

Figure 1. Maximum likelihood estimate of the multistage dose-response model for a hypothetical data set

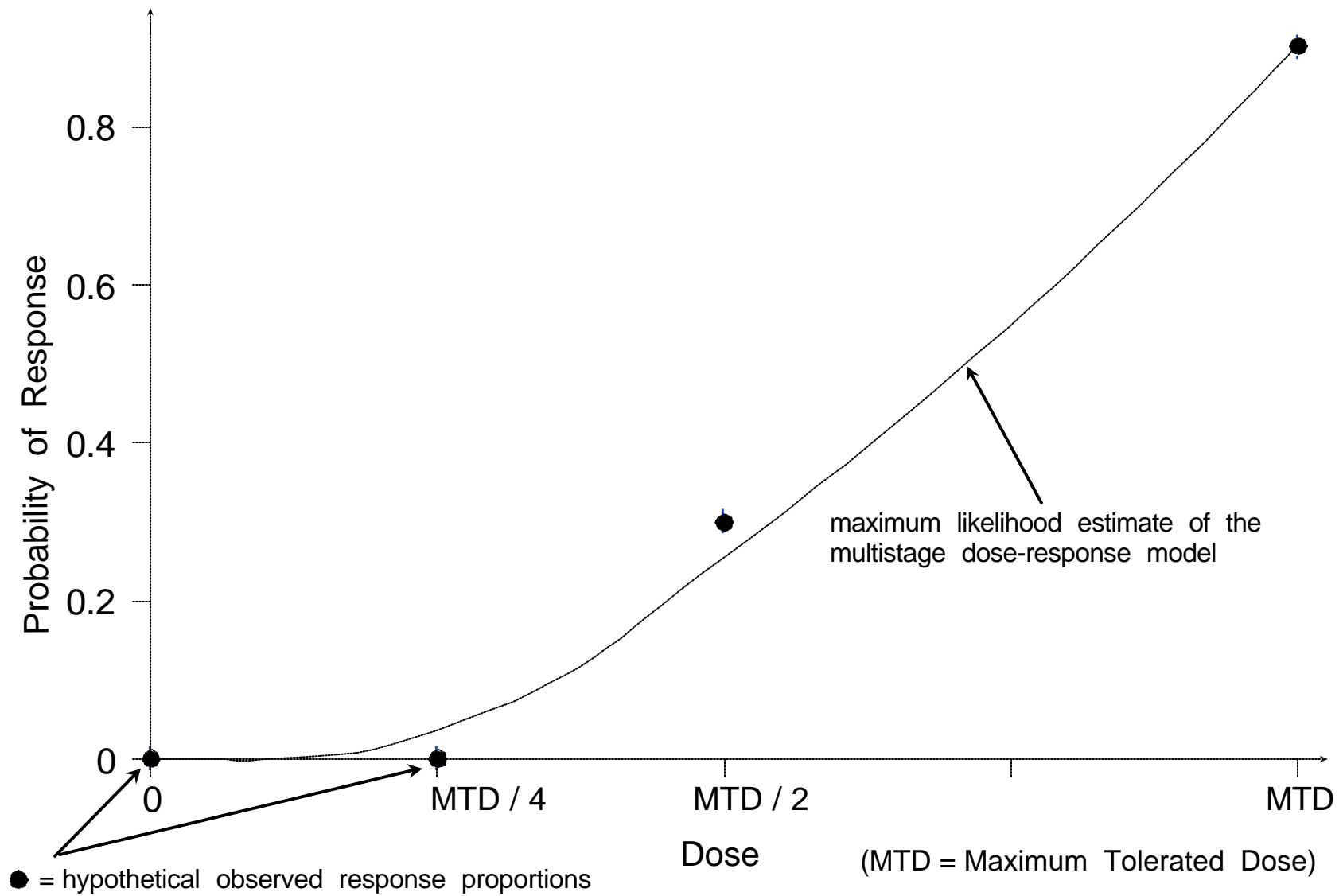


Figure 2. Regulatory dose-response models like the multistage dose-response model always force the maximum likelihood estimate of the risk at low doses to be increased relative to the background risk at dose zero regardless of the observed data

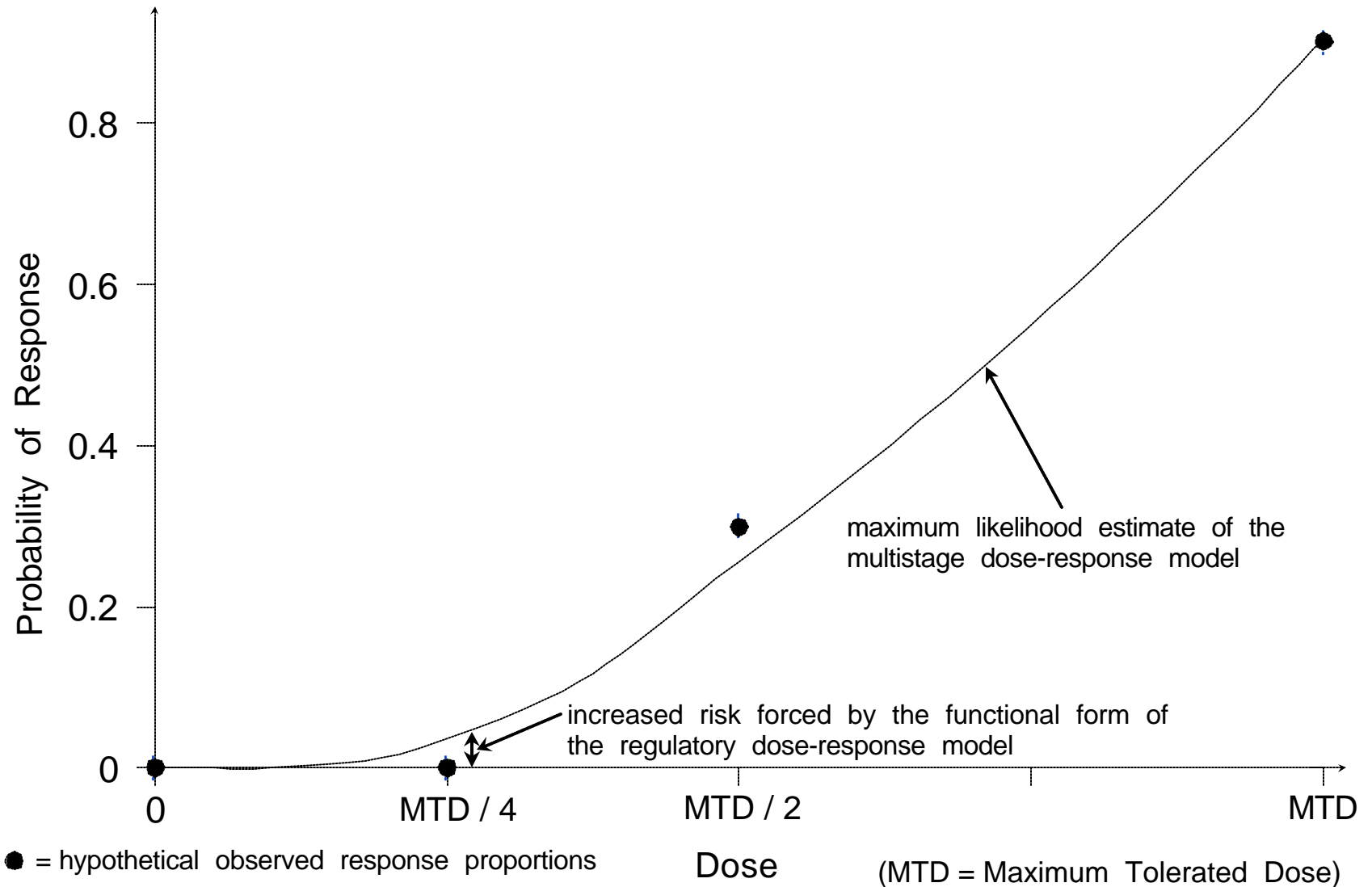


Figure 3. Overstatement of the added risk at low-doses using a potency inferred from high-dose data rather than the multistage dose-response model's maximum likelihood estimates at low doses

