



# Exponent<sup>®</sup>

Health Sciences Group

*Center for Exposure Assessment  
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# Generic Hockey-Stick Model for Estimating Benchmark Dose and Potency

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**Dose-Response 2010: Implications for Toxicology,  
Medicine, and Risk Assessment**

9<sup>th</sup> Annual Meeting of the International Dose-Response Society

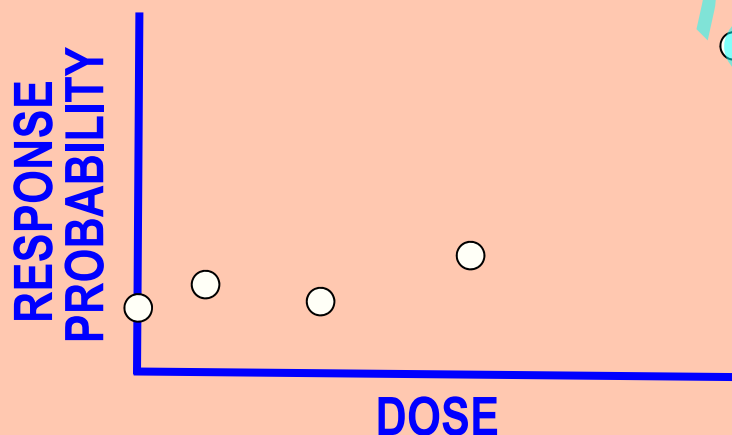
April 27–28, 2010

University of Massachusetts, Amherst, MA



# U.S. EPA BMDS Modeling Approach is Now Widely Used to Estimate BMD and Potency (Slope)

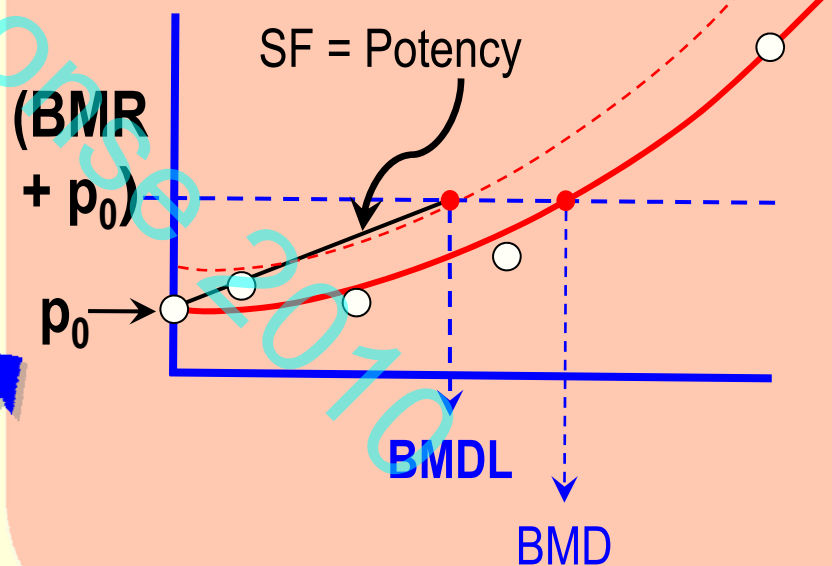
## Dose-Response Data



BMDS Analysis

## BMDL and Slope Factor

$$\text{Slope Factor (SF)} = \text{BMR} / \text{BMDL}$$





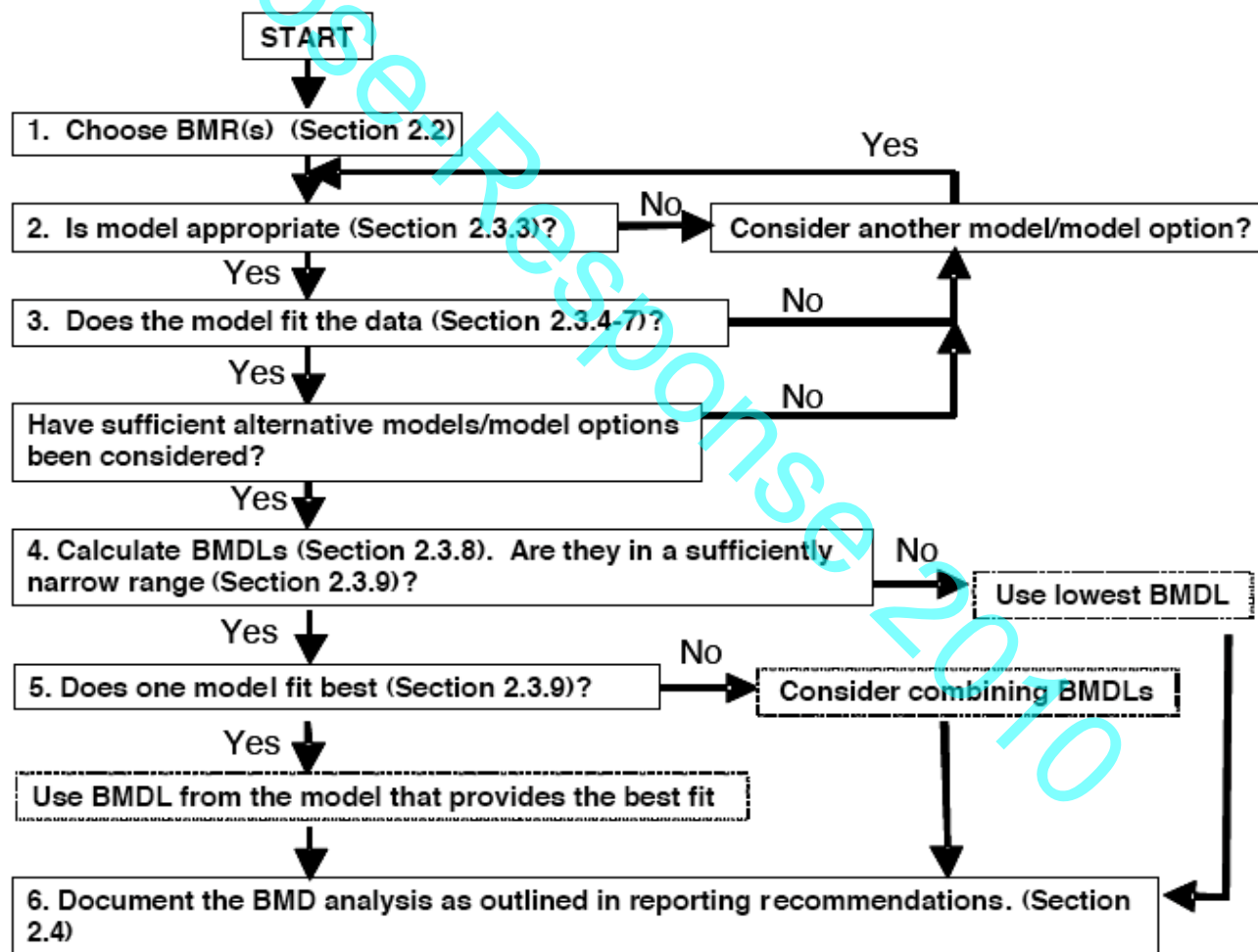
## Some Quantal Models Used by BMDS v. 2.1.1

