Approaches to Human Health Risk Assessment Based on the Signal-To-Noise Crossover Dose

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We acknowledge the effort of Sand et al. (2011) in striving to develop a transparent, objective procedure for point of departure (POD) estimation, as encouraged by scientific review groups (National Research Council 2009). Although additional characterization of the statistical properties of the signal-to-noise crossover dose (SNCD) may be warranted, the goal of Sand et al. (2011) appears consistent with the intent of the POD to characterize "the beginning of extrapolation to lower doses" [U.S. Environmental Protection Agency (EPA) 2005]. In this letter we respond to the authors' illustration of their approach using cancer bioassay data to develop reference doses (RfDs) that target a 1/1,000 risk through linear extrapolation from the POD by highlighting opportunities to augment their statistically based approach with biological considerations.

For most carcinogens, the U.S. EPA develops cancer potency estimates as follows (U.S. EPA 2005). A POD associated with a benchmark response level (BMR) is derived and converted to human-equivalent units (incorporating information about cross-species dose scaling). The BMR is then divided by the human-equivalent POD to obtain a potency estimate, under the assumption that risks extrapolate linearly with doses below the BMR. For Sand et al. (2011), the upper-bound extra risk estimate (UER_{SNCD}) is the BMR associated with the SNCD, but we recommend expressing SNCDs in human equivalents before deriving potency estimates.

For nonlinear extrapolation resulting in a RfD (which the U.S. EPA uses for noncancer effects and carcinogens with a threshold mode of action), Sand et al. (2011) chose to linearly extrapolate to a 1/1,000 risk in the test animal, which they considered analogous to applying a 100-fold uncertainty factor to a $BMDL_{10}$ (lower bound on the benchmark dose corresponding to 10% extra risk). Several aspects of this proposal merit further consideration. First, margins of exposure much larger than 100-fold would be typical for cancer. Furthermore, whereas linear extrapolation involves extrapolation in the same population to a smaller level of effect, the standard uncertainty factor approach involves extrapolation across populations at a fixed level of effect. The alternative we propose separately accounts for these biologically unrelated processes.

Motivating our proposal is the need highlighted by Sand et al. (2011) to clearly separate statistical factors supporting the level of effect associated with the POD while also fully incorporating biological considerations. We propose specifying "target" effect levels (TELs) associated with different end points based on biological considerations, independent of data set. The TELs could then be compared with the lowest practical BMR for a given data set—the UER_{SNCD} used by Sand et al. The UER_{SNCD}/TEL ratio is a diagnostic of the extent of extrapolation to the TEL. If $UER_{SNCD} \leq$ TEL, then the BMD at the TEL does not involve extrapolation and can serve as the POD. For a $UER_{SNCD} >$ TEL, the greater the ratio, the greater the uncertainty in the BMD at the TEL from extrapolation below the SNCD. In this case, the SNCD could serve as the POD, and the gap between the UER_{SNCD} and the TEL could be bridged by an additional factor (analogous to the LOAEL-to-NOAEL factor) or linear extrapolation. Then, interspecies, intraspecies, and any other adjustments for deriving RfDs would be applied as usual. Thus, this approach separately takes into account biological considerations related to the severity of the end point (via the TEL), statistical considerations related to the study data (via the UER_{SNCD}), and adjustments from the test species to sensitive humans (via uncertainty factors or chemical-specific adjustments).

In sum, the work of Sand et al. (2011) advances the development of approaches for providing a transparent, objective method to demark where "extrapolation begins." However, for human health risk assessment, we propose augmenting statistically based approaches so that inter- and intraspecies adjustments and biological considerations relating to the end points are explicitly addressed. Although consensus on specifying TELs may be challenging, particularly for precursor or toxicogenomic end points, clearly separating biological and statistical considerations will enhance the transparency and consistency of chemical assessments.

The views in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

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References

National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC:National Academies Press.

