EPA's Response to Selected Interagency Comments on the Final Interagency Science Discussion Draft of the IRIS Toxicological Review of Methanol (noncancer)

September 2013

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where the Executive Office of the President and other federal agencies can comment on draft assessments. Comments on the Final Interagency Science Discussion drafts of the IRIS Toxicological Review of Methanol (noncancer) and IRIS Summary for Methanol (noncancer) (Step 6b) were provided by the National Institute for Occupational Safety and Health (NIOSH) and Centers for Disease Control and Prevention /Agency for Toxic Substances and Disease Registry (CDC/ATSDR) and the Council on Environmental Quality (CEQ). Most of the comments were editorial in nature and were appropriately incorporated into the assessment. The following are EPA's responses to selected interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to posting on the IRIS database.

For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

Selected Interagency Science Discussion Comments and Responses:

Topic #1: Overall Comments – *In general, the interagency reviewers indicated that EPA revisions to the methanol (noncancer) assessment were appropriate and responsive to prior review comments. NIOSH also commented that "the Toxicological Review and IRIS Summary are logical, clear, and concise with appropriate tables and figures."*

EPA Response: No response required.

Topic #2: Neurotoxicity – *NIOSH requested that a supporting reference for statements about acute central nervous system (CNS) toxicity in humans be added to the first paragraph in the Hazard Identification section of the Executive Summary. With regard to discussions in Section 4.4.2 of the toxicological review, NIOSH agreed with EPA that "stellate cell responses" reported by NEDO (1987) in subchronically and chronically exposed monkeys are likely "astrocytes" and provided two references, Sofroniew and Vinters (2010) and O'Calaghan and Sriram (2005), to support that the presence of hypertrophic astrocytes are evidence of CNS injury.*

> **EPA Response:** A supporting reference was added to the first paragraph of the Hazard Identification section of the Executive Summary. Text has also been added to the existing discussion in the toxicological review (Section 4.4.2) of the potential relevance of the stellate cell response reported by NEDO (1987). The added text cites the two studies provided by NIOSH as indicating that the presence of hypertrophic astrocytes would be evidence of CNS injury.

Topic #3: Clarification on Model Sensitivity – *CDC/ATSDR requested that EPA provide "…further clarification that the model is likely sensitive to a change in the RfC or RfD for a population, but not for an individual" in EPA's response to external peer review and public comments.*

> **EPA Response:** Text has been added to the responses to peer review (A.1. of appendices) and public comment (A.2.2. of appendices) to clarify that the population shift analysis that ATSDR commented on was presented as an example which illustrates that daily exposures of the entire population to methanol at the RfC or RfD exposure is estimated to increase the percentage of individuals with peak methanol blood levels at or above 2.5 mg/L from ~7% to ~14%. The EPA responses also state that "these estimates are not precise and do not account for interindividual variability." Clarifying text was also added to the Executive Summary and Section 5.3.6 of the toxicological review.