Risk Model Name <sup>a</sup>	Symbol	Risk Model Function, $P(d)$ , of Dose $d$
Linear (Quantal Linear)	<b>L</b> <b>(QL)</b>	$1 - (1-p_0)\exp(-q_1d)$
Linear-Quadratic (Multistage)	<b>LQ</b> <b>(MS)</b>	$1 - (1-p_0)\exp(-q_1d - q_2d^2)$
Probit	<b>PR</b>	$1 - (1-p_0)\Phi[(d - \mu)/\sigma]$
Logistic	<b>LG</b>	$p_0/[p_0 + (1-p_0)\exp(-q_1d)]$
Weibull	<b>WB</b>	$p_0/[p_0 + (1-p_0)\exp(-q_1d^n)]$
Gamma	<b>GM</b>	$1 - (1-p_0)[\Gamma(a, b) - \Gamma(a, d)]$
Among BMDS models there is no hormetic model, such as:		
Hormetic	<b>H</b>	LQ model with $q_1 < 0$

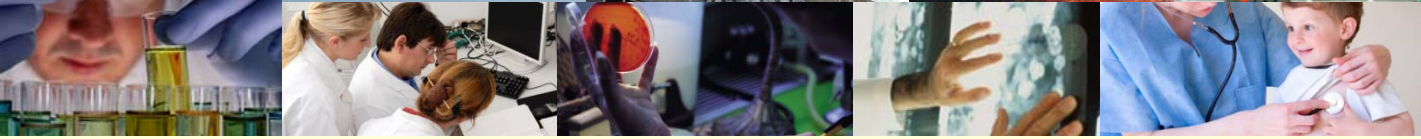
<sup>a</sup> BMDS-equivalent names appear in parentheses



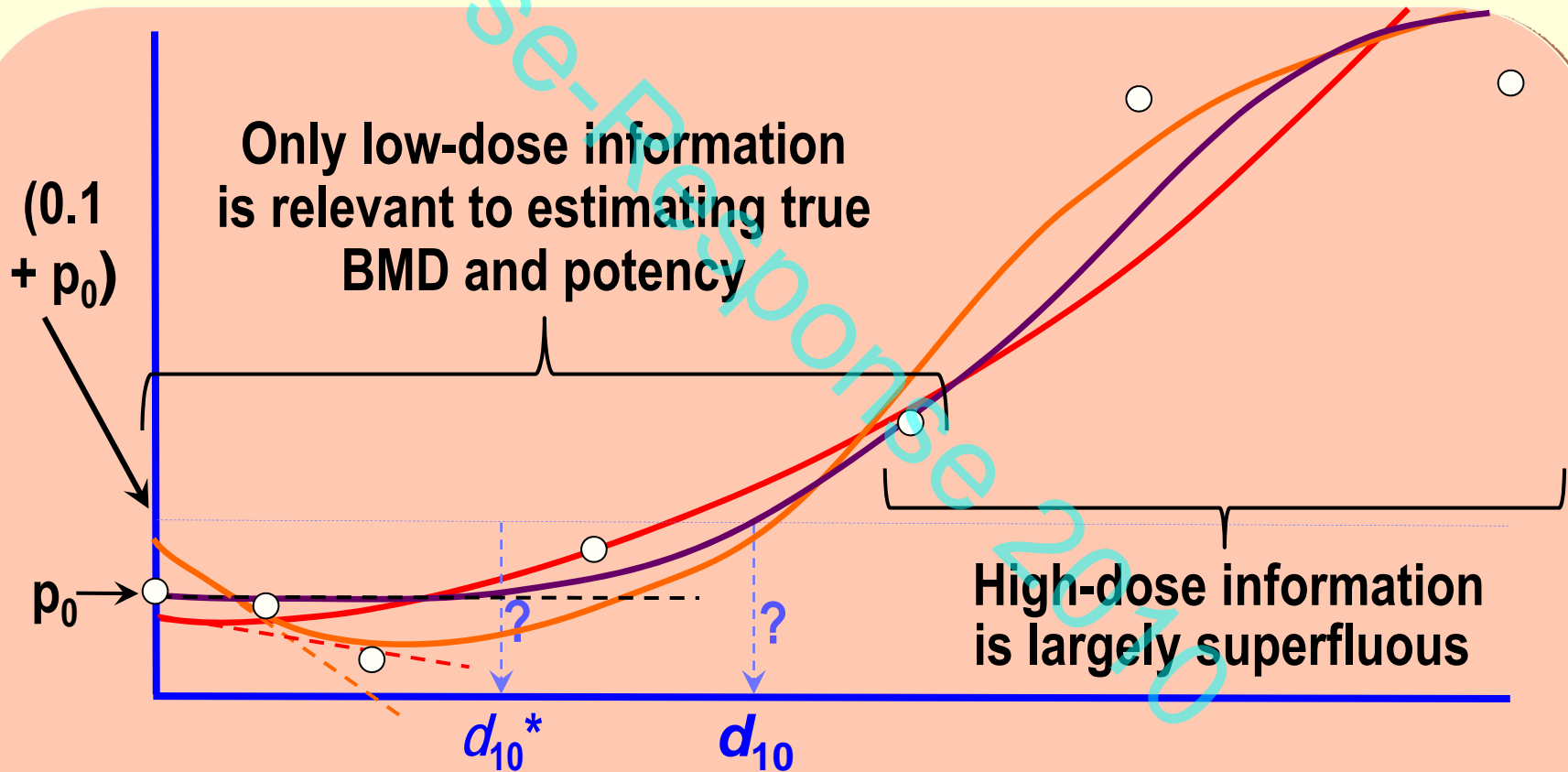
# U.S. EPA BMD Decision Tree<sup>a</sup> is Complex and May Impose Unquantified Bias or Error