Sand S, Portier CJ, Krewski D. 2011. A signal-to-noise crossover dose as the point of departure for health risk assessment. Environ Health Perspect 119:1766–1774.

U.S. EPA (U.S. Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Washington, DC:U.S. EPA. Available: http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.pdf [accessed 8 June 2012].

Signal-To-Noise Crossover Dose: Sand et al. Respond

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We appreciate the opportunities highlighted by Chiu et al. to augment the concept of the signal-to-noise crossover dose (SNCD) (Sand et al. 2011) with biological consideration. In similarity to our interpretation of the SNCD concept, Chiu et al. note that our approach provides a transparent and objective method to demark where extrapolation begins and that it appears consistent with the intent of the point of departure (POD) to characterize "the beginning of extrapolation to lower doses" (U.S. Environmental Protection Agency 2005).

In our article (Sand et al. 2011), we compared the SNCD with traditional PODs used in risk assessment [i.e., the benchmark dose (BMD) and the no observed adverse effect level (NOAEL)]. In addition, we compared human exposure guidelines [generally referred to as reference doses (RfDs) in our article] resulting from using the SNCD, the BMD, and the NOAEL as PODs. The SNCD-based exposure guideline was derived by linear extrapolation from the upper bound on extra risk at the SNCD (UER_{SNCD}) down to a target risk of 1/1,000. When considering new risk assessment strategies, an initial step is to address how they compare against more traditional approaches. The specific settings we used in the derivation of the SNCD-based exposure guideline were selected primarily as a result of such considerations; that is, using these settings, the SNCD concept can be compared to more standard BMD and NOAEL approaches at the level of the human exposure guideline in a calibrated manner, providing a starting point for further discussion.

In our article (Sand et al. 2011) we suggested that further development of the SNCD concept could involve the use of alternative target risks (e.g., based on public health considerations, as well as alternative low-dose extrapolation models), and we also pointed out that animal-to-human extrapolation may be regarded as a separate step after the SNCD-based POD has been established. This appears to be in line with the developments proposed by Chiu et al. in their letter. Generally speaking, they suggest an approach that separately takes into account biological considerations related to the severity of the end point via the target effect level (TEL), statistical considerations related to the study data via the UER_{SNCD}, and adjustments from the test species to sensitive humans, after the POD associated with the TEL has been derived, via uncertainty factors or chemical-specific adjustments.

Chiu et al. suggests in more detail that if $UER_{SNCD} < TEL$, the POD corresponding to that TEL can be derived directly, whereas the case $UER_{SNCD} > TEL$ indicates that low-dose extrapolation from the SNCD is required to reach the dose associated with the TEL (where UER_{SNCD}/TEL measures the extent of extrapolation). In principal, this appears reasonable provided that the SNCD concept is generalized to any type of response data (i.e., not only cancer, but continuous or quantal end points in general). The SNCD may then represent a starting point for low-dose extrapolation when the upper bound on risk (extra risk) or continuous effect (e.g., relative effect) at the SNCD is higher than what is considered acceptable from a biological or risk management point of view; although TELs should ideally be fully biologically based, a certain level of policy is likely to be involved, including use of default values. It remains to be seen in practice how the SNCD compares with PODs corresponding to default benchmark response (BMR) levels, TELs, or other such measures, for various types of response data.

We are in the process of extending the comparison of different PODs performed in our previous study (Sand et al. 2011) to the case of high throughput screening data. Accounting for the severity of effect for such data is a major challenge, for example, using a TEL/BMR concept or perhaps requiring development of multivariate/multidimensional extensions thereof. We agree that separating biological and statistical considerations will enhance the transparency and consistency of chemical assessments.

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References

Sand S, Portier CJ, Krewski D. 2011. A signal-to-noise crossover dose as the point of departure for health risk assessment. Environ Health Perspect 119:1766–1774.

U.S. EPA (U.S. Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Washington, DC:U.S. EPA. Available: http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.pdf [accessed 8 June 2012].