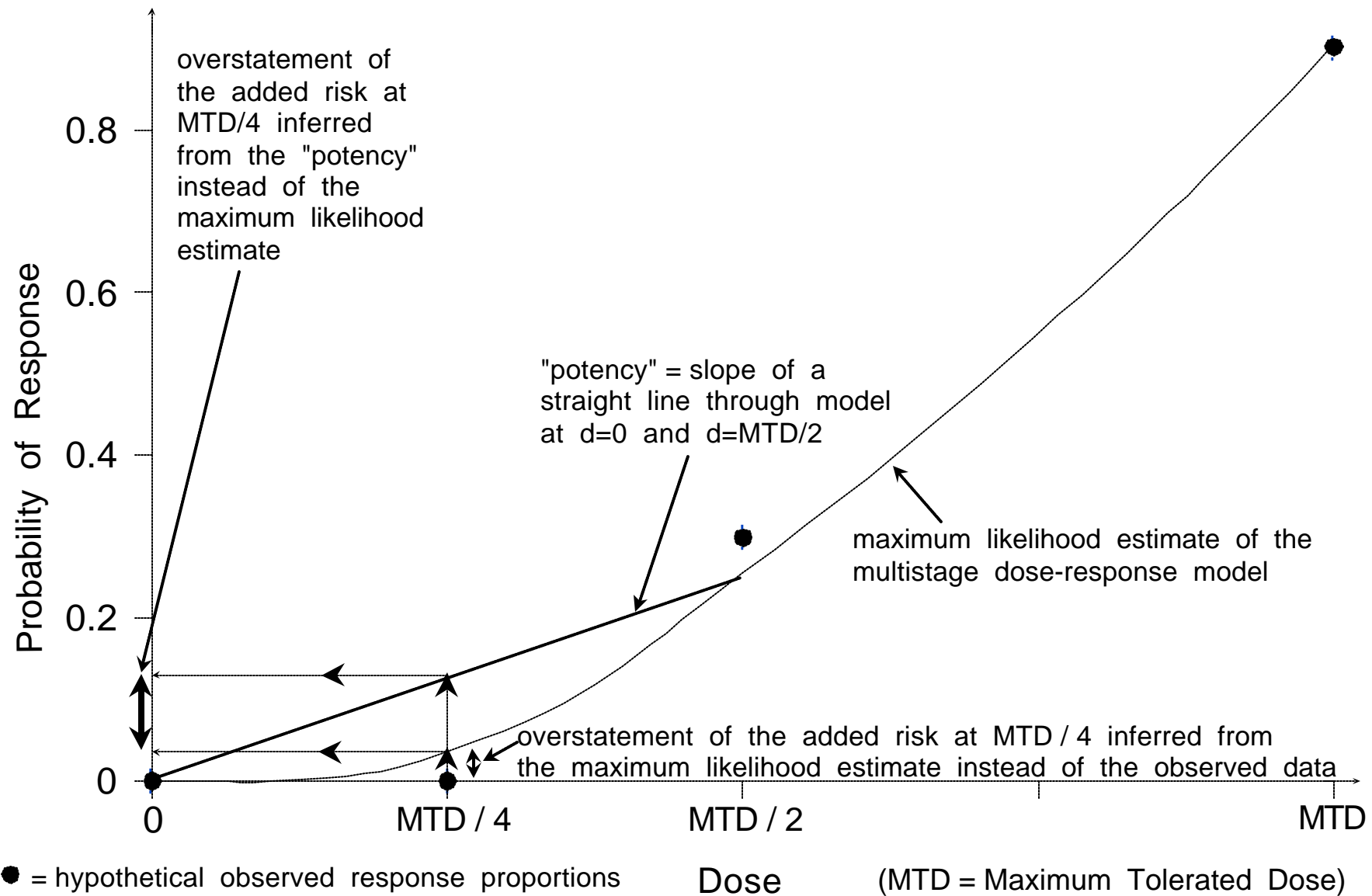


Figure 4. Maximizing the upper bound on the added risk at low doses by the regulatory agencies' use of the linearized multistage model which is based on the largest low-dose slope that does not produce a statistically detectable bad fit to the observed data

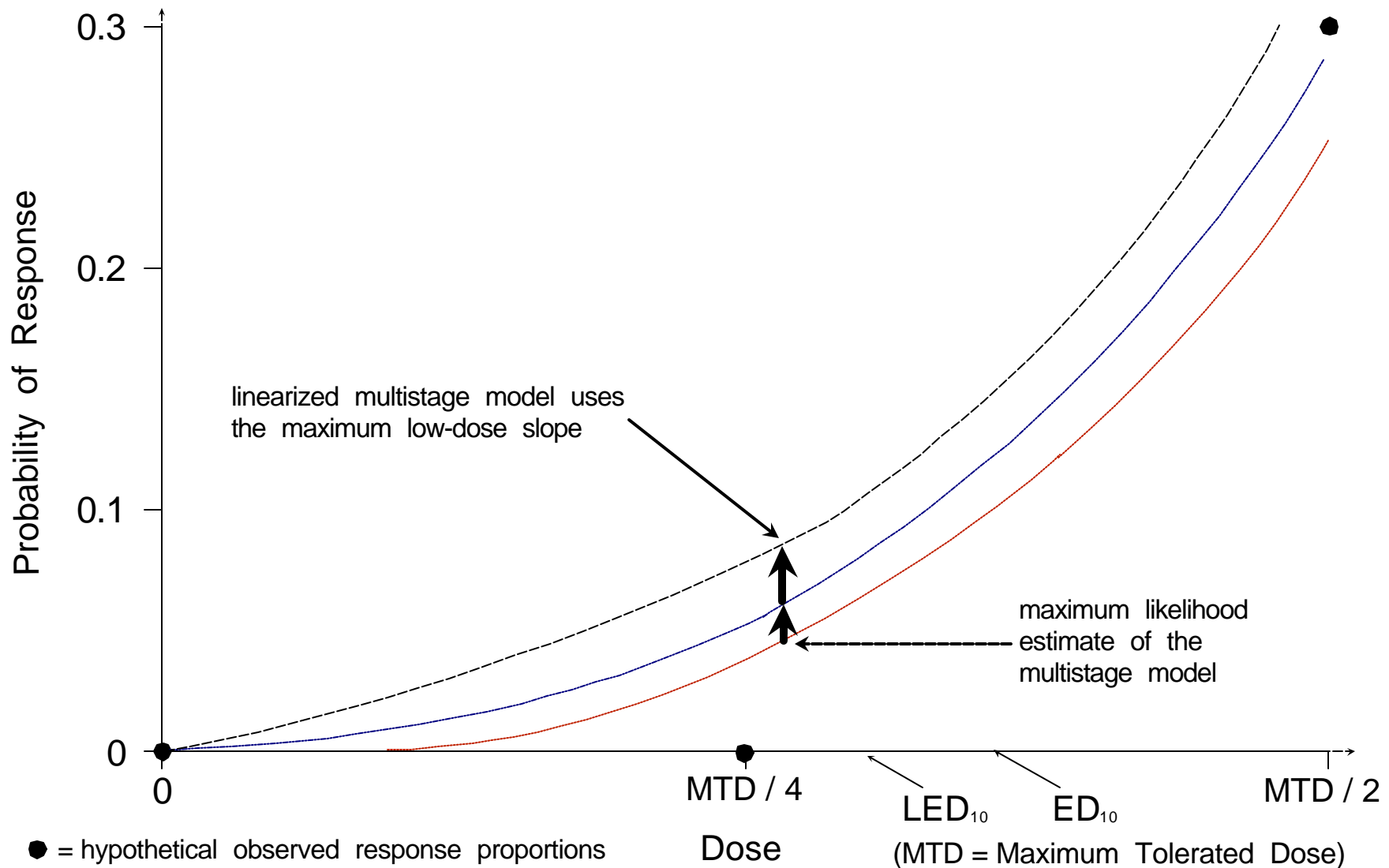


Figure 5. The upper bounds on risk in the linearized multistage model versus the maximum likelihood estimates of risk in the multistage model

