

## Clarifications/Comments for the SAB Draft Peer Review Report on Ammonia: Public Teleconference

December 17, 2014

- We'd like to note that it would be most helpful in moving forward with implementing the panel's advice if the peer review report is specific on which recommendations are intended for the ammonia assessment to be implemented now and which recommendations are for future assessments (e.g., strategy for screening studies for relevance, application of study quality criteria, core elements considered in the overall evaluation of the evidence).
- Throughout the draft report the panel has included bracketed notes highlighted in yellow. In each of these instances, EPA agrees that the specified additional information would be very helpful.
- p. 24, lines 37-38: The panel identified 3 additional lines of evidence to consider in the evaluation of carcinogenicity. More detailed information on the 3<sup>rd</sup> line of evidence would be helpful: "clinical experience of high serum levels of ammonia not associated with cancer (Cooper, personal communication)."
- pp. 28-29, and pp. 34-35. Could the panel be more specific in their recommendations related to hyperammonemia and hyperammonemic encephalopathy?
  - To what extent should the Tox Review provide additional consideration of the results of experimental models that simulate hyperammonemia and encephalopathy?
  - To what extent are models that produce hyperammonemia in rats relevant to an assessment of chronic oral or inhalation exposures?
  - How much additional discussion (beyond what's in the Tox Review currently) on hyperammonemia associated with clinical disease is needed?
- p. 28, lines 35-36: Report notes systemic effects following oral ingestion of ammonia such as erythematous/edematous effects on the lips and drooling. Does the panel consider these to be systemic effects?
- p. 37, line 19 – p. 39, line 19: The report includes a fairly lengthy discussion of endogenous production. Could the panel be more specific in their recommendations for how to revise the Tox Review on this topic?
- p. 39, line 21 – p. 40, line 35. The report includes a fairly lengthy discussion of ammonia in expired air. In their concluding paragraph of this section, the panel notes that: "In conclusion to this section, there is no doubt that ammonia in expired breath is increased in pathological conditions (such as liver disease) that give rise to hyperammonemia. However, because of confounding problems with "contaminating" ammonia in the expired air and difficulties associated with its actual measurement, it may be challenging to correlate prior chronic exposure of individuals to ammonia with alveolar ammonia concentrations."
  - Could the SAB/CAAC be more specific in their recommendations?
  - EPA would like to clarify: discussion of ammonia in expired air in the Tox Review was not intended to establish a correlation between prior exposure of individuals to ammonia and alveolar ammonia concentrations or concentrations in exhaled breath, rather it was intended to provide context for the draft RfC, which falls within the range of concentrations in breath exhaled from the mouth.