***THIS DOCUMENT DELIVERED ELECTRONICALLY***

March 13, 2018

Dr. Shaunta Hill-Hammond
Biologist and Designated Federal Officer
U.S. EPA: Office of the Administrator, Science Advisory Board Staff Office
1200 Pennsylvania Avenue, NW (1400R)
Washington, DC 20460-0001
Hill-Hammond.Shaunta@epa.gov

**Re: EPA Science Advisory Board (SAB) Review of EPA's Draft Assessments entitled Toxicological Review of Ethyl Tertiary Butyl Ether and Toxicological Review of *tert*-Butyl Alcohol (*tert*-Butanol)**

Dear Dr. Hill-Hammond:

LyondellBasell appreciates the opportunity to provide comments to the U.S. Environmental Protection Agency (EPA) and the SAB Chemical Assessment Advisory Committee on the SAB's Draft report reviewing the two draft assessments entitled *Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE) (External Review Draft, EPA/635/R-15/016a, June 2017)* and *Toxicological Review of tert-Butyl Alcohol (tert-Butanol; tBA) (External Review Draft, EPA/635/R-17/015a, June 2017*. LyondellBasell, as a producer of ETBE and tBA (TBA), has a significant interest in any review of ETBE and TBA's health and environmental risks by an authoritative body. We are committed to accurate and up-to-date scientific information and assessments of our products and hence we have reviewed and provide comments on the SAB's ETBE and TBA draft report to assure that the latest information is available so that the best possible assessment is achieved.

In view of the very short comment period allowed for stakeholders, our comments are brief. We plan on submitting additional detailed comments to EPA in the near future.

1. LyondellBasell concurs with conclusions that quantitative assessment is not appropriate for ETBE or TBA, and suggests SAB clarify apparent conflicting statement that the "oral slope factor chosen by the agency is scientifically supported".
2. We agree with statements in some parts of the EPA SAB report that ETBE is not genotoxic, but disagree with later contradictory comments on genotoxicity and the conclusion that acetaldehyde is a "plausible" contributor to human ETBE genotoxicity and carcinogenicity.

3. A clear conclusion of the SAB report is that there was a lack of consensus on the human relevance of the rat kidney toxicity, but there are a large number of statements that contradict this conclusion that make the SAB report confusing and internally inconsistent.

4. Given the lack of consensus among the SAB concerning the human relevance of the kidney effects, important Tier 1 recommendations are for EPA to (a) derive an RfD and RfC values for both a kidney and non-kidney endpoint, and (b) strengthen the scientific arguments in the EPA reports supporting the lack of human relevance of the kidney toxicity.

5. Although LyondellBasell agrees that PBPK modeling is a scientifically preferred approach to develop the cancer unit risk, we disagree that the PBPK ETBE-TBA model should be used to develop an oral slope factor for cancer given that ETBE is not carcinogenic when tested in drinking water at its limit of water solubility, while the inhalation exposure concentration (5000 ppm) that causes liver tumors results in systemic ETBE dose levels that would not be physically attainable from drinking water exposures.

6. The SAB is to be applauded for suggesting to the EPA that they include maternal systemic toxicity endpoints when evaluating reproductive and developmental outcomes, and that the description of "minimal effects at otherwise toxic dose levels" be applied to male and female reproductive toxicity endpoints for ETBE.

We urge EPA SAB to revisit our detailed comments on the External Review Drafts for ETBE and TBA that were submitted July 31, 2017:

- LyondellBasell Comments on Charge Questions to the Science Advisory Board for the IRIS Toxicological Review of Ethyl Tertiary Butyl Ether. June 2017. Submitted July 31, 2017.

- LyondellBasell Comments on Charge Questions to the Science Advisory Board for the IRIS Toxicological Review of *tert*- Butyl Alcohol. June 2017. Submitted July 31, 2017.

These comments provide important details and comprehensive explanations that further support our comments to the SAB especially with respect to the mode of action for non-cancer kidney, genotoxicity and carcinogenicity.