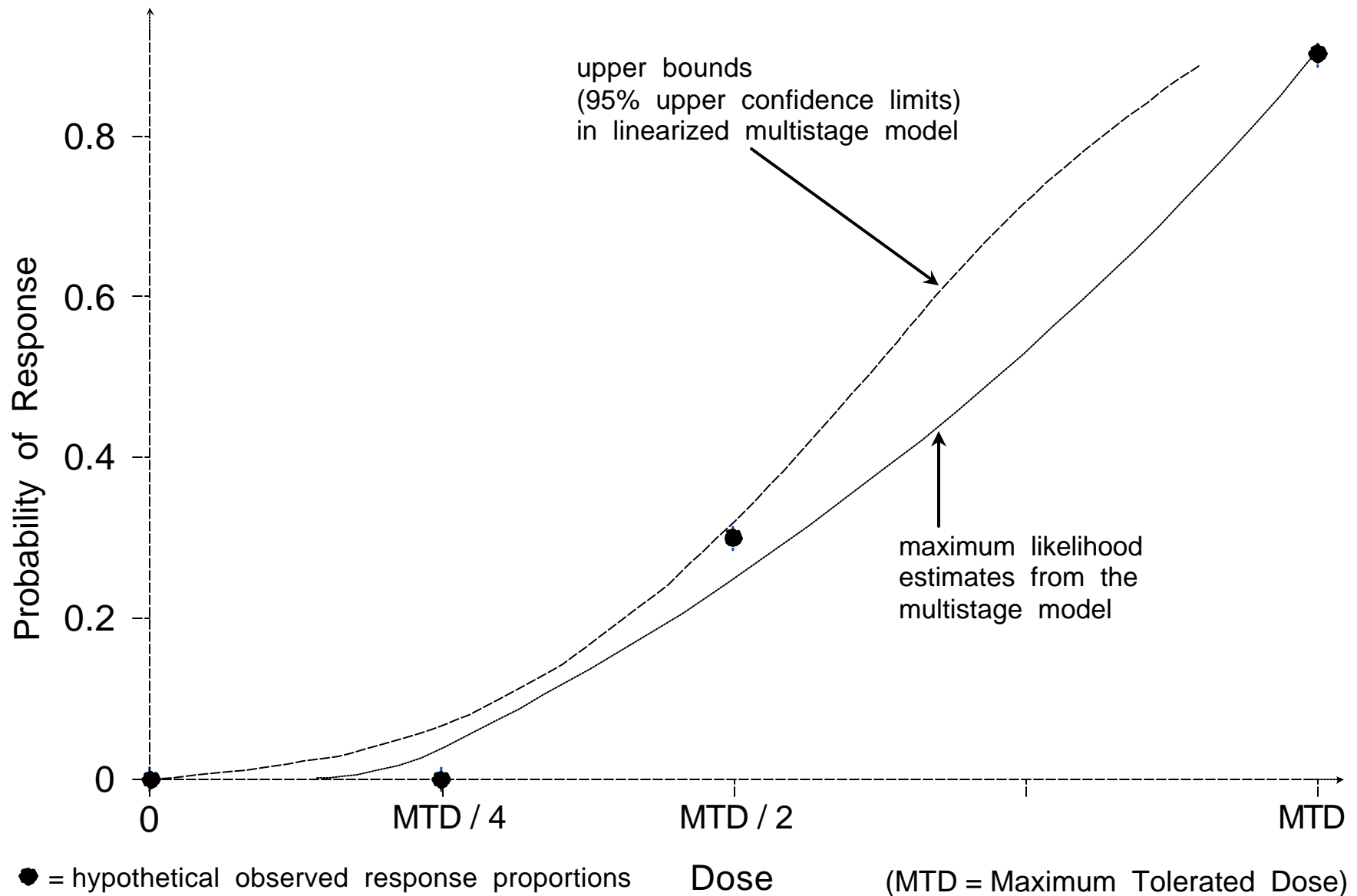
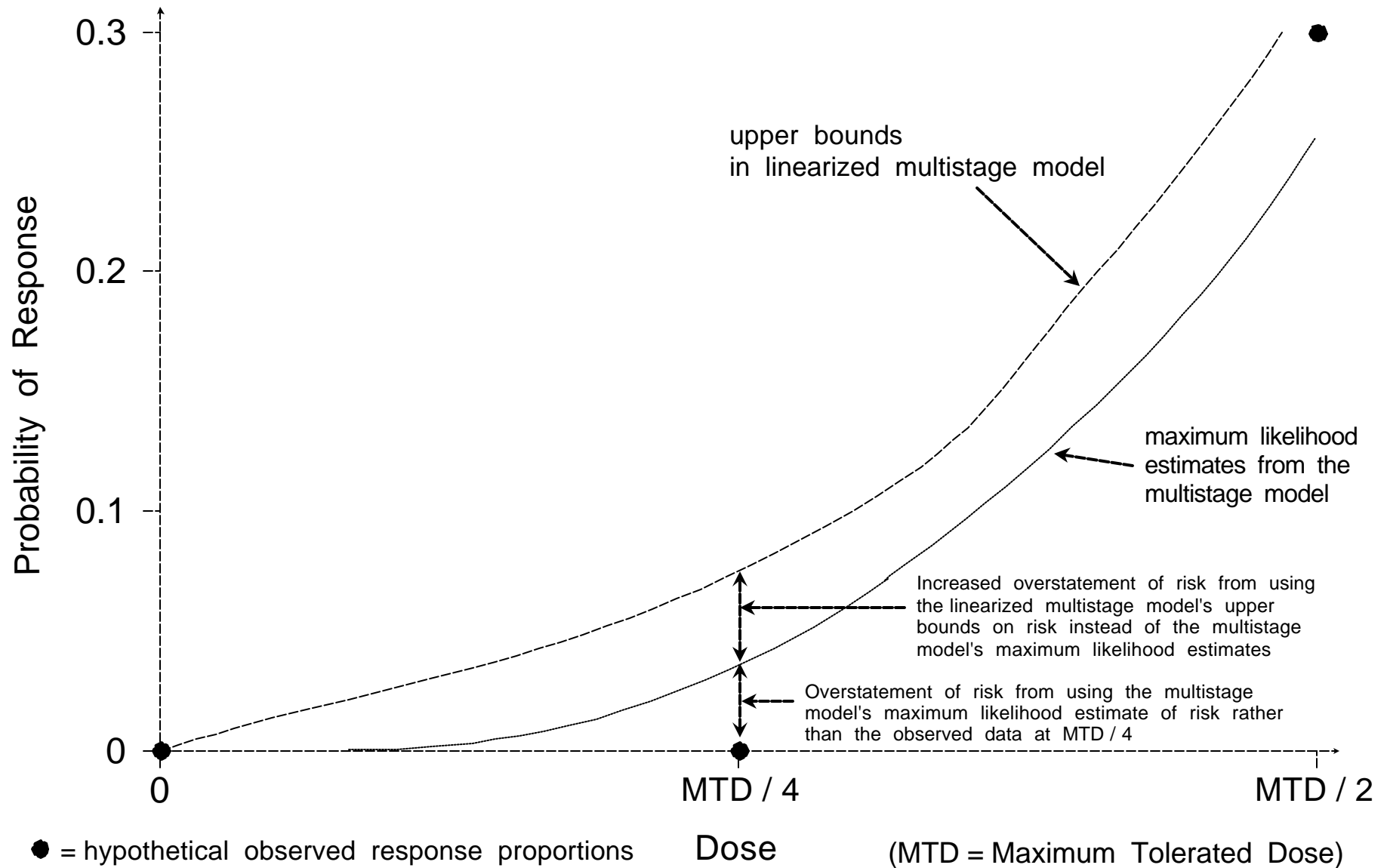
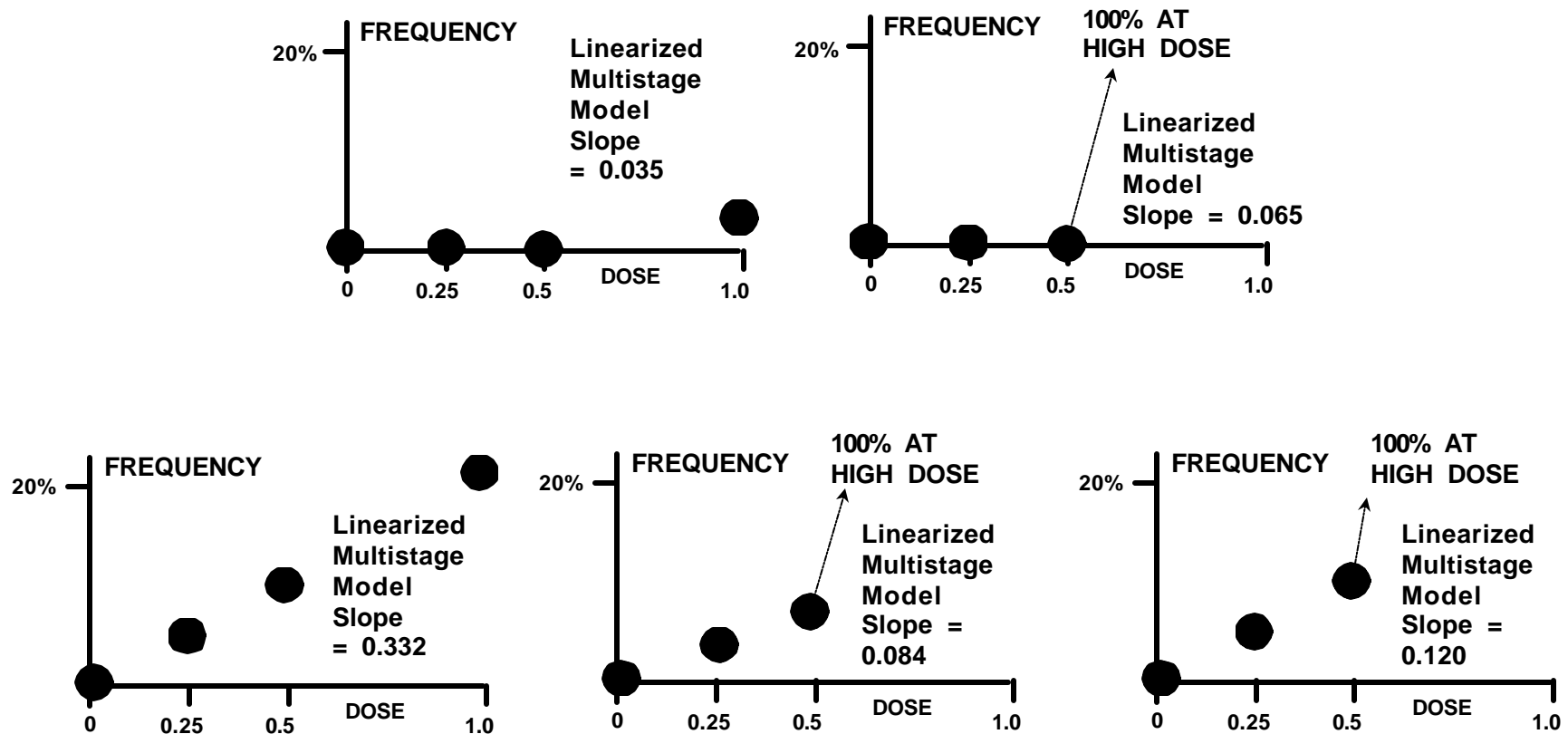


