha_1}, & \alpha_1 > 0 \\ \eta_c, & \alpha_1 = 0 \\ -\frac{\log(1 - \alpha_1 \eta_c)}{\alpha_1}, & \alpha_1 < 0, \end{cases}$$

and for $\eta_c < 0$ $[logit(r) < \beta_0]$,

$$G_c(\boldsymbol{\alpha}, \eta) = \beta_0 + \begin{cases} \frac{1 - \exp(-\alpha_2 \eta_c)}{\alpha_2}, & \alpha_2 > 0 \\ \eta_c, & \alpha_2 = 0 \\ \frac{\log(1 + \alpha_2 \eta_c)}{\alpha_2}, & \alpha_2 < 0, \end{cases}$$

where $\eta \equiv \eta(d)$, $r \equiv R(d)$, $\eta_c = \eta - \beta_0$, and $logit(r) = log[r/(1-r)]$.

Benchmark Dose Estimation

- An expression for *BMD*:

$$BMD = S(\delta) = S_1(\delta)I_{\{LBMR \geq \beta_0\}} + S_2(\delta)I_{\{LBMR < \beta_0\}},$$

where $LBMR = \log(\frac{BMRE}{1-BMRE})$.

- The functions $S_1(\delta)$ and $S_2(\delta)$ are given by

$$S_1(\delta) = \begin{cases} \frac{\log[\alpha_1(LBMR-\beta_0)+1]}{\alpha_1\beta_1}, & \alpha_1 > 0 \\ \frac{LBMR-\beta_0}{\beta_1}, & \alpha_1 = 0 \\ \frac{1-\exp[-\alpha_1(LBMR-\beta_0)]}{\alpha_1\beta_1}, & \alpha_1 < 0, \end{cases}$$

and,

$$S_2(\delta) = \begin{cases} -\frac{\log[1-\alpha_2(LBMR-\beta_0)]}{\alpha_2\beta_1}, & \alpha_2 > 0 \\ \frac{LBMR-\beta_0}{\beta_1}, & \alpha_2 = 0 \\ \frac{\exp[\alpha_2(LBMR-\beta_0)]-1}{\alpha_2\beta_1}, & \alpha_2 < 0. \end{cases}$$

Asymptotic Results

- The score function $\frac{\partial l(\delta)}{\partial \delta} \overset{a}{\sim} MN(\mathbf{0}, \mathbf{J}_n)$.
- The MLE of δ, $\hat{\delta} \overset{a}{\sim} MN(\delta, \mathbf{J}_n^{-1})$.
- The estimate $\widehat{BMD} = S(\hat{\delta})$ is a consistent estimator for BMD.

BMDLs Estimation

- **Using ML Estimates:** A $100(1-\tau)\%$ confidence interval for BMD is $[S_L, S_U]$, where $S_L = Min\{S(\boldsymbol{\delta}) : \boldsymbol{\delta} \in \mathbf{C}\}$, and $S_U = Max\{S(\boldsymbol{\delta}) : \boldsymbol{\delta} \in \mathbf{C}\}$ with

$$\mathbf{C} = \{\boldsymbol{\delta} \in \mathbf{R}^p : (\hat{\boldsymbol{\delta}} - \boldsymbol{\delta})' \Sigma^{-1} (\hat{\boldsymbol{\delta}} - \boldsymbol{\delta}) \le \chi^2_{p,(1-\tau)}\}$$

- **Using LR test:** We test the null hypothesis $H_0 : R_E(d) = BMR_0$ vs $H_1 : R_E(d) \neq BMR_0$. A $100(1-\tau)\%$ confidence interval is $[L_{min}, L_{max}]$, where

$$\begin{aligned} L_{min} &= Min\{d \in \mathbb{R} : L(d) \le \chi^2_{p,(1-\tau)}\}, \text{ and} \\ L_{max} &= Max\{d \in \mathbb{R} : L(d) \le \chi^2_{p,(1-\tau)}\} \end{aligned}$$

BMDLs Estimation (continued..)

- **Using score test:** Let us denote $T(d) = u_0^2/\hat{\sigma}_0^2$, where $u_0 = \left[\frac{\partial l}{\partial \beta_0}\right]_{\hat{\delta}_0}$. A $100(1-\tau)\%$ confidence interval for *BMD* is $[T_{min}, T_{max}]$, where $T_{min} = min\{d \in \mathbb{R} : T(d) \leq \chi^2_{1,(1-\tau)}\}$, and $T_{max} = max\{d \in \mathbb{R} : T(d) \leq \chi^2_{1,(1-\tau)}\}$.
- **Using bootstrap technique:** We generate l responses from the fitted model to have a sample $\{BMD_1, BMD_2, \ldots, BMD_l\}$ for *BMD*. A $100(1-\tau)\%$ bootstrap lower confidence limit for BMD is the τth quantile of the sample.

Example

Table 2. Estimated values of BMD (ppm) and the corresponding BMDL (ppm) within bracket by four methods calculated using the family of response functions, and also the same derived from Wheeler and Bailer (2012) by semi-parametric (diffuse), semi-parametric (historical controls), model-averaging, and quantal-linear.

	BMR	
Method	0.01	0.1
Family of response functions	8.6 (6.3, 6.2, 6.2, 7.4)	68.9 (61.8, 50.0, 49.8, 57.8)
Semi-parametric (Diffuse)	6.1 (2.1)	56.6 (17.5)
Semi-parametric (Historical controls)	6.6 (1.6)	97.1 (23.1)
Model-averaging	1.1 (0.14)	51.1 (17.2)
Quantal-linear	7.8 (5.2)	81.5 (55.0)

Conclusions

- The proposed method FR is consistent with the existing results in the literature.
- The family of response functions provides a better approach than model averaging method.
- The method FR outperforms MA for most of the scenarios.
- The LR is best among the four methods of estimating BMDL.

References

- C. Czado, *On selecting parametric link transformation families in generalized linear models*, Journal of Statistical Planning and inference **61** (1997), 125–139.
- Susan J. Simmons, Cuixian Chen, Xiaosong Li, Yishi Wang, Walter W. Piegorsch, Qijun Fang, Bonnie Hu, and G. Eddie Dunn, *Bayesian model averaging for benchmark dose estimation*, Environmental and Ecological Statistics **22** (2015), no. 1, 5–16.
- T. A. Stukel, *Generalized logistic models*, Journal of the American Statistical Association **83** (1988), 426–431.
- Matthew Wheeler and A John Bailer, *Monotonic bayesian semiparametric benchmark dose analysis*, Risk Analysis **32** (2012), no. 7, 1207–1218.

Questions ??