Statement of Kevin L. Bromberg
Assistant Chief Counsel for Environmental Policy
Office of Advocacy
US Small Business Administration

Before the EPA Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC) Reviewing ETBE and tBA

August 15, 2017

These comments are submitted on behalf of the US Small Business Administration Office of Advocacy (Advocacy) with respect to the most recent draft assessment of ETBE and tBA, now being reviewed by the SAB Chemical Assessment Advisory Committee (CAAC) assigned to this task This draft assessment was developed after the June 2016 IRIS public meeting which preliminarily addressed the hazard assessment issues presented in today's meeting. Although EPA has made vast improvements in the IRIS process over time, including providing for substantial public input both before and after the development of the draft assessment, the agency has fallen short in incorporating the public advice, and implementing IRIS procedures. We have several suggestions for improvement.

In particular, we note that EPA continues to have difficulty with literature search strategy implementation and documentation, in responding to public comments, and providing transparency behind its scientific judgments. In addition, we suggest an improvement in one of the charge questions that would improve the peer review process.

I. Literature Search Strategy/ Study Selection Review Charge Question:

The EPA IRIS program presents the standard softball literature search question used in some previous reviews, but this question was substantially improved in at least two recent IRIS reviews:

Current Question #1:

> **Please comment on the strategies for literature searches, criteria for study inclusion or exclusion and evaluations of study methods and quality discussed in the Literature Search Strategy/Study Selection and Evaluation section. Were the strategies clearly described and objectively applied?**

We suggest a more robust literature search question based on the question from BaP and ammonia reviews employed by the SAB in 2014 after modifying the question above:

Proposed Revised Question #1:

> The process for identifying and selecting pertinent studies for consideration in developing the assessment is detailed in the *Literature Search Strategy/Study Selection and Evaluation* section. Please comment on whether the literature search approach, screening, evaluation, and selection of studies for inclusion in the assessment are clearly described and supported. **Please comment on whether EPA has clearly identified the criteria (e.g., study quality, risk of bias) used for selection of studies to review, the influential studies to select for inclusion in the assessment, and the key studies used in the development of reference values. Can you recommend improved approaches or criteria to be employed by the agency? (bolded for emphasis)** Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of tBA and ETBE.

This revised question asks whether EPA should have chosen a different approach, and how can the approach be improved. This question addresses whether EPA selected the correct criteria for screening, evaluation and selection. This question specifically asks about the selection of studies for the development of reference values. This question requests the identification of missing peer-reviewed studies, although later charge questions may remedy this omission in part.

Using a robust question is an opportunity to improve the assessment taken by the BaP and Ammonia panels not taken by this panel. EPA has the opportunity to perform an improved literature search/study selection based on peer review advice.

The identification of the appropriate literature and identification of the key studies for development of reference values, for example, is extremely important, and yet the EPA question did not yield significant substantive advice on these issues. See attached responses in the back of this testimony.

These are not surprising responses from this question posed by the IRIS program which focuses on "clear" descriptions "objectively" applied. We highly recommend that this panel revise the peer review question.

II. Kidney Effects in Humans Not Scientifically Supported for tBA/ETBE

There was considerable discussion in the June 30th IRIS public science meeting by experts explaining that EPA had misinterpreted and misapplied the rat kidney studies, and that all the data are explained by other modes of action that were not relevant to humans. According to some knowledgeable comments, EPA has failed to properly address these issues in the new draft assessment. Here is an excerpt from Dr. Sam Cohen's written TBA

comments today (Dr. Cohen was a participant in the recent pathology working group organized for TBA):

Following is a summary of the comments that I made at the IRIS Public Science Meeting held on June 30, 2016 on tert-butyl alcohol (TBA). Most of my comments regard the male rat kidney issue, but I will also provide a few comments regarding the mouse thyroid.

With respect to the rat kidney, it is my impression that the report needs to be completely redrafted, and the input of a pathologist in the evaluation is essential. That became apparent during the discussion at the Public Meeting.

TBA produces an increased incidence of renal cell tumors (mostly adenomas) along with an increased incidence of atypical tubular hyperplasia (ATH), the precursor of the adenomas. There is substantial evidence supporting modes of action for these tumors as α_{2u}-globulin nephropathy combined with enhanced chronic progressive nephropathy (CPN). The evidence supporting these two modes of action is robust. In addition, evaluation for alternative modes of action provide ample evidence to exclude other possibilities. Both modes of action (α_{2u}-globulin and CPN) are not relevant to humans, therefore, the male rat kidney tumors detected following administration of TBA are not relevant to human cancer risk assessment.

A similar comment was provided by API for this meeting.