Figure 6. Increased overstatement of the added risk using the linearized multistage model's upper bounds on risk instead of the multistage model's maximum likelihood estimates of risk



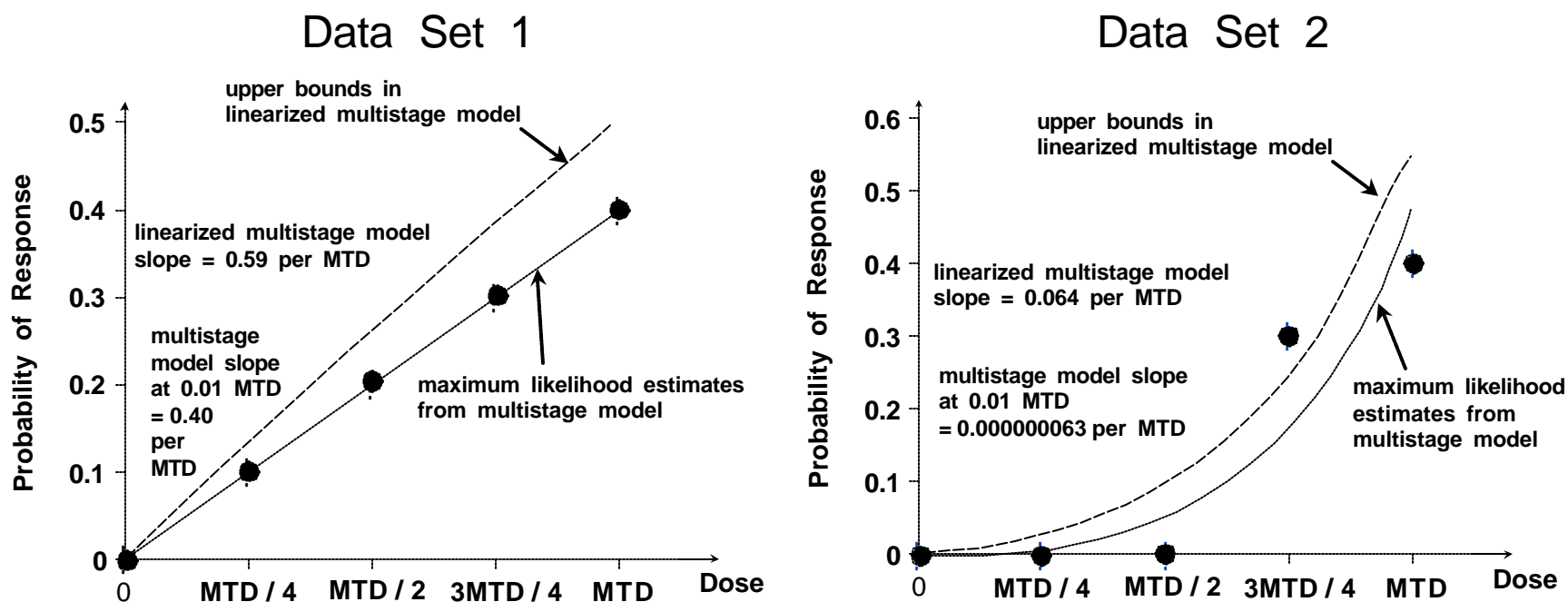
## Figure 7. Nonresponsiveness of current regulatory upper bound potency measures to experimental data:

Five hypothetical experimental outcomes with very different dose-response relationships yet the largest of the six corresponding potency measures differs from the smallest by less than one order of magnitude (10 fold)



The potency measure is that used currently by the U.S. EPA and equals the slope of the linearized multistage model in the lower dose region. Here the slope is evaluated for DOSE = 0.1 when the maximum tolerated dose (MTD) = 1. The observed response frequencies are indicated by the ● and correspond to an experiment with 50 subjects at each dose level.