LyondellBasell appreciates your consideration of our comments.

Regards,

LyondellBasell

Attachment

**LyondellBasell Comments on Science Advisory Board (SAB) Draft Report (02/21/2018) on the EPA's Draft Toxicology Review of Ethyl Tertiary Butyl Ether and Toxicological Review of tert-Butyl Alcohol**

**March 13, 2018**

1. ***LyondellBasell concurs with conclusions that quantitative assessment is not appropriate for ETBE or TBA, and suggests SAB clarify apparent conflicting statement that the "oral slope factor chosen by the agency is scientifically supported".***

LyondellBasell concurs with the primary CAAC draft report conclusion that:

> "…it is highly unlikely that performing a quantitative assessment of the potential carcinogenic data would be useful for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities for either ETBE or TBA" (Letter to Administrator, p.2, lines 30-33; Executive Summary, p.4, lines 7-10 [ETBE] and l.24-27 [TBA]).

LyondellBasell interprets this conclusion to mean that the SAB has determined that derivation of inhalation Unit Risk (IUR) and/or oral cancer slope values for ETBE and TBA, as presented in the draft IRIS assessments for these chemicals, is not justified by the data and thus should be deleted from those assessments. This interpretation is consistent with SAB Tier 1 conclusions that:

> "EPA should refrain from conducting a quantitative analysis for ETBE [and TBA] carcinogenicity or explain the limitations of the analysis and clearly state the intended purpose is to simply provide some sense of the magnitude of the potential risks." (SAB report, p.42, lines 4-6; p.43, lines 25-27);
>
> and also with the statement addressing ETBE liver tumors (p.41, lines 18-19):
>
> "Any quantitative analysis based on this limited evidence would be highly uncertain and potentially misleading" [tumors (almost entirely benign) in one tissue (liver), only at one dose (highest), and in one sex/species]

The SAB conclusions are in full accord with EPA Cancer Risk Assessment Guidelines (EPA, 2005) that state "(w)hen there is suggestive evidence [as SAB has concluded for ETBE and TBA carcinogenicity; Executive Summary, p.3, lines 43-460], the Agency generally would not attempt a dose-response assessment as the nature of the data would not support one". The SAB draft report appropriately justifies its conclusion by noting that ETBE-induced liver tumors and TBA thyroid tumors were limited only to the highest tested dose, and thus do not offer data that "…are sufficiently robust to provide a meaningful quantitative estimate of human cancer risk" (Executive Summary, p.4, lines 21-22 [ETBE], lines 30-31 [TBA]). The SAB report amplifies

this justification for ETBE by specifically noting that "…the quality of the data supporting this designation [suggestive evidence] is weak, even for the relatively low threshold for evidence needed for that designation." (SAB report, p.38, lines 31-32).

Despite the clear SAB conclusions that quantitative risk assessments of ETBE and TBA cancer responses are not justified, the Letter to the Administrator and related sections of the draft report require further clarification of this important primary conclusion. In the Letter to the Administrator, the paragraph immediately following the conclusion that performing quantitative cancer risk analyses would be "highly unlikely" to be "useful", the SAB states:

> "The SAB agrees that the oral slope factor chosen by the agency is scientifically supported for both ETBE and TBA. No consensus was reached regarding EPA's calculation of [an] inhalation unit risk for ETBE." (Letter to the Administrator, p.2, lines 35-37)

As currently written, this statement appears to be directly opposed to the primary SAB conclusions that tumor responses observed with ETBE and TBA are not sufficient, given only "suggestive evidence" of carcinogenicity, to justify derivation of oral slope factors or inhalation IURs for these agents. However, detailed text in the body of the SAB report (p.44, lines 31-36) appears to offer clarifying commentary on its intended meaning of why derivation of the oral slope factor for ETBE was "scientifically supported" in stating:

> "The SAB agrees that oral slope factor chosen is scientifically supported. The draft ETBE assessment noted that 1) the high dose used in Saito et al. (1993) did not exceed the Maximum Tolerated Dose (MTD), and 2) EPA policy permits the dose-response modeling of tumor data where only the high dose induces a significant tumor increase. The SAB has no alternative approach suggestion for developing an oral cancer slope factor, and noted that the oral slope factor derivation was well described. The SAB also agrees that the modeling was performed correctly."

