

## **Responses to EPA's clarifications regarding benchmark dose modeling of the Crouse et al. dose-response data by Dr. Alan Stern.**

### **EPA**

The [EPA's Benchmark Dose] guidance's recommendation to be "mindful" of the degree of uncertainty is cautionary rather than prescriptive. That is, the guidance statement on comparing the BMD and BMDL for excessive divergence indicates a way to assess the adequacy of the BMD estimation, not an explicit recommendation to select a BMR only "near the low end of the observable range". The guidance also highlights that "[b]ecause different study designs have different dose selections and different sensitivities (i.e., statistical power) to observe adverse effects at various doses, the low end of the observations can correspond to disparate response levels across studies,...." The intent was not to fix the BMR near the low end of the observable range.

### **RESPONSE**

It is recognized that to some extent benchmark dose modeling is driven by professional judgement. From that standpoint, It is agreed that the EPA's BMD guidance regarding the "distance between" the LOAEL and the BMR is cautionary rather than prescriptive. Given that it seems that the issue here is whether BMD modeling is intended to *per se* model the dose-response, or to address issues regarding the insufficiency of the available dose-response data in the range of interest. If the former (which reflects my understanding of the intent behind EPA's development of its BMDS software), then the BMR should be governed by the data themselves rather than by uncertainty about data gaps in the dose-response range of interest. In that case, concerns about uncertainty are appropriately addressed in the UF adjustments. If the latter, however, the concern on my part is that there are fewer guidelines for how the BMD modeling should be applied and interpreted, and a large amount of weight is placed on less objective professional judgement. In this context, as EPA states, "The intent was not to fix the BMR near the low end of the observable range, " and the question can then be posed as to what general principle did govern EPA's choice of BMR.

### **EPA**

In the cover letter, as well as the table and accompanying text on page 27, lines 24-35, the SAB-CAAC states that the use of a 1% ER BMR constitutes excessive extrapolation below the LOAEL at 8 mg/kg-day with a 15% response. EPA would like to clarify that in general, selecting the BMR based on extrapolation from the LOAEL ignores the dose-response pattern in the data. EPA notes that the 0% response at the NOAEL of 4 mg/kg-day provides an informative limit on the extrapolation. The BMD estimate for the selected model was 3.02 mg/kg-day, which EPA considers near the low end of the observed range.

### **RESPONSE**

In examining the fitted benchmark dose model in Fig. D3 of the supplemental data to the draft RDX Support Document, it does not appear that the data below the LOAEL is informative regarding the dose response pattern of the data below the LOAEL. That is, all one can conclude from the data at doses below the LOAEL is that at some undetermined dose below the LOAEL, the response goes to zero. It should also be noted that in this clarification, EPA states that "The BMD estimate for the selected model ... EPA considers near the low end of the observable range." This is not consistent with EPA's previous

clarification that states that "The intent was not to fix the BMR near the low end of the observable range, "

#### **EPA**

EPA would like to clarify that the BMD technical guidance states (p. 19), "Selecting a BMR(s) involves making judgments about the statistical and biological characteristics of the dataset and about the applications for which the resulting BMDs/BMDLs will be used," that is, weighing both biological and statistical considerations on a case-by-case basis. In this case, frank effects such as convulsions are biologically significant. Additionally, the twofold dose spacing and lack of response at 4 mg/kg-day in the Crouse study support a degree of low dose extrapolation. Note that dose spacing was tenfold in the Cholakis study.

#### **RESPONSE**

The response to this clarification is largely addressed in the first response, above. Also, since we have not recommended BMD modeling of Cholakis et al., it is not clear how the comparative dose spacing in Crouse and Cholakis enters into consideration in the BMD modeling.

#### **EPA**

The recommendations of the SAB-CAAC regarding the selection and application of a BMR for convulsions were guided by the panel's interpretation of EPA's BMD technical guidance. EPA also notes that the BMD technical guidance was not intended to provide specific guidance in selecting BMRs, because of the need to consider biological issues specific to each dataset. EPA would like to suggest that the SAB-CAAC also take into account that identifying a POD for this RfD (an application not specifically addressed by the BMD technical guidance) needs to address a level of exposure that avoids an appreciable risk of convulsions in sensitive human populations. A POD with a 5% response level for a frank effect is essentially a LOAEL, and would still need adjustment to a lower level to avoid this appreciable risk. It seems constructive to avoid an additional uncertainty factor when a dose-response model can provide some clarity. EPA requests the SAB-CAAC consider whether clarification in the draft report is necessary in light of this information.

#### **RESPONSE**

EPA states that, "A POD with a 5% response [as recommended in our draft report] level for a frank effect is essentially a LOAEL." The basis for this statement is not clear. The response at the LOAEL in Crouse is 15%. Thus, a 5% response would not be a LOAEL. If EPA's intent is to say that a 5% response for a frank effect is *too close* to the LOAEL to be protective, then I think that we and EPA are in essential agreement. The disagreement here (and basically in all of these discussions about the application of BMD modeling to the Crouse data) is, as described in the response above to the first BMD clarification, whether the role of dose-response analysis, including BMD modeling, should be to address uncertainties in the dose-response data.