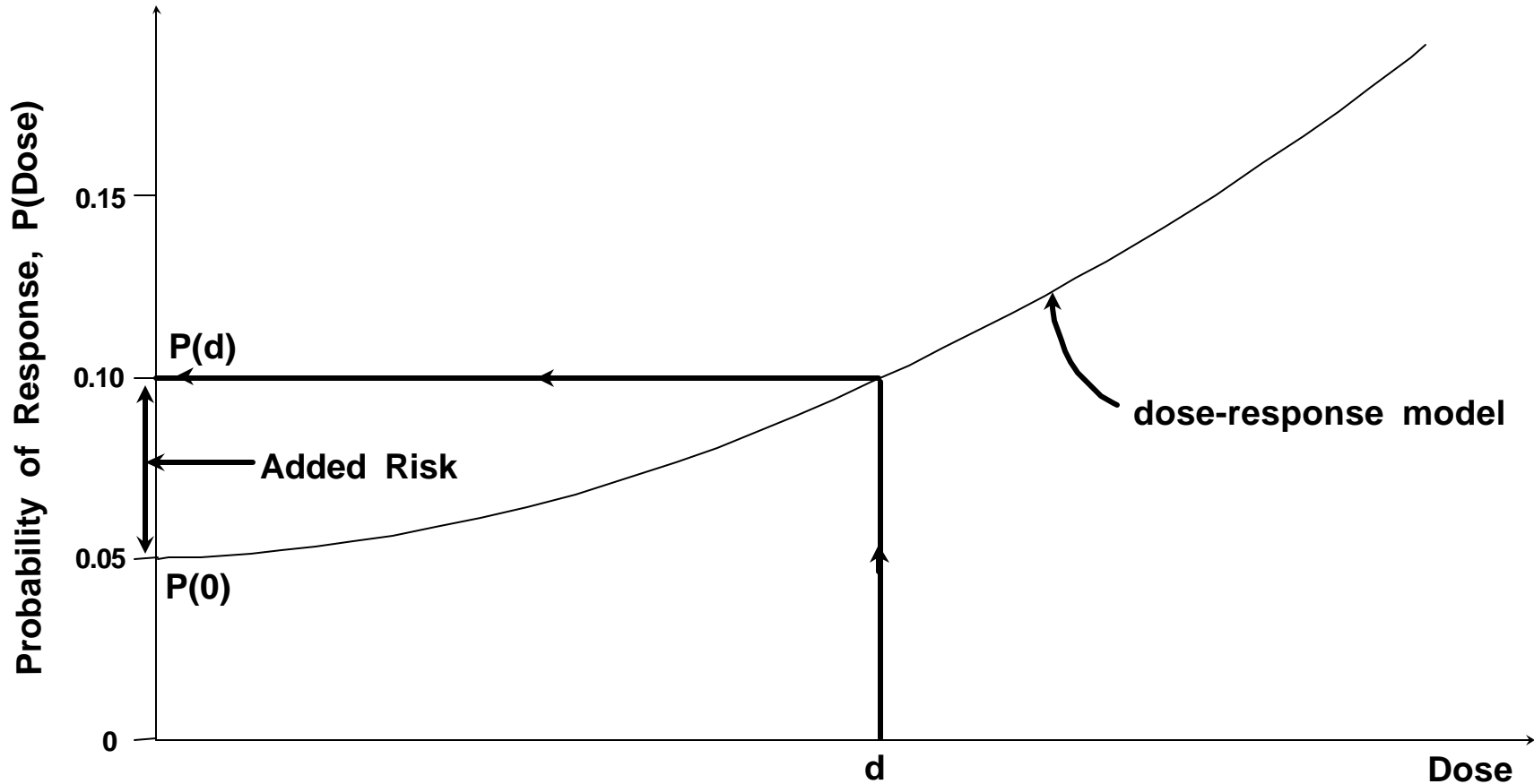
Figure 8. The multistage model's maximum likelihood estimates greater responsiveness to the observed data and greater capability to differentiate between the dose-response relationships of different chemicals than the current regulatory upper bound potency measures based on the linearized multistage model



(MTD = Maximum Tolerated Dose)

● = hypothetical observed response proportions

Figure 9. Definitions of added risk and extra risk



$$\text{Added Risk} = P(d) - P(0)$$

$$\text{Extra Risk} = [ P(d) - P(0) ] / [ 1 - P(0) ] = [ \text{Added Risk} ] / [ 1 - P(0) ]$$

Extra Risk = Added Risk if  $P(0) = 0$

Extra Risk > Added Risk if  $P(0) > 0$

Figure 10. Linear and nonlinear dose-response models and a dose-response model including a threshold.

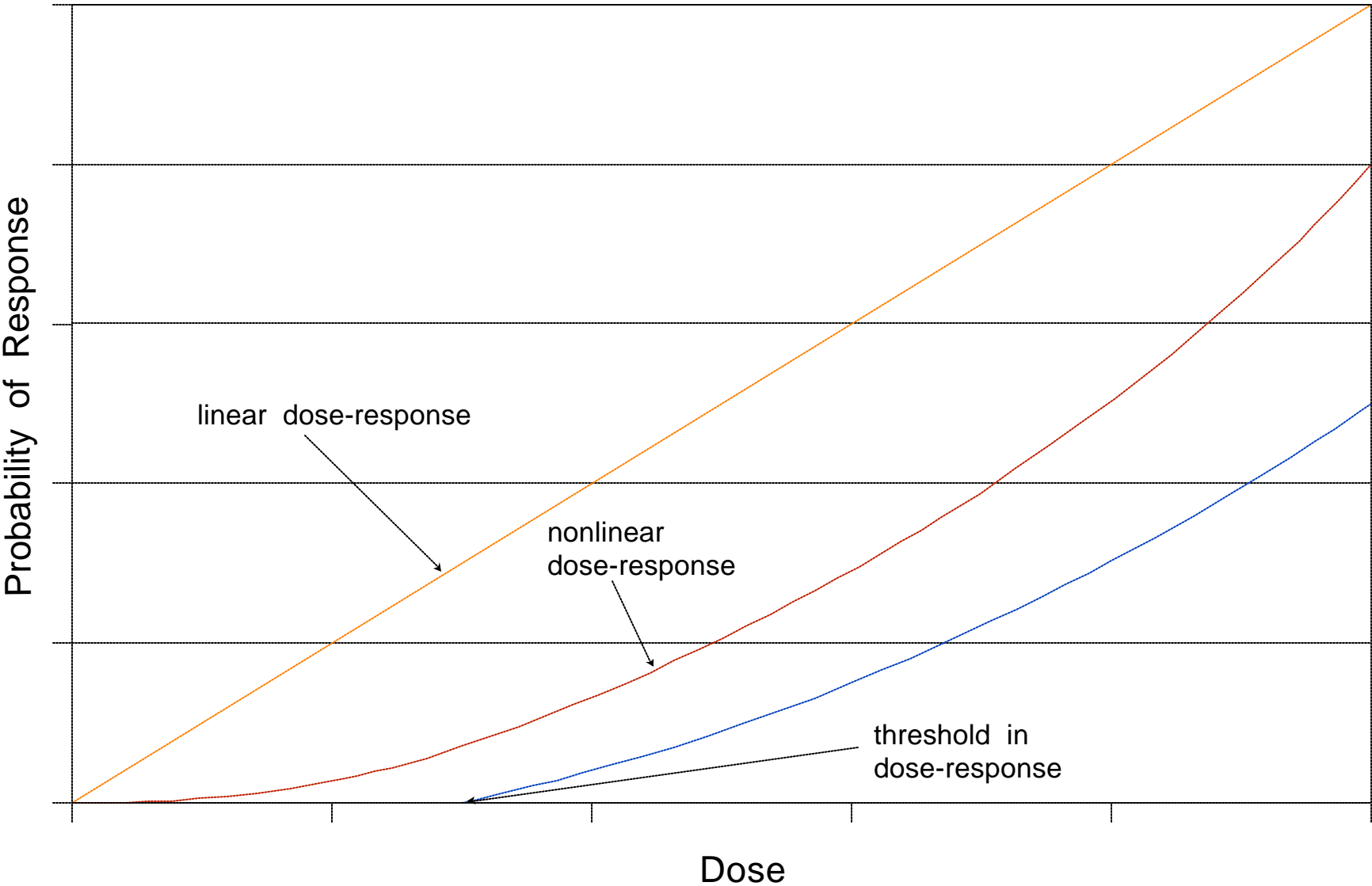


Figure 11. The failure of the multistage model's maximum likelihood estimates and the current regulatory potency measures based on the linearized multistage model to reflect dose levels that are likely to be without appreciable risk of deleterious effects during a lifetime