This text appears to indicate that "scientifically supported" means that, while EPA may have used methodology that was technically acceptable and consistent with the EPA guidance policy for derivation of an oral slope factor, the application of that methodology to ETBE was concluded by SAB as inappropriate based on the already identified limitations of the ETBE carcinogenicity data. Clarification of the meaning of "scientifically supported" is essential to assuring that the primary Tier 1 SAB recommendations that quantitative cancer risk assessments are not justified by the rodent cancer data is not misinterpreted by the EPA and future risk assessors.

It should be noted that the potential clarification of the "scientifically supported" text cited above from the SAB report also erroneously states that the "high dose in Saito et al. (1993) did not exceed the Maximum Tolerated Dose (MTD)." Saito et al. (1993) reports that final body weights in the 5,000 ppm ETBE treatment were 75% and 78% of controls for males and females,

respectively. These severe high-dose specific depressions in body weight are well beyond the 10% body weight loss defined as an MTD (an MTD was not exceeded in the two lower 500 and 1,500 ppm ETBE exposures). The conclusion that the 5000 ppm exposure exceeded an MTD is also consistent with other SAB text (p.44, line 15) in which it is stated "[t]he ETBE inhalation concentration which induced liver tumors was excessively high."

In addition to body weight evidence that an MTD was substantially exceeded, two additional factors support the SAB conclusion that the top ETBE dose was "excessively high" and thus not suitable for quantitative cancer risk assessment. Saito et al. (2013) estimated a daily inhaled dose of 4,222 mg/kg/day ETBE at the 5,000 ppm exposure (assumed rat minute volume of 561 ml/min and lung absorption of 100%). This dose is substantially greater than the 1,000 mg/kg/day limit dose recommended by EPA and OECD dose selection guidance for rodent cancer bioassays (EPA, 1998; OECD, 2009). The limit dose would still be exceeded even it is more reasonably assumed that only 40-50% of an inhaled ETBE dose is systemically absorbed, as has been demonstrated for the structurally-related fuel oxygenate, MTBE (McGregor, 2006). The OECD dose selection importantly notes that a "…limit of 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used." The exception for use of a higher test concentration is not fulfilled for ETBE. Eitaki et al. (2011) report that breathing zone air concentrations of fuel station pump attendants is less than 0.1 ppm (fuel re-fueling operations generally represent the highest exposure potential to ETBE).

The SAB also concludes that the TBA drinking water bioassay findings were not suitable for developing an oral cancer slope factor because of concerns for "a lack of biological relevance due to the magnitude of the high dose and the *possibility of nonlinear metabolism kinetics at that dose* [emphasis added]" (p.45, 17-19). LyondellBasell agrees with the SAB observation that TBA thyroid tumors observed at an excessively high dose and above the onset of nonlinear toxicokinetics lack biological relevance. However, given this conclusion for TBA, a parallel conclusion should be logically reached for ETBE liver tumors, and which would be further consistent with the SAB Tier 1 conclusion that a quantitative risk assessment of ETBE liver tumors is not useful. Not only was the top ETBE exposure excessively toxic as indicated by severe body weight loss, LyondellBasell comments submitted to SAB on the draft ETBE IRIS (LyondellBasell, July 31, 2017) noted that inhalation toxicokinetics in F344 rats also were distinctly nonlinear at ETBE concentrations of 1,750 and 5,000 ppm (Borghoff and Asgharian, 1996).

