

James S. Bus, Exponent, Inc., on behalf of LyondellBasell: Oral clarifying comments on the EPA Science Advisory Board discussions of the draft EPA IRIS Toxicological Reviews of Ethyl Tertiary Butyl Ether (ETBE) and *tert*-Butyl alcohol (tBA).

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During its March 22 meeting the EPA SAB discussed the important issue of whether it was within EPA policy and guidance to include derivation of alternative RfD or RfC values based on endpoints other than kidney, even though those endpoints have Point of Departure doses that may be greater than the kidney response. As noted in previous LyondellBasell written and oral comments, inclusion of alternative endpoints is particularly important for ETBE and TBA because of the clear lack of consensus regarding the human relevance of the kidney toxicity findings. To further clarify this issue, we note that various EPA policy and guidance documents encourage use of multiple endpoints in development of RfD and RfC values in order to adequately characterize uncertainties and avoid potential misinterpretation of potential health risks.

First, the IRIS Preamble<sup>1</sup> itself states that candidate values, defined as RfC, RfD and cancer slope factors, should be derived from each “suitable data set” and should include organ- and system-specific values in order to “cover all health outcomes.”

Second, a 2002 EPA Risk Assessment Forum report<sup>2</sup> addressing processing for derivation of RfD and RfC values concludes that “...presenting only a single critical effect and the critical study from which it was derived ...could be misleading” to the “...reader who is unfamiliar with the risk assessment.”

Third, the 2014 EPA Framework for Human Health Risk Assessment to Inform Decision Making<sup>3</sup> specifically notes that “a key question addressed in the risk characterization is whether the risk assessment would change if the data were interpreted differently,” and that “it is essential, however, to describe uncertainty and variability so that the impact will not be overlooked or misinterpreted.”

Fourth, the EPA 2005 Cancer Risk Assessment guidance<sup>4</sup> states that when there are alternative procedures that are biologically supported, the Agency encourages assessments be performed using these alternatives in order to shed light on the uncertainties of the risk assessment.

Finally, as an example of the practical implementation of the above policies and guidance, LyondellBasell refers the SAB to the EPA IRIS review of benzo[a]pyrene<sup>5</sup> issued in 2017 in which multiple RfD values are developed, and importantly, ranked with respect to confidence in the scientific underpinnings of each of the derived values.

In conclusion, LyondellBasell offers these comments to clarify that EPA guidance documents strongly encourage derivation of RfD and RfC values that are based on multiple endpoints in order to adequately capture the range of uncertainty and confidence in deriving final values that are appropriately protective of human health.

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<sup>1</sup> IRIS Preamble, Section 7, General Approach

<sup>2</sup> EPA Risk Assessment Forum. A review of the reference dose and reference concentration processes. EPA/630/P-02/002F, December, 2002.

<sup>3</sup> EPA Risk Assessment Forum. Framework for Human Health Risk Assessment to Inform Decision Making. EPA/100/R-14/001, April 2014.

<sup>4</sup> EPA Risk Assessment Forum. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F, March, 2005.

<sup>5</sup> EPA IRIS. Toxicological Review of Benzo[a]pyrene, January, 2017.