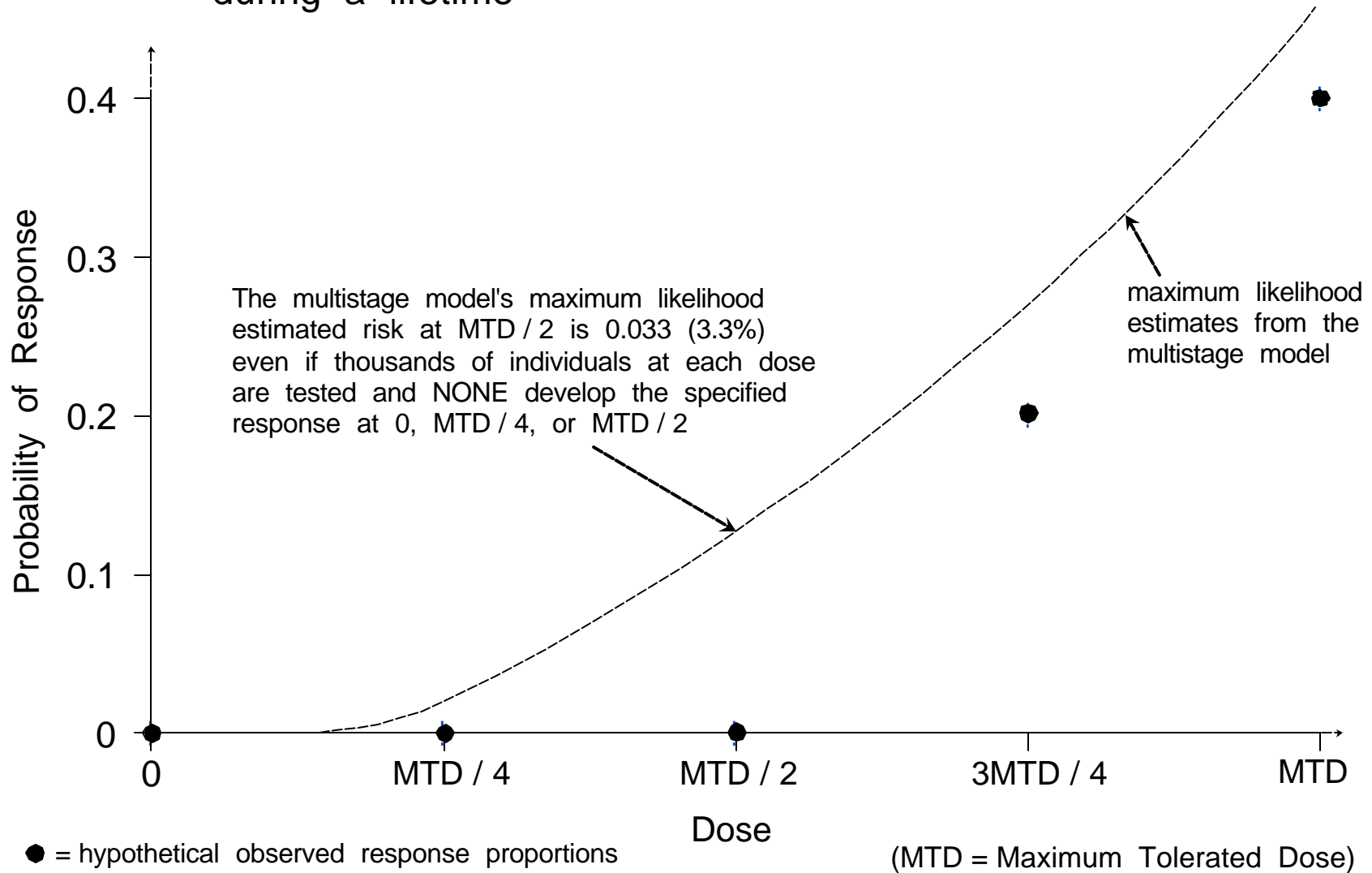


Figure 12. The ability of classical measures of toxicity like the No-Observed-Adverse-Effect-Level (NOAEL) to reflect dose levels that are likely to be without appreciable risk of deleterious effects during a lifetime