API believes the kidney changes observed in rats following repeated exposure to ETBE are associated with modes of action (α2u-globulin nephropathy and Chronic Progressive Nephropathy or CPN) that have been characterized as rodent specific and are considered not relevant to humans. Therefore, these effects are inappropriate for characterizing potential human risk and should not be used as a basis for EPA's noncancer risk assessment of ETBE. Characterization of CPN and its relevance to humans has been discussed extensively, predominantly in publications by Hard et al. (2004; 2005; 2009; 2012; 2013). The weight of evidence supports an absence of a renal counterpart in humans. EPA acknowledges that there is no known counterpart to rat CPN in aging humans, and that interpretation of non-neoplastic kidney endpoints in rats is complicated by the common occurrence of age-related spontaneous lesions characteristic of CPN. The kidney effects of ETBE identified in the Draft Review as urothelial hyperplasia are directly linked to these rodent specific effects. Thus, the rat kidney effects of ETBE exposure are considered inappropriate for characterizing potential human risk and should not be used as a basis for EPA's noncancer risk assessment of ETBE.

Dr. Cohen also notes in his written ETBE comments for today:

At the previous review held in June, 2016, the scientists involved in the production of the IRIS document were strongly recommended to seek expertise in pathology for review of the animal studies, in particular, those related to the kidney. It is striking to me that this advice has not been followed by the IRIS scientists. There is no pathologist listed in their assessment team, contributors to the document, the production team, or contractor support. In addition, I do not see any pathologists selected for the Scientific Advisory Board (SAB) that is reviewing this document, nor is pathology listed as one of the areas of expertise to be represented on the SAB. I believe this to be a

significant deficiency, as my comments below will indicate. Many of these comments were made at my presentation and discussion at last year's review, as well as in my previous comments to the docket on TBA.

One of the peer reviewers, Dr. Rhomberg, in his preliminary comments notes:

In public comments, some strong views, supported by analysis of a specifically convened PWG, are expressed regarding whether the kidney endpoints are separable, whether they are better considered as various aspects of Chronic Progressive Nephropathy (CPN), and whether they are relevant to processes that could occur in humans. Importantly, the endpoint chosen as critical, urothelial hyperplasia, is characterized by the PWG as a stage in CPN. In sum, the question of the validity and applicability of the endpoints analyzed for the oral RfD needs to be carefully examined. [Tier 1] Even if the decision is to use them, that use must be couched in prominent caveats that acknowledges a significant dissenting body of expert opinion.

Even if one decides to employ these endpoints, it has been said by knowledgable public commenters that, because the endpoints are seen as a suite of CPN manifestations, not all appearances will necessarily be noted in pathological examination, and the counts (and denominators) may be inappropriate. This question needs a clear resolution if the data are to be taken as valid for analysis. [Tier 1]

Given these strong comments, I hope that EPA will seek input from one or more pathologists, and redraft its assessment. Important information obtained during the Public Science Meetings that precede the draft assessments should be seriously addressed. The Public Science Meetings are a key component to improving the assessments, an idea formulated by Ken Olden, the previous Director of NCEA.

III. Transparency of Scientific Determinations

The NRC Formaldehyde report spent considerable effort addressing the need for EPA to increase the transparency of the science related decisionmaking, including improvements in the discussion of the literature search/study selection. In his preliminary comments, Dr. Rhomberg asks for more transparency with respect to the scoring of individual studies on the named criteria and for clarity with respect to the reasons for which individual studies were categorized. In another example, excerpted below, Dr. Clewell points to an absence of a rationale for performing a quantitative analysis for ETBE liver cancer, a key portion of the assessment, for which EPA properly assigned a charge question.

Dr. Harvey Clewell

4c. Cancer toxicity values. Section 3 of EPA's cancer guidelines (2005) states: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the data usually would not support one. However, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence."

Please comment on whether Sections 2.3 and 2.4 of the draft assessment adequately explain the rationale for including a quantitative analysis given the "suggestive evidence" descriptor.

I could not find any rationale for performing a quantitative analysis for ETBE liver cancer in Sections 2.3 or 2.4, or indeed anywhere else in the document. Rather than providing a rationale for the decision, the assessment merely cites the EPA (2005) Guidelines for Carcinogen Risk Assessment to demonstrate that they do have the option of performing one:

"When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however when the evidence includes a well-conducted study, quantitative analysis may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities." What is missing in the document is any rationale for performing a quantitative analysis in the case of ETBE. In particular, no rationale is presented to suggest that performing a default low-dose linear dose-response assessment for high-dose-only liver tumors in rats exposed to ETBE would be useful for any purpose.

In Section 1.3.2 (p. 1-112, lines 9-11), the agency summarizes the limited evidence for ETBE carcinogenicity: "The results for ETBE raise a concern for cancer, but the effects were limited primarily to one tissue (liver), at one dose (highest), and in one sex/species combination (male rats), which were almost entirely benign." I do not see any way in which performing a low-lose linear extrapolation of these data could possibly provide a sense of the magnitude and uncertainty of potential risks, help to rank potential hazards, or set research priorities. In fact, I believe that providing only a default linear dose-response assessment for ETBE would be highly misleading.
.

EPA should seek to improve the transparency of these and other issues in the final assessment.