<sup>a</sup> EPA 2008 Benchmark Dose Technical Guidance



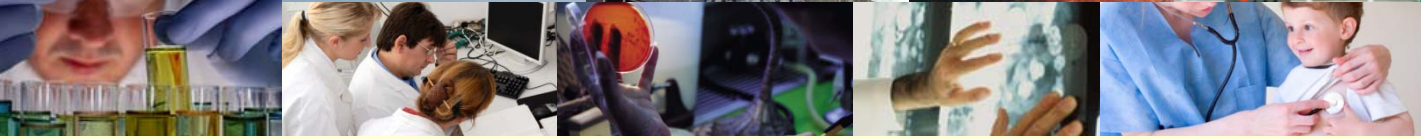
# U.S. EPA BMDS Model Selection and Estimation Process has a Dubious Statistical Basis





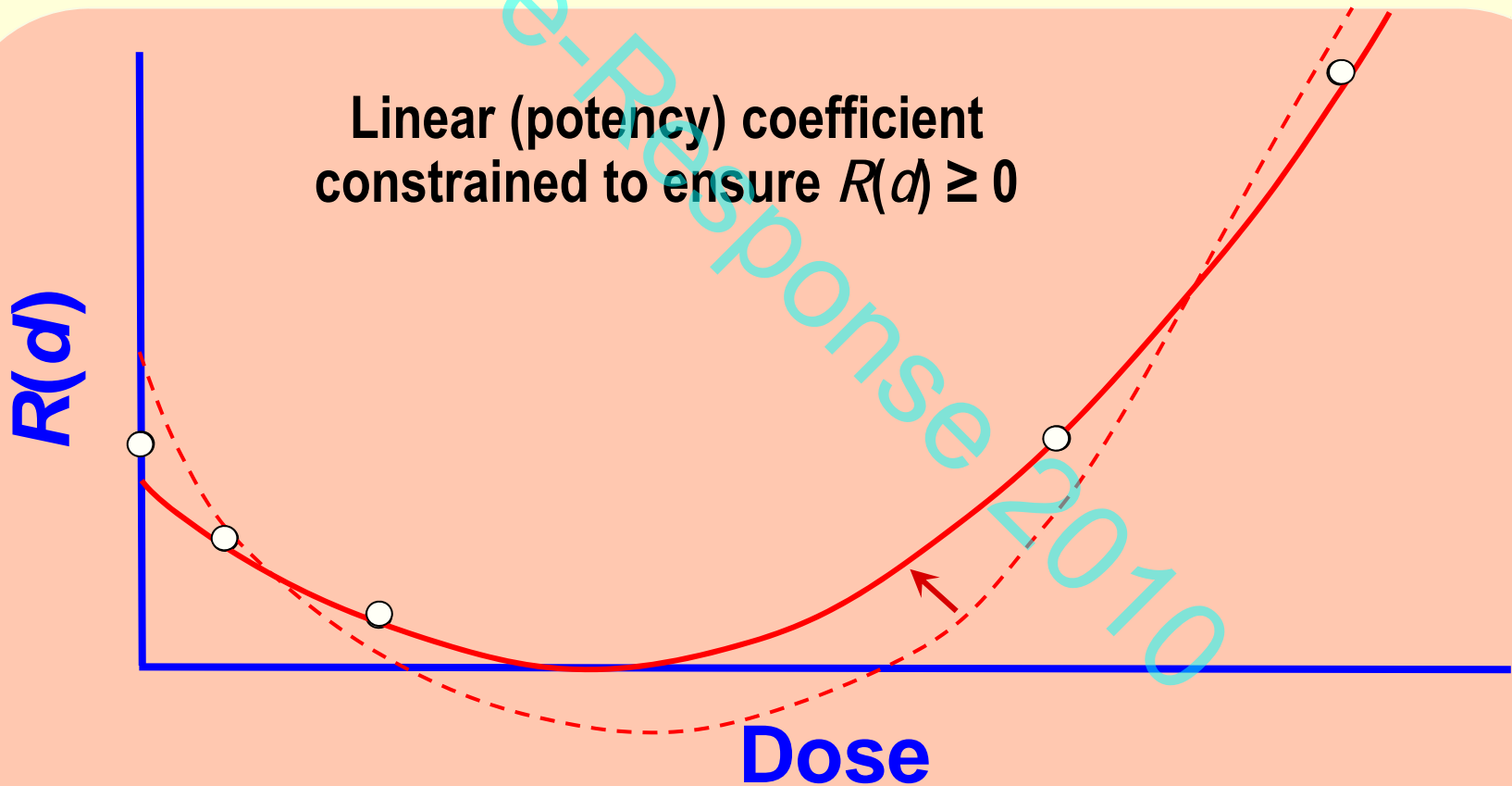
## A Single, “Generic Hockey-Stick” (GSH) Model Suffices to Estimate BMD and Potency

