TBAC Peer Consultation Panel Charge Questions

1) Were the following toxicology tests for tertiary-butyl acetate (TBAC) performed in accordance with the agreed upon protocols and best laboratory practices?

- WIL Research Labs. (2006a). A 13-week subchronic inhalation toxicity study of tertiary-butyl acetate in CD-1 mice. Report WIL-14061. October 31, 2006.
- WIL Research Labs. (2006b). A combined 13-week subchronic inhalation toxicity study and reproductive toxicity screening test of tertiary-butyl acetate in rats. WIL-14060. October 31, 2006.
- WIL Research Labs. (2008). A Toxicity Study of Tert-Butyl Acetate (TBAC) in Mated Female Rats. WIL-14069. September 2, 2008.
- WIL Research Labs (2007). A Two-week Inhalation Toxicity Range-finding Study of Tertiary-Butyl Acetate in CD-1 Mice. WIL-14053. March 6, 2007.
- ILS Inc. (2006) Quantitation of the Concentration of a2u-Globulin in Kidneys from Male Rats Exposed to Tertiary-Butyl Acetate (TBAC). ILS Study No.:C145-001. May 24, 2007.

2) Are there sufficient data to determine if tertiary-butyl alcohol (TBA) or TBAC are genotoxic or mutagenic? Does the weight of the evidence support the conclusion that either TBA or TBAC are genotoxic or mutagenic?

3) In previous chronic testing of TBA (NTP 1995), an increase in renal tumors in male rats was observed. Are the previous TBA data and the results of the 2006 toxicology tests for TBAC adequate to support the conclusion that a) the observed increase in renal tumors in male rats due to TBA exposure is related to the α2μ-globulin mode of action; b)that TBAC is likely to act by the same mechanism; and, c) that the renal tumors observed in male rats with TBA and, potentially, for TBAC are not relevant for human risk assessment? If these data are not adequate, what further tests are recommended to understand these effects?

4) In previous chronic testing of TBA (NTP 1995), a slight increase in mouse thyroid tumors was observed at the highest dose. Do the 2006 toxicology tests for TBAC provide any clues as to a potential mode of action for thyroid tumor formation or suggest that TBAC would also induce these tumors in mice? Are additional tests necessary to support or refute this conclusion? If so, which ones?

5) Do the 2006 toxicology tests and metabolic data for TBAC suggest that there are sufficient similarities between the toxicities of TBA and TBAC to allow the use of TBA chronic data to estimate TBAC chronic risks? Given the existing data for chronic exposure to TBA (NTP, 1995; 1997), the genotoxicity data for TBA and TBAC, and the metabolic data for TBAC, does the existing evidence support classifying either TBA or TBAC as human carcinogens? Is a 2-year bioassay for TBAC needed to make this determination, or is the existing evidence sufficient?

6) In the previous chronic testing of TBA and the 2006 toxicology tests for TBAC, effects on the liver were observed. Are the observed liver effects sufficiently similar to indicate a common mode of action (MOA) for TBA and TBAC? Given the metabolic and toxicokinetic profile of TBAC, do the data suggest that TBAC is acting through the TBA metabolite? If the data are not adequate to make this determination, what further tests could be conducted to reduce the uncertainty?

7) Do the data (including the 2006 toxicology tests for TBAC focused on the estrous cycle) support the conclusion that reproductive toxicity is not a key concern for TBAC? Do the data suggest that TBA or TBAC have an effect on reproductive or developmental function or induce hormonally-mediated reproductive effects? Are further tests required to reduce the uncertainty?

8) Do the data (including the 2006 immunotoxicology tests for TBAC and database for TBA immunotoxicity) suggest immunotoxicity concerns for TBAC? If so, are further tests required to understand these effects?

9) The assessment concludes that transient clinical signs of hyperactivity is the critical effect (i.e., lowest observed adverse effect) for calculation of toxicity reference values for TBAC. Is the selection of this as the critical effect for calculating reference values correct and supported? If not, what endpoint should be used?

10) In the Hazard Assessment for TBAC, were the acute and chronic toxicity reference values calculated in an appropriate manner?

11) In the assessment document, are the uncertainties fully described and appropriately characterized?

12. Are there additional issues or questions related to the toxicity or risk characterization of TBAC that should be discussed?