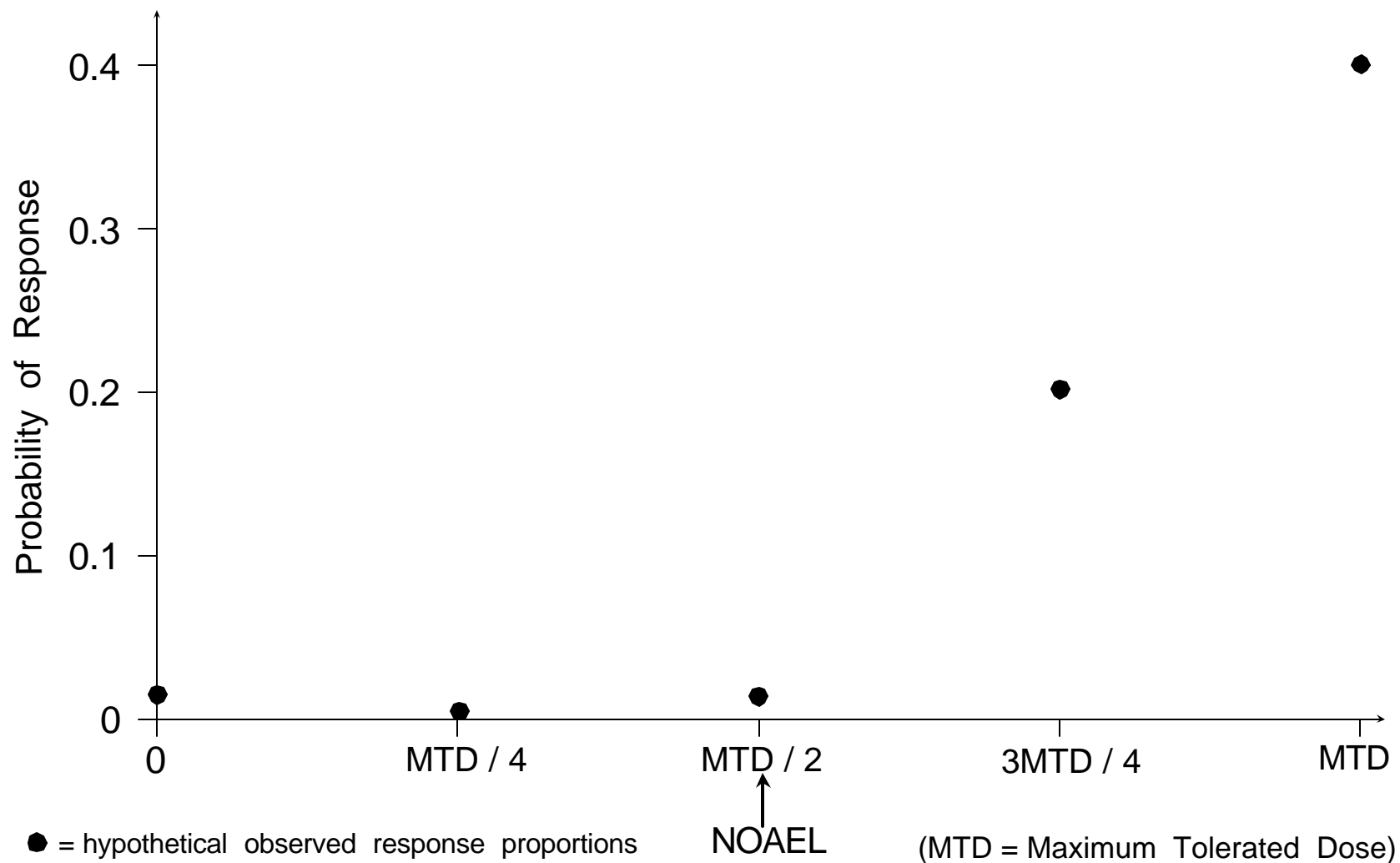
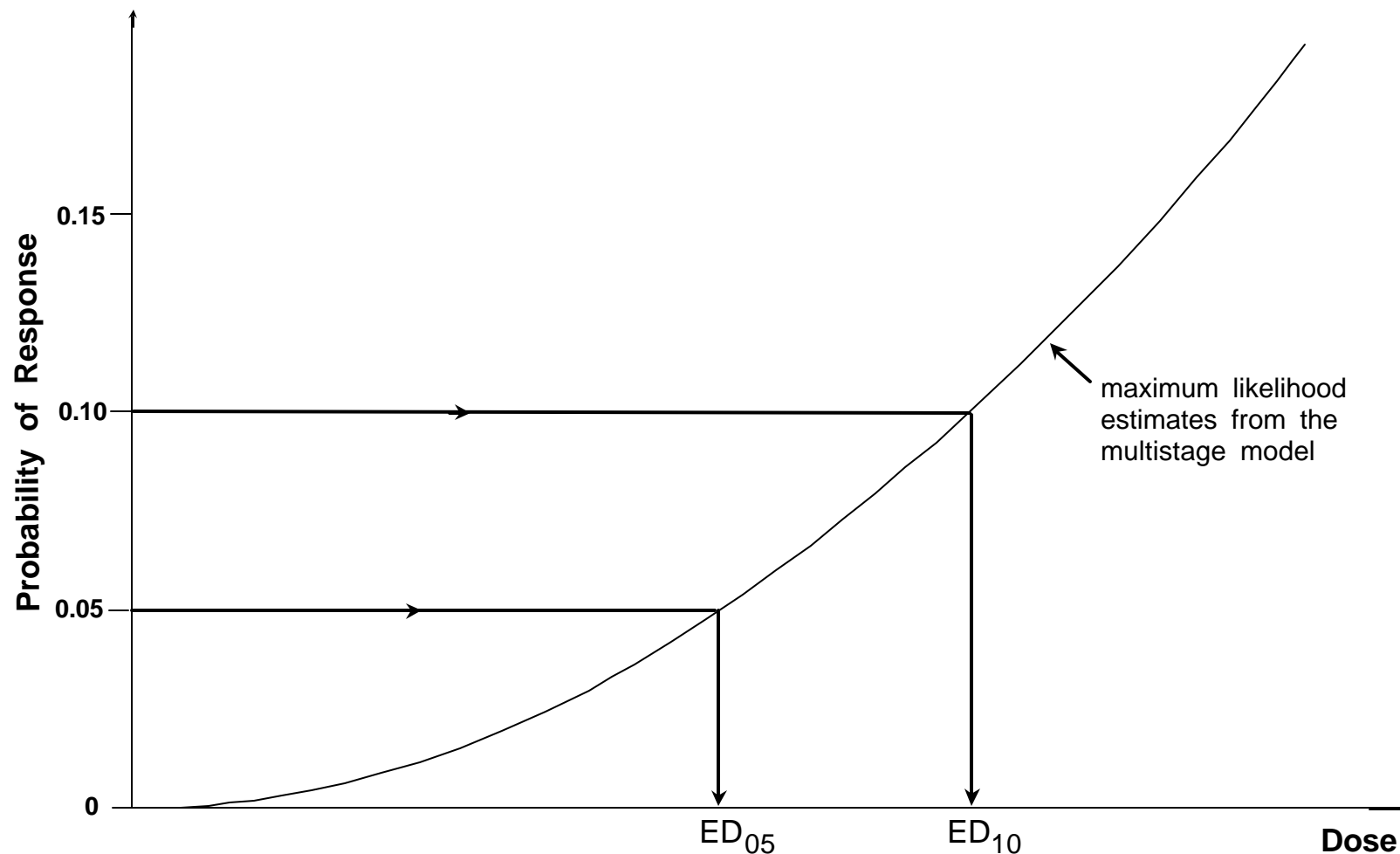


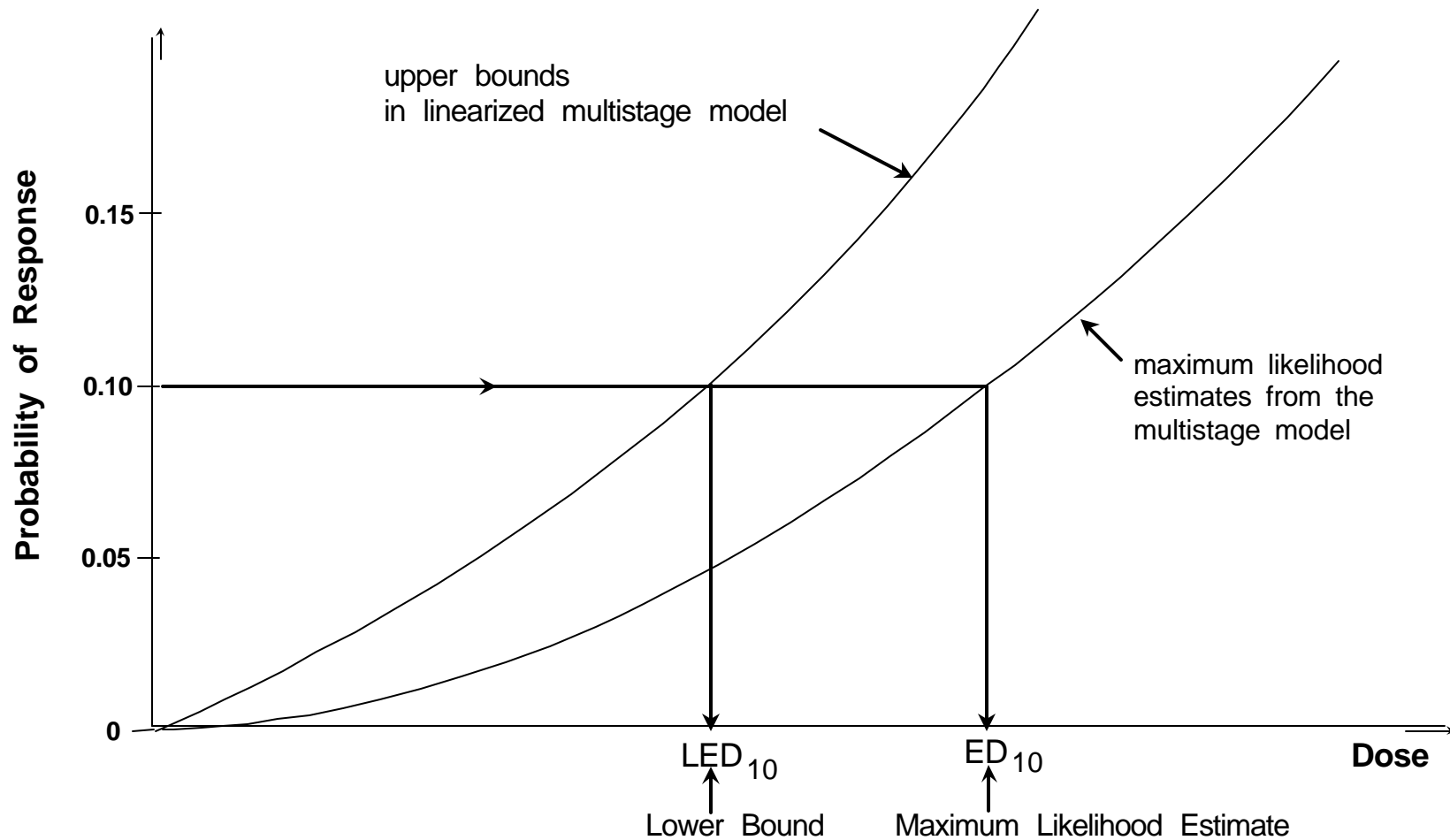
Figure 13. Examples of benchmark doses based on the maximum likelihood estimates of risk in the multistage model