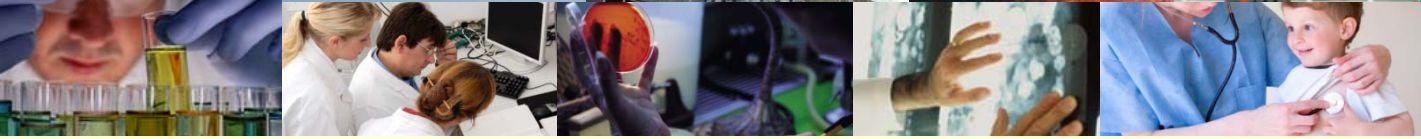
- **Modified “linearized” multistage model:**
  - $1 - \exp[-\sum q_i d^i]$  for  $i \in G(g)$  for  $g$  dose groups
  - $G(g)$  = any subset of  $\leq g$  elements of  $G = \{0, 1, \dots, g-1, g+1\}$
- **All nonlinear coefficients  $q_i (i \neq 1) \geq 0$**
- **Linear (“potency”) coefficient  $q_1$  is constrained only to ensure that  $R(d) \geq 0$  over the experimental dose range**



## A GSH Model is Adequate to Estimate BMD and Potency *(continued)*

Linear (potency) coefficient  
constrained to ensure  $R(d) \geq 0$





## A GSH Model is Adequate to Estimate BMD and Potency *(continued)*

- All possible coefficient combinations are optimized *analytically*, by iterative, weighted, constrained linear regression on logit-transformed data
- Best-estimate coefficients are those that minimize chi-square using the observed data
- Confidence bounds on  $q_1$  and BMD are calculated by the Monte Carlo bootstrap-percentile method



# Simulated Quantal-Response Data were used to Compare the Reliability of BMDS versus GHS Estimates

Risk Model	Doses $d_j$ , $j = 1, \dots, 5$ (mg/kg/day)	$P(d = 0) = p_0$	Risk Model, $P(d)$ Parameters	Expected Potency, $q_1 P(d)$ (mg/kg/day) <sup>-1</sup>	Expected BMD <sup>a</sup> $d_{10} P(d)$ (mg/kg/day)
L			$q_1 = 0.04$	<b>0.04</b>	<b>2.63</b>
LQ	0, 1, 2, 4, 10	0.05	$q_1 = 0.02, q_2 = 0.005$	<b>0.02</b>	<b>3.01</b>
PR			$\mu = 7, \sigma = 2.5$	<b>0</b>	<b>3.80</b>
LG			$q_1 = 0.25$	<b>0.0225</b>	<b>2.99</b>
WB	0, 1, 2, 4, 10	0.10	$q_1 = 0.075, n = 1.5$	<b>0</b>	<b>4.63</b>
GM			$a = 1.1, b = 20$	<b>0</b>	<b>2.74</b>
H	0, 1, 3, 9, 27	0.10	$q_1 = -0.04, q_2 = 0.004$	<b>-0.04</b>	<b>12.2</b>

<sup>a</sup> Benchmark dose (BMD) =  $d_{10} = d| (BMR = P(d) - p_0 = 0.10)$

BMR = Benchmark Response

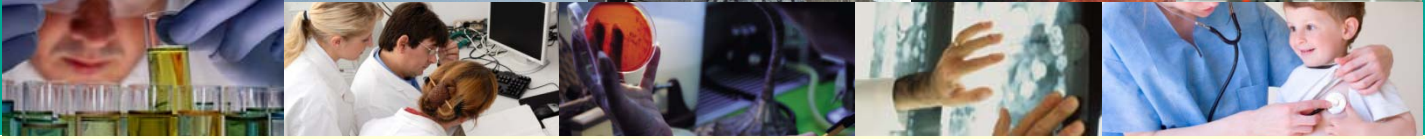


# BMD ( $d_{10}$ ) and BMDL ( $d_{10}^*$ ) Estimates from BMDS Fits to Simulated Data

Model Used to Generate Data	$n^a$	Expected Value, $Ed_{10}$	Average Simulated Value, $Ad_{10}$	Bias, $Ad_{10} - Ed_{10}$	Bias P-Value	95% LCL, $Ad_{10}^*$	$d_{10}^*$ Coverage <sup>b</sup>
L	93	2.63	3.41	0.78	$6 \times 10^{-6}$	2.37	0.68
LQ	99	3.01	3.04	0.03	0.78	2.24	0.79
PR	96	3.80	3.59	-0.21	0.19	2.76	0.94
LG	96	2.99	2.83	-0.15	0.46	2.04	0.90
WB	96	4.63	4.09	-0.54	0.0046	2.85	0.98
GM	94	2.74	3.21	0.47	0.0028	2.19	0.72
H	65	12.2	12.7	0.56	0.30	9.18	0.98

<sup>a</sup>  $n$  = # good fits to 100 simulated data sets

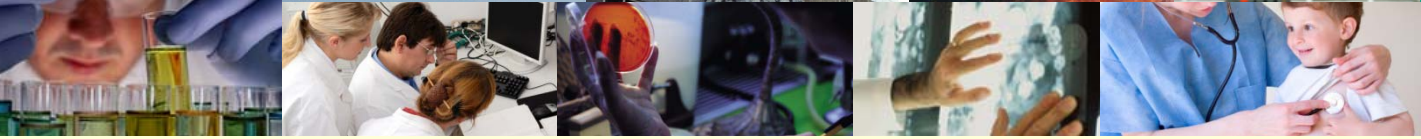
<sup>b</sup> Coverage =  $\Pr(d_{10}^* \leq Ed_{10})$



# Potency ( $q, q^*$ ) Estimates from BMDS Fits to Simulated Data

Model Used to Generate Data	$n$	Expected Value, $E_q$	Average Simulated Value, $A_q$	Bias, $A_q - E_q$	P-Value	$A_{q^*}$	$q^*$ Coverage <sup>a</sup>
L	93	0.04	0.034	-0.0063	$2 \times 10^{-6}$	0.048	0.66
LQ	99	0.02	0.037	0.017	0	0.051	1
PR	96	0	0.030	0.030	0	0.038	1
LG	96	0.0225	0.042	0.019	0	0.058	1
WB	96	0	0.028	0.028	0	0.039	1
GM	94	0	0.036	0.036	0	0.051	1
H	65	-0.04	0.0082	0.048	0	0.011	1 (0)

