

National Institute for Occupational Safety and Health (NIOSH) Comments on the Interagency Science Discussion Draft IRIS assessment of Methanol (Noncancer) (dated July 2013)

Date: August 23, 2013

Informal Comments on the Draft Toxicological Review and IRIS Summary on Methanol (noncancer) August 23, 2013

The National Institute for Occupational Safety and Health (NIOSH) thanks the U.S. Environmental Protection Agency (EPA) for the opportunity to comment on the July 2013 draft Toxicological Review and Integrated Risk Information System (IRIS) Summary on Methanol (noncancer). The comments are from one NIOSH subject matter expert.

Overall Comments

1. The Toxicological Review and IRIS Summary are logical, clear, and concise with appropriate tables and figures. The review presents the essential elements of the risk assessment. Items based on the best available information and EPA policies and guidelines include: a) inhalation rather than oral route data; b) critical effects associated with methanol exposure; c) methods of assessments; d) selection of uncertainty factors; e) use of a modified and restructured physiologically-based pharmacokinetic (PBPK) model for route-to-route extrapolations and predicting the pharmacokinetics of methanol in humans.
2. The revised draft Toxicological Review and IRIS summary (inhalation) adequately address most comments from external and public reviewers.

Specific Comments

1. List of Abbreviations: NIOSH is the National Institute **for** Occupational Safety and Health.
2. The first paragraph in the Hazard Identification section (page xx) needs a supporting reference for statements about acute central nervous system (CNS) toxicity in humans.
3. Section 4.4 Neurotoxicity:
 - a. The term “stellate cells of the CNS” is somewhat unusual because stellate cells usually refer to the mesenchymal cells of the liver located in the space of Disse that when activated can produce liver fibrosis due to the production of collagen. Use of “stellate cells of the CNS” and “fibrosis of responsive stellate cells” as evidence of “neurological disease” rather than hypertrophy of astrocytes (star-shaped glial cells) in response to injury may be due to translation from Japanese

to English or a nomenclature issue (page 4-51, lines 18–31). Also, the New Energy Development Organization (of Japan) (NEDO) monkey study uses inconsistent terminology when describing “stellate cell responses” (e.g., “degree of hyperplasia” versus “degree of fibrosis”.) Thus, whether this nomenclature reflects the same phenotypic change is unknown. The toxicological review is likely correct in interpreting the statements concerning “stellate cells” as referring to an astrocyte response to the putative CNS injury caused by methanol exposure. The presence of hypertrophic astrocytes is considered evidence of CNS injury [Sofroniew and Vinters 2010].

- b. Page 4-52, lines 26–30: note that to determine the neurotoxic potential of an agent, it is not necessary for the astrocyte response to persist after neurodegeneration has occurred [O’Callaghan and Sriram 2005].
- c. The database uncertainty value (UF_D) is set at 3 and this level is deemed appropriate although a 3-fold uncertainty factor was previously criticized by several reviewers as being too high. The UF_D level was questioned because the extant toxicological database for methanol is extensive. Further, the Burbacher et al. and NEDO primate studies were considered valid and robust enough to serve as support for the use of the NEDO rat study brain weight data to derive the RfC. However, the response provided by EPA in Section 5.1.3.2.3 and in the Appendices of the Toxicological Review (A-35) provides sufficient additional rationale for the UF_D to remain at 3-fold. EPA considers the existing database to be deficient in relevant neurotoxicological data. Thus, a 3-fold UF_D allows for a lowered RfD/RfC, providing for a greater margin of health protection.

References

O’Callaghan JP, Sriram K [2005]. Glial fibrillary acidic protein and related glial proteins as biomarkers of neurotoxicity. *Expert Opin Drug Saf* 4(3):433–442
[<http://informahealthcare.com/doi/abs/10.1517/14740338.4.3.433>].

Sofroniew MV, Vinters HV [2010]. Astrocytes: biology and pathology. *Acta Neuropathol* 119:7–35.