### 2. *The metabolism of ETBE to acetaldehyde does not provide "plausible evidence" for a vulnerable subgroup to ETBE exposure and possible genotoxicity.*

We agree with statements in some parts of the EPA SAB report that ETBE is not genotoxic, but disagree with later contradictory comments on genotoxicity and the conclusion that acetaldehyde is a "plausible" contributor to human ETBE genotoxicity and carcinogenicity. There is very

strong evidence that ETBE and TBA are not genotoxic, and the EPA SAB report should consistently indicate that, as stated, the "preponderance of data" indicate that ETBE and TBA are not genotoxic. The genotoxicity data were reviewed in detail in previous comments on the draft assessment by LyondellBasell for both ETBE and TBA (July 31, 2017).

The Executive Summary concludes that there is "plausible evidence" of ETBE susceptible sub-populations and life stages based on the observation that ETBE is metabolized to acetaldehyde and some individuals have genetic variations in the ALDH2 (aldehyde dehydrogenase) gene controlling the otherwise efficient detoxification of this ETBE metabolite. However, this high-level conclusion appears inconsistent with a Tier 2 conclusion offered in the body of the SAB report (p.36, l.38-41):

> "Acetaldehyde is proposed as a strong candidate MOA for male rat liver tumors, but the plausibility of this MOA is not well explored. Evidence for this MOA should be developed and presented more thoroughly; or, alternatively, the *agency is encouraged to reduce emphasis on this MOA in the final assessment* [emphasis added]."

LyondellBasell agrees with the SAB conclusion that EPA should "reduce emphasis on this MOA in the final assessment." In previous detailed comments to the SAB (LyondellBasell, July 31, 2017), further evidence was presented that the acetaldehyde mode of action hypothesis lacks plausible quantitative dose relevance to adverse human health risks given the extremely low amounts of acetaldehyde generated under conditions of worst-case real-world ETBE human exposures. The LyondellBasell comments observed that the systemic dose of acetaldehyde resulting from

> "…a 2 hr 50 ppm ETBE exposure [in humans] is equivalent to [a systemic acetaldehyde dose resulting from ethanol consumption] of approximately 0.004 of a can of beer (1.4 ml). It is important to note, however, that actual breathing zone exposures in Japanese gasoline station pump workers and fuel tanker drivers have been shown as generally less than 0.1 ppm ETBE (Eitaki et al., 2011). Assuming 100% conversion of absorbed ETBE to acetaldehyde, the acetaldehyde metabolically delivered from 0.1 ppm ETBE exposure is equivalent to acetaldehyde formed from consumption of 0.003 ml of beer (or 16% of one drop of beer assuming 50 μl/drop)."

The minuscule systemic dose of acetaldehyde resulting from likely worst-case ETBE occupational and consumer exposures indicates that individuals expressing genetic polymorphisms in ALDH2 are not a reasonable susceptible subpopulation for vulnerability to ETBE-associated health risks.

The SAB report concludes that the "preponderance of data" indicates a lack of ETBE genotoxicity (p. 38, line 35), which provides further support to a conclusion that acetaldehyde is not likely involved in the etiology of male rat liver tumors. However, this SAB conclusion

should be clarified given statements of "…supporting evidence from …genotoxicity studies that ETBE is carcinogenic" (p.41, 17-18) and that acetaldehyde is a "genotoxic carcinogen" (p.46, l.35). As described above, acetaldehyde as a metabolite of ETBE should not be interpreted as "plausible" evidence of potential human carcinogenicity because acetaldehyde produced from metabolism of worst-case human inhalation exposures is essentially *de minimis.*

### *3. The SAB discussion on rat kidney toxicity was confusing because of statements that were unclear and/or appeared to contradict the SAB's stated "lack of consensus"*

A clear conclusion of the SAB report is that there was a lack of consensus on the rat kidney toxicity, but there are a large number of statements that contradict this conclusion that make the SAB report confusing and internally inconsistent. The following four statements in the SAB's draft letter to EPA Administrator Pruitt illustrate the inconsistencies that are pervasive in the EPA SAB report:

- Regarding non-cancer kidney effects, the SAB is unable to reach consensus with respect to how the agency interpreted the ETBE database for non-cancer kidney effects. There was considerable disagreement as to whether non-cancer