AUGSUST 7 PRELIMINARY COMMENTS ON LITERATURE REVIEW

Dr. Deborah A. Cory-Slechta*

1. Literature Search Strategy/ Study Selection and Evaluation-Systematic Review Methods. Please comment on the strategies for literature searches, criteria for study inclusion or exclusion and evaluations of study methods and quality discussed in the Literature Search Strategy/Study Selection and Evaluation section. Were the strategies clearly described and objectively applied?

The literature search and study selection were clearly described and objectively applied. In addition, the criteria for inclusion are well described and appropriate inclusion and exclusion criteria, as well as criteria of study quality for inclusion applied.

Dr. W.M. Foster*

1. **Literature Search Strategy/Study Selection and Evaluation.**

I found the keywords selected for search using the online venues of scientific databases (PubMed, Toxline, Web of Science, and TSCATS) to be appropriate for ETBE. The resulting Table information defining the searched literature, Tables LS-1, LS-2 (review reports), and LS-3, were lucid and identified the temporal end point (Nov, 2015) of the applied searches, and the inclusion/exclusion criteria utilized. The overall success of the search approach as presented in Fig. LS-1 seemed adequate. The search selections appeared appropriate and on target for determining health effects of exposure to ETBE in animal models for extension to humans.

Dr. Karen Chou

1. **Literature Search Strategy/Study Selection and Evaluation.**

Yes, the strategies are clearly described.
Recommended correction, p. 1-2, Line 7: Citation mistake. It should be Nihlen et al., "1998a".

Dr. Harvey Clewell

1. **Literature Search Strategy/ Study Selection and Evaluation**

I found the strategies for literature searching, study inclusion and evaluation to be clearly described and objectively applied.

An asterisk * denotes that the reviewer is assigned to the Literature Charge Questions

Dr. Deborah A. Cory-Slechta*

1. **Literature Search Strategy/ Study Selection and Evaluation**

Yes, the strategies were clearly described and objectively applied. An extensive search was undertaken after which inclusion and exclusion criteria were applied and these criteria were appropriate, including elimination of studies of mixtures exposures as the toxicological review is specific to tert-butyl alchohol and thus mixture studies introduce problems of defining sources of the mixture responsible for an effect. In addition, the criteria used for evaluation were also appropriate with respect to suitability for inclusion in derivation of reference doses/concentrations.

Dr. W.M. Foster*

1. Literature Search Strategy/Study Selection and Evaluation.

I found the keywords selected for search using the online venues of scientific databases (PubMed, Toxline, Web of Science, and TSCATS) to be appropriate for tBA. The resulting Table information defining the searched literature: Tables LS-1, LS-2 (review reports) were lucid and identified the temporal end point (May, 2015) of the applied searches, and Table LS-3 clearly listed the inclusion/exclusion criteria utilized for valuation of reports downloaded from the literature searches. Success of the search approach as overviewed in Fig. LS-1 seems adequate. One concern at this point, is the reliance on older reports, for example, the animal model data base (n=14 reports in total, pg. LS-8) utilized for validity of injury and assessing risk, all were accomplished prior to 1998, except for a single, industry sponsored, reproductive study accomplished in 2004.
The summarization of animal model studies utilized and listed in Table l-5 (pg. LS-8), provide, and establish an understanding of the reproducibility of the animal model data base for modes of exposure (oral, inhalation), duration of exposure (sub-chronic, chronic), and scope or focus (developmental, neurodevelopmental, reproductive) of the subsequent to exposure, tBA-induced injury. The search selections appear appropriate and on target for determining health effects of oral exposure to tBA in animal models for extension to humans.

A report that appeared later in time (online, 2016) than the May, 2015, cut-off date for search inventory, given its subject matter would be reasonable to review for information pertinent to pharmacokinetic models of tBA using oral exposure; additionally, the report supports a male-rat-specific mode of action for tBA-induced kidney tumors [SJ Borghoff et al, J. Appl. Toxicol. 37: 621–640 (2017)].

Dr. Karen Chou

1. **Literature Search Strategy/ Study Selection and Evaluation- Systematic Review Methods.**

Yes, the strategies are clearly stated.

Dr. Harvey Clewell

1. **Literature Search Strategy/ Study Selection and Evaluation- Systematic Review Methods.**

I found the strategies for literature searching, study inclusion and evaluation to be clearly described and objectively applied.

Dr. James Bruckner Preliminary Comments 8/9/17 *
Ethyl Tertiary Butyl Ether (ETBE) Charge Questions

1. Literature Search Strategy/Study Selection and Evaluation Systematic Review Methods

The scientific literature search and screening strategy were clearly described on pp. xxvii – xxxiv of the IRIS document. This was a very thorough and effective approach to identify the most pertinent publications. Tables summarizing what appears to be the more important health effects information were constructed as recommended by the NRC (2011). This allows readers to survey and compare results/data available on particular health effects and species. I found the detailed evaluations of the 30 key study design and quality considerations useful.