<sup>a</sup> Coverage =  $\Pr(q^* \geq E_q)$ ; in parentheses:  $\Pr(q^* < 0)$



## BMDS Model Fits Tend to Mis-Specify the True Model used to Simulate Data that were Fit

Model Used to Generate Data	<i>n</i>	Percent of BMDS Fits Indicating the Following “Best” BMDS Model (percent)					
		QL	MS	PR	LG	WB	GM
L	93	67.7	1.1	19.4	7.5	4.3	0
LQ	99	19.2	20.2	23.2	19.2	18.2	8.1
PR	96	0	51.0	2.1	30.2	11.5	5.2
LG	96	29.2	20.8	18.8	27.1	11.5	8.3
WB	96	4.2	24.0	18.8	33.3	3.1	16.7
GM	94	22.3	9.6	11.7	20.2	2.1	40.4
H	65	0	47.7	0	3.1	49.2	0



# BMD ( $d_{10}$ ) and BMDL ( $d_{10}^*$ ) Estimates from GHS Fits to Simulated Data

Model Used to Generate Data <sup>a</sup>	Expected Value, $Ed_{10}$	Average Simulated value, $Ad_{10}$	Bias, $Ad_{10} - Ed_{10}$	Bias P-Value	$Ad_{10}^*$	$d_{10}^*$ Coverage <sup>b</sup>
L	2.63	3.41	0.78	$6 \cdot 10^{-5}$	1.28	0.98
L <sub>1</sub>	2.63	2.83	0.19	0.12	1.16	0.98
LQ	3.01	3.13	0.12	0.44	1.39	0.97
PR	3.80	3.96	0.16	0.28	2.02	1.00
LG	2.99	3.37	0.38	0.099	1.24	0.96
WB	4.63	4.76	0.13	0.44	1.67	0.98
GM	2.74	3.49	0.74	0.002	1.26	0.97
H	12.2	13.0	0.84	$9 \cdot 10^{-5}$	7.75	0.98
H <sub>1</sub>	12.2	11.9	-0.25	0.095	6.91	1.00

<sup>a</sup> Model L<sub>1</sub> and H<sub>1</sub> fits were all conditioned on  $|q| > 0$

<sup>b</sup> Coverage =  $\Pr(d_{10}^* < Ed_{10})$



# Potency ( $q, q^*$ ) Estimates from GHS Fits to Simulated Data

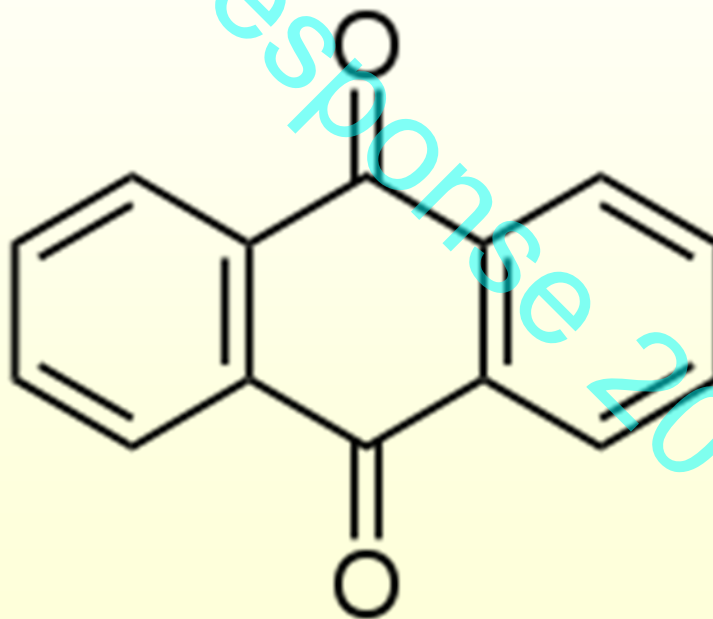
Model Used to Generate Data	Expected value, $E_q$	Average Simulated Value, $A_q$	Bias, $A_q - E_q$	P-Value	$A_{q^*}$	$q^*$ Coverage <sup>a</sup>
L	0.04	0.032	-0.0085	0.001	0.092	0.97
L <sub>1</sub>	0.04	0.038	-0.0019	0.39	0.10	0.98
LQ	0.02	0.027	0.0068	0.13	0.085	0.97
PR	0	0.00051	0.00051	0.84	0.053	0.83
LG	0.0225	0.025	0.0024	0.84	0.10	0.96
WB	0	-0.0012	-0.0012	0.84	0.080	0.83
GM	0	0.028	0.028	0	0.11	1.00
H	-0.04	-0.026	0.014	0	0.025	1 (0.78)
H <sub>1</sub>	-0.04	-0.038	0.0024	0.034	0.0176	1 (0.99)

