June 3, 2014
Lori White, Designated Federal Officer for the BSC
Office of Liaison, Policy and Review, Division of NTP
NIEHS
P.O. Box 12233, K2-03
Research Triangle Park, NC 27709

Re: Comments regarding NTP Research Concept for Alkylbenzenes for the NTP Board of Scientific Counselors Meeting June 17-18, 2014

Dear Dr. White:

The American Chemical Council's Cumene Panel (the "Panel") appreciates the opportunity to comment on NTP's Research Concept for Alkybenzenes. After evaluation of the NTP Research Concept for Alkylbenzenes, the Panel takes exception to the reference of cumene as one of the isomers of the C9 fraction with carcinogenic activity. Also, the weight of evidence does not support the reference to cumene as "recommended for listing as reasonably anticipated to be a human carcinogen" in the 13th Report on Carcinogens (RoC; page 4) is warranted.

Significant concerns have been raised about the scientific integrity, credibility and relevance of the scientific evaluation process used in the 12th RoC.[1] The current approach employed by NIEHS/NTP for RoC evaluations does not meet HHS's Policies and Principles for Assuring Scientific Integrity. To address the shortcomings of the current RoC process, the National Academies of Science (NAS) was charged with examining the scientific evaluation policies and procedures employed by NTP for data evaluation, for integrating studies to weigh the overall evidence for determining cause and effect, and the criteria for determining the potential for carcinogenic hazards to humans at environmentally relevant levels of exposures. Over the next few months, the NAS is scheduled to release a scientific peer review of the 12th RoC determinations related to formaldehyde and styrene and the scientific rigor of the RoC evaluation and review processes. The current 13th RoC assessment process reflects the same deficiencies as the 12th RoC, including a strength of evidence approach which uses default options over data and over-relies on opaque study integration procedures in lieu of an objective and transparent weight of evidence evaluative framework which uses mode of action as its central organizing principle.

The 13th RoC proposes cumene to be listed as "reasonably anticipated to be a human carcinogen based on sufficient evidence in experimental animals" even though there is considerable evidence, documented in NIEHS/NTP's own analysis, which shows cumene is likely not genotoxic and that the documented cumene-induced kidney tumors in male rats and lung tumors in mice likely occur via modes of action that are not relevant to humans.[2] The authors of the NTP Cumene Monograph concluded that

cumene showed clear evidence of carcinogenicity based on rodent bioassays which identified male and female mouse lung tumors, female mouse liver tumors, and male rat kidney tumors. Mode of action (MOA) investigations of cumene and structural analogs (e.g., ethylbenzene, styrene, etc.) suggest a high plausibility that the three tumor findings of concern are likely mediated through non-genotoxic MOAs and are of questionable qualitative and/or quantitative relevance to human cancer outcomes. The male rat kidney toxicity and resulting tumors fit the alpha-2u-globulin MOA. This MOA does not occur in humans and, therefore, these tumors are not relevant for human risk assessment. [3]

The mouse lung tumors are mediated through species specific metabolic activation via CYP2F2 that induces a non-genotoxic and cytotoxic, cell-regenerative MOA that is quantitatively and likely qualitatively irrelevant to human lung toxicity and cancer.[4] Species differences observed between mouse and rat are likely attributed to different enzymatic metabolism by CYP2F2 in mouse and CYP2F4 in rat. The human counterpart, CYP2F1, is much less prevalent in these tissues and is much less effective at metabolizing these compounds than either 2F2 or 2F4.[5] Therefore, this MOA is of low relevance for humans.

In addition, mouse liver tumors are plausibly mediated through a phenobarbital-like liver enzyme induction MOA that is not a quantitatively relevant cancer hazard to humans. Cumene-induced tumors were associated with the hallmark features of a phenobarbital-like enzyme induction MOA that has been qualified as to its kinetic and quantitative relevance to human tumor outcomes.[6] Those features include rapid and early onset of liver enlargement; evidence of saturated metabolism leading compensatory induction of CYP2B1/2B2; association of tumors with eosinophilic foci (a biomarker of this mode of action); and late developing tumors. Both these features and several additional features of a phenobarbital-like MOA for cumene are further informed by read-across information from close structural analogs ethylbenzene, 1-phenylethanol, and n-propylbenzene including increased mitogenic cell replication at tumorigenic doses; evidence of saturated P450 metabolism at tumorigenic doses; confirmed induction of CYP2B related enzymes; and increased liver hypertrophy.

In conclusion, when knowledge of MOA is used as the central organizing element, the weight of evidence shows cumene is not genotoxic, that the induction of rat kidney tumors occurs by accumulation of alpha-2-urinary globulin (a conclusion that the NTP supported in its 2-year carcinogenicity assessment of cumene19 – NTP TR-542), a species-specific MOA that does not operate in humans, and that mouse lung tumor induction is also entirely consistent with a species specific mode of action that does not operate in humans.[7] The species and organ-specific nature of cumene-induced rodent tumors (the MOA which have been well characterized in published literature) is not consistent with the RoC's recommendations that the multi-organ nature of these tumors is "sufficient evidence of carcinogenicity." Therefore, the overall evidence-based assessment of cumene by NTP does not fulfill the expectation that cumene should be "reasonably anticipated to be a human carcinogen".

The American Chemistry Council Cumene Panel appreciates the opportunity to submit these comments. If you have any questions, please contact Angela Lynch at 202-249-6708 or Angela_Lynch@americanchemistry.com.

Sincerely,

[Redacted]

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References

1) Letter from Cal Dooley, ACC CEO to HHS Secretary Sebelius dated May 24, 2012
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5) Cruzan, G, Bus, J. Hotchkiss, J, Sura, R, Moore, C, Yost, G, Banton, M, Sarang, S. Studies of styrene, styrene oxide and 4-hydroxystyrene toxicity in CYP2f2 knockout and CYP2F1 humanized mice support lack of human relevance for mouse lung tumors. Reg. Toxicol. Pharmacol., 2013
6) Holsapple, M, Pitot, H, Cohen, S, Boobis, A, Klaunig, J, Pastoor,T, Dellarco, V, Dragan, Y. Mode of action in relevance of rodent liver tumors to human cancer risk. Tox. Sci. 89: 51-56, 2006
7) NTP Technical Report on the Toxicology and Carcinogenesis Studies of Cumene (CAS NO. 98-82-8) in F344/N Rats and B6C3F1Mice (Inhalation Studies). February 2009. http://ntp niehs nih.gov/files/542_final_web.pdf