$ED_{10}$  = Estimated dose corresponding to an increase of 0.10 in the probability of the specified response relative to the probability at dose zero

$ED_{05}$  = Estimated dose corresponding to an increase of 0.05 in the probability of the specified response relative to the probability at dose zero

Figure 14. Comparison of the ED<sub>10</sub>, a benchmark dose based on the best fit of the multistage model to the observed data, to the LED<sub>10</sub>, a benchmark dose based on the linearized multistage model's upper bounds on the risk

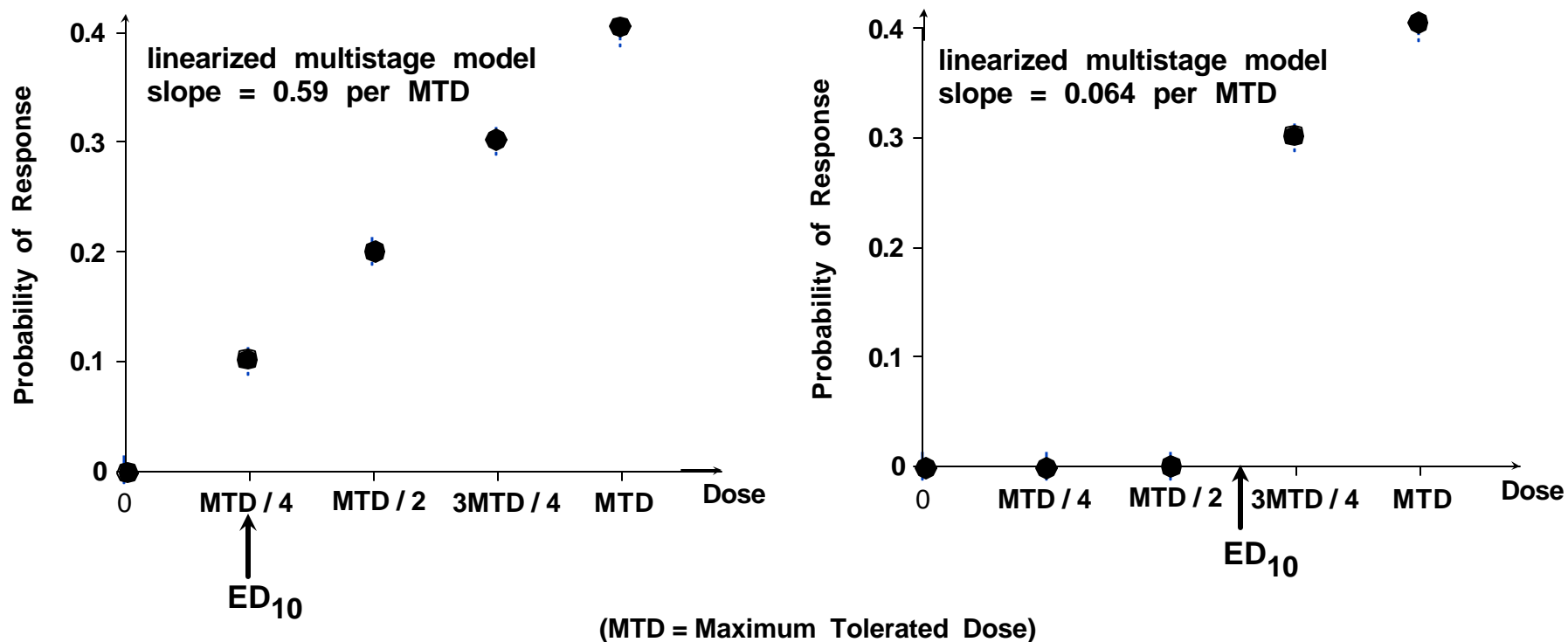


ED<sub>10</sub> = Maximum likelihood estimate of the dose corresponding to an increase of 0.10 in the probability of the specified response relative to the probability at dose zero

LED<sub>10</sub> = Lower bound (95% lower confidence limit) on the dose corresponding to an increase of 0.10 in the probability of the specified response relative to the probability at dose zero

Figure 15. Benchmark doses such as the ED10 are more closely related to the observed dose-response data than the current regulatory potency measures based on the linearized multistage model

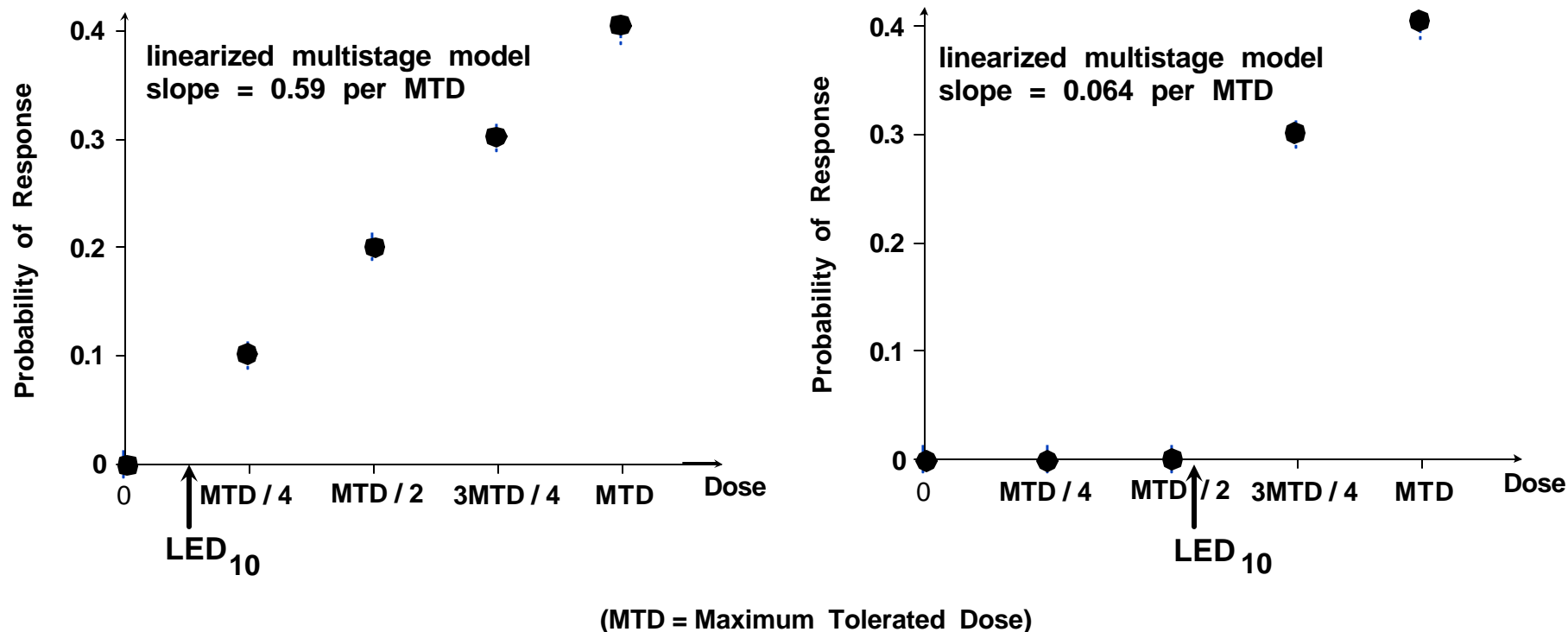
$ED_{10}$  = Maximum likelihood estimate of the dose corresponding to an increase of 0.10 in the probability of the specified response relative to the probability at dose zero



● = hypothetical observed response proportions

Figure 16. Benchmark doses such as the LED10 are more closely related to the observed dose-response data than the current regulatory potency measures based on the linearized multistage model

**LED<sub>10</sub>** = Lower bound (95% lower confidence limit) on the dose corresponding to an increase of 0.10 in the probability of the specified response relative to the probability at dose zero



● = hypothetical observed response proportions