<sup>a</sup> Coverage =  $\Pr(q^* \geq E_q)$ ; in parentheses:  $\Pr(q^* < 0)$



## Illustrative GHS Model Application:

Anthraquinone (AQ): A known rodent carcinogen and anti-carcinogen



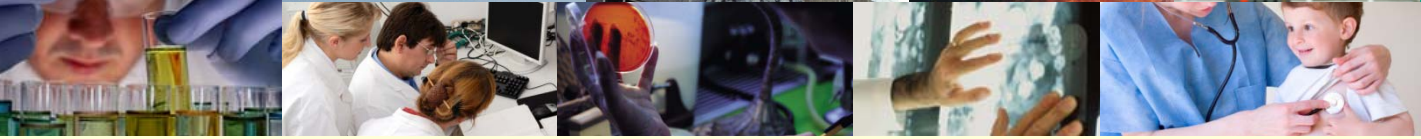


# GHS Estimates of AQ Tumor Potency ( $\sim 100$ )

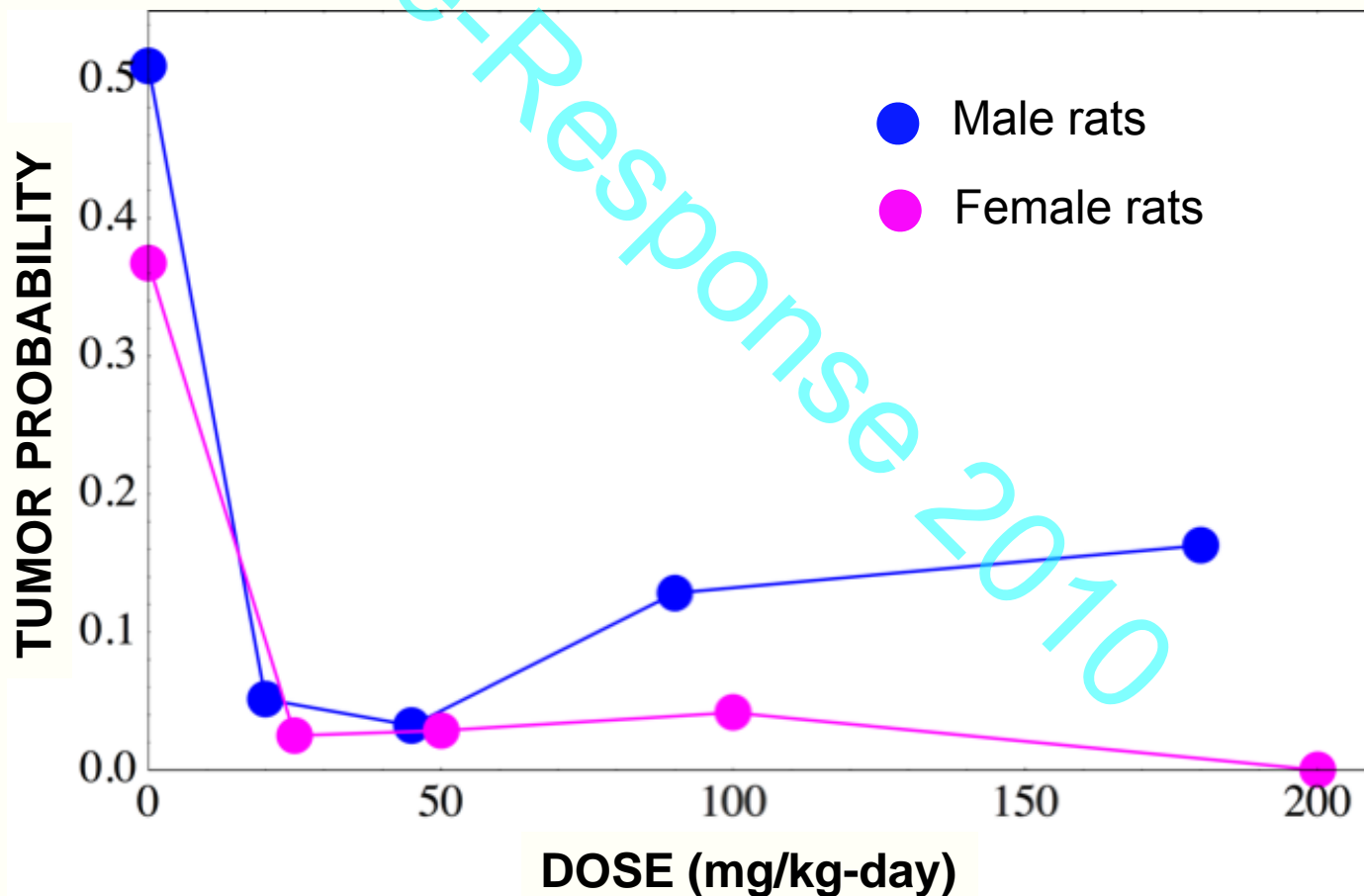
Species, Sex	Tumor Type <sup>a</sup>	$q$ (mg/kg/day) <sup>-1</sup>	$q^*$ (mg/kg/day) <sup>-1</sup>	HE <sup>b</sup> $q$ (mg/kg/day) <sup>-1</sup>	HE <sup>b</sup> $q^*$ (mg/kg/day) <sup>-1</sup>
Rat, M	MCL	-13	(-24, -5.0)	-68	(-130, -27)
Rat, F	MCL	-5.2	(-11, -1.0)	-33	(-67, -6.3)
Rat, F	RTAC	0.34	0.72	2.1	4.5
Mouse, M	HB	0.091	0.18	1.0	2.0
Mouse, M	HC or HB	0.22	0.34	2.5	3.8
Mouse, M	HAC or HB	0.48	0.90	5.4	10
Mouse, F	HC	0.015	0.059	0.16	0.63
Mouse, F	HAC or HB	1.1	1.7	12.	18.

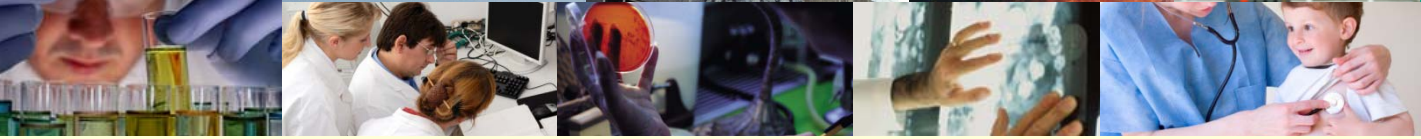
<sup>a</sup> MCL = mononuclear cell leukemia, RTAC = renal cell adenoma or carcinoma, HB = hepatoblastoma (benign or malignant), HC = hepatocellular carcinoma, HAC = hepatocellular adenoma or carcinoma.

