Kan Shao, PhD
Assistant Professor
Department of Environmental and Occupational Health
School of Public Heath
Indiana University
1025 E 7th Street
Bloomington, IN 47405 USA
Tel: (812) 856-2725
Email: kshao@indiana.edu

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Re: Public Comments on NTP Proposed Approach to Genomic Dose-Response Modeling

Comment:

The default BMR proposed by NTP is 1.349 multiplied by estimated SD at zero dose. The justification for this particular choice is that "it approximates a 10% increase in the number of extreme responses of treated groups relative to the response of controls". So, if the BMD is defined by changes in extreme responses on the tails of response distribution, then why not directly use the "hybrid approach" proposed by Crump (1995) which is the origin of EPA's default BMR of one SD?

In EPA's default one SD BMR definition, the "extreme response" is implicitly defined as the 1% above the 99th percentile of the control distribution (for increasing trend data) or the 1% below the 1st percentile of the control distribution (for decreasing trend data). It was not explicitly specified in this document, but based on my calculation, NTP considers responses above 99.5th percentile (for increasing trend) or below 0.5th percentile (for decreasing trend) as "extreme" (corresponding to 1.349*SD). It is OK to use the current BMR definition if constant variance is assumed. However, if "in the future, a non-constant variance will be used in the modeling when appropriate", then 1.349*SD will become inadequate. As pointed out in Shao et al (2013), large variance (a common situation in genomic expression data) can have significant impact on the BMD estimates defined by responses on tails.

The main concern (i.e., discrepancy) is that adversity is defined by the extreme responses on the tails (which is appropriate for genomic expression data) but the BMD is calculated using changes in central tendency.

Reference:

Crump, KS. 1995. Calculation of benchmark doses from continuous data. Risk Analysis. 15 (1): 79–89.

Shao K, Gift JS, Setzer RW. 2013. Is the Assumption of Normality or Lognormality for Continuous Response Data Critical for BMD Estimation? Toxicology & Applied Pharmacology. 272(3): 767-779.