<sup>b</sup> HE = human equivalent

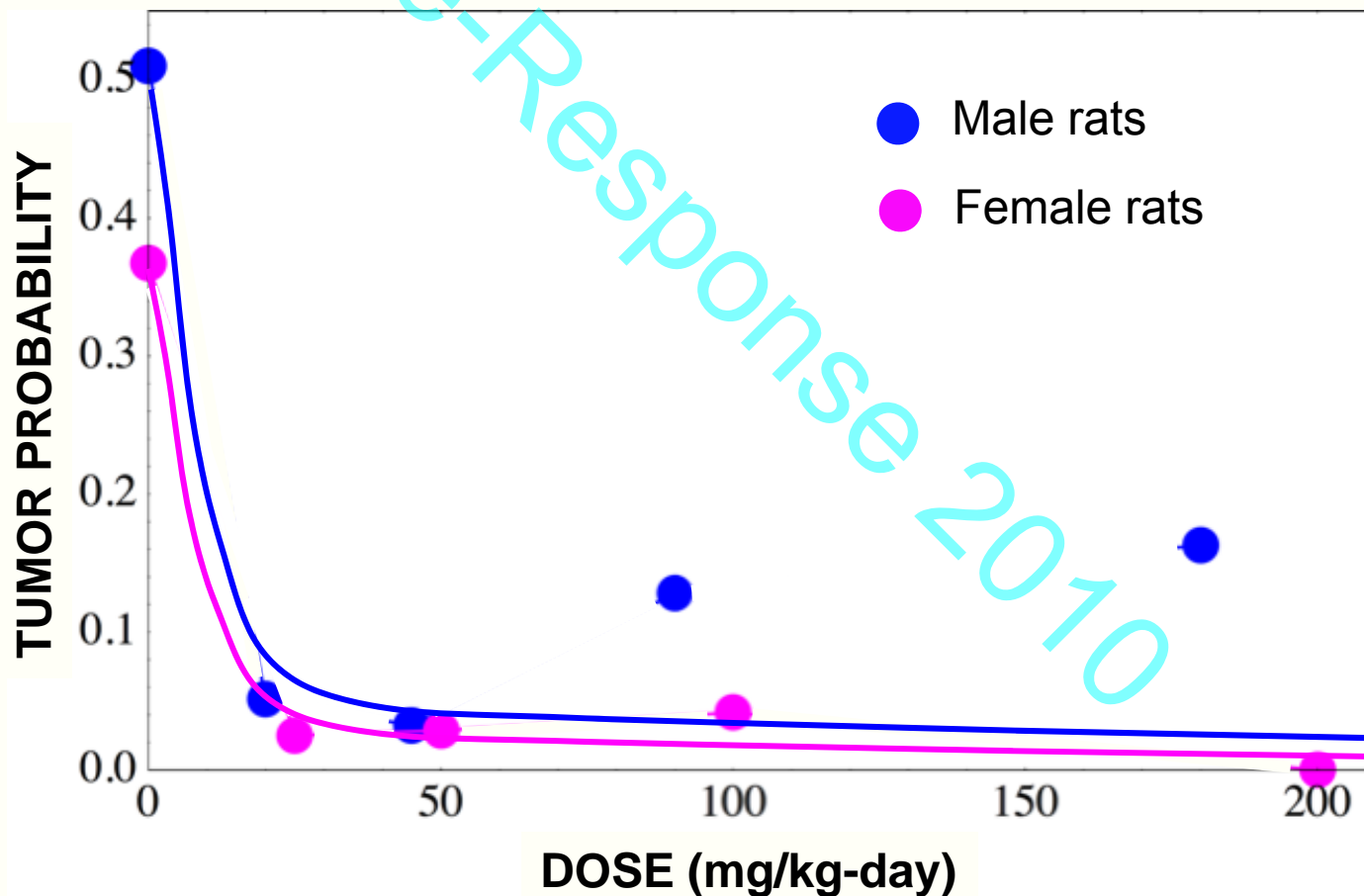


# AQ Suppresses Mononuclear Cell Leukemia (MCL) in Male and Female F344/N Rats



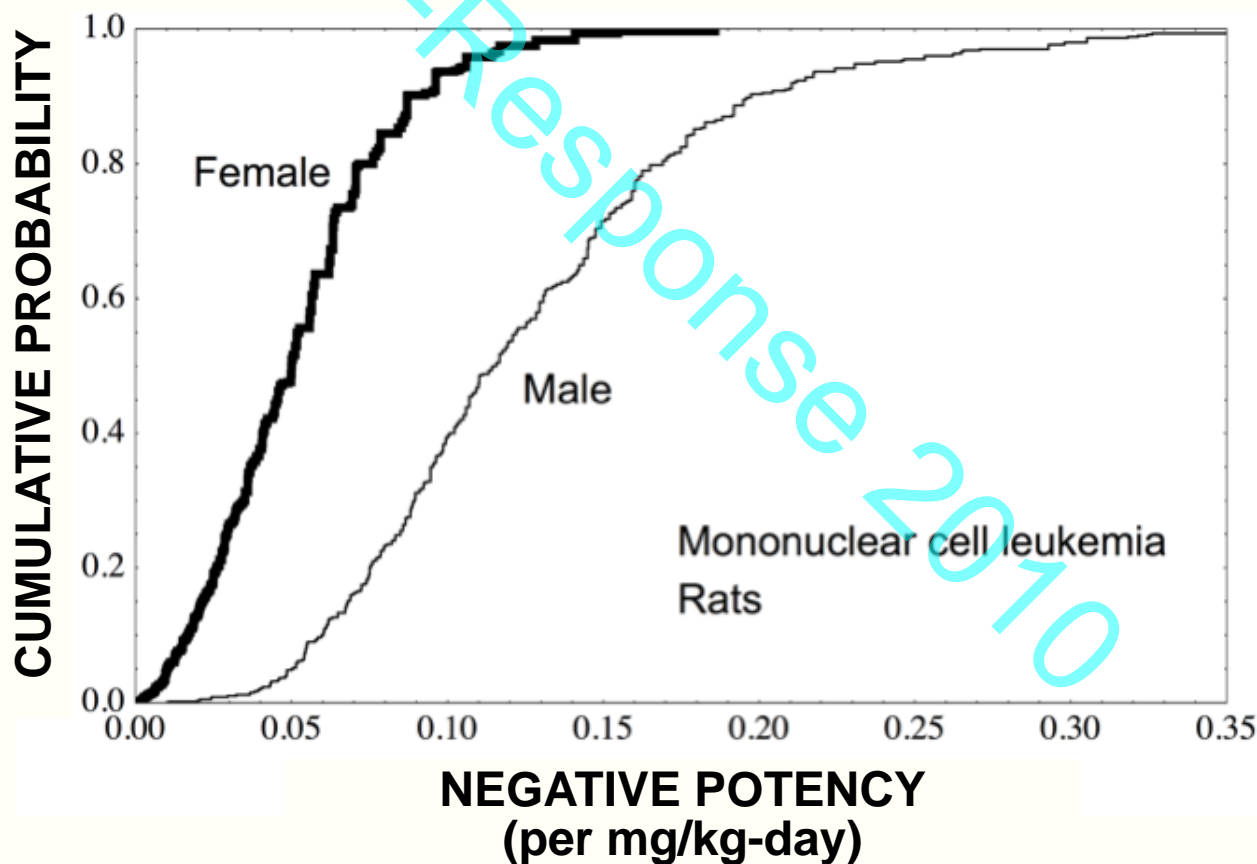


# AQ Effect on MCL in Rats Modeled as Pure Suppression (i.e., Exponential Loss)





# GHS Estimates of AQ Potency for Suppressing Spontaneous MCL in Rats





## Net Potency Calculation

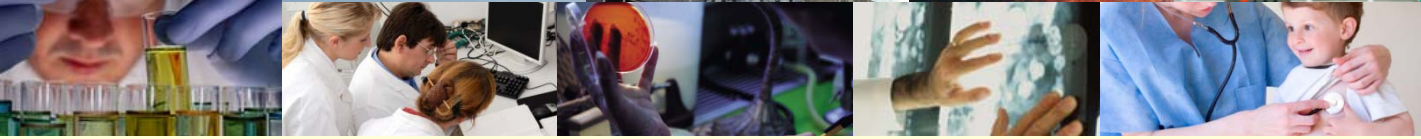
- *Net* potency  $Q$  of joint effects involving tumors induced at potencies  $q_i$  must adjust for estimated background rates  $r_j$  of any tumor types *purely suppressed* at rates  $a_j$

$$Q = \sum_{i=1}^{n_i} q_i - \sum_{j=1}^{n_j} \frac{r_j}{1-r_j} a_j$$

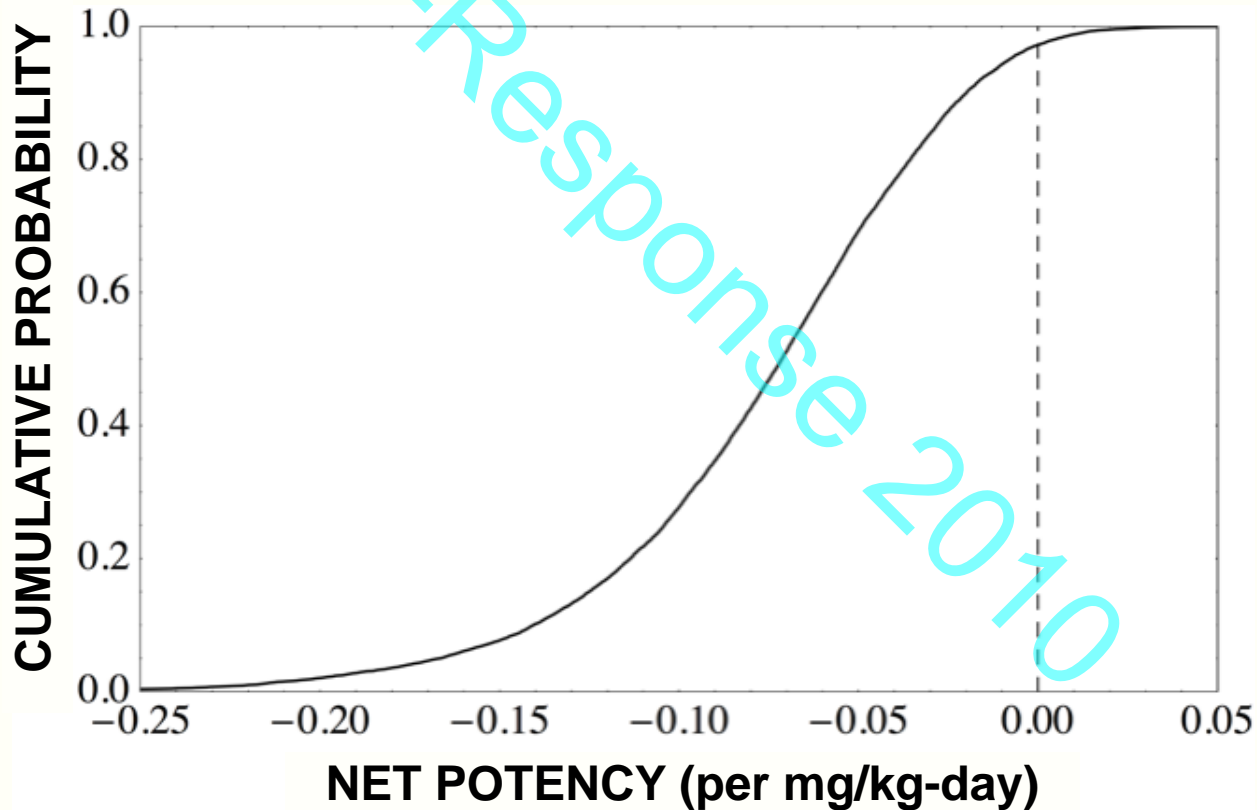


## Net Human-Equivalent AQ Potency: Approach

- Equal weights were used to aggregate estimated potencies for
  - MCL suppression in male vs. female rats
  - Tumor suppression vs. induction in rats
  - HAC or HB induction in male vs. female mice
  - Tumor induction in mice vs. rats
- Standard animal-to-human surface-area adjustment



# Net Human-Equivalent AQ Potency: Result





## Conclusions

- The USEPA BMDS procedure does not reliably identify dose-response relationships
- BMD & potency estimates are easier to obtain by the GHS than by the BMDS procedure
- GHS estimation performs as well or better than BMDS estimation (at least for quantal data)
- The GHS model can be used to test objectively for, and to characterize, negative dose-response patterns such as AQ-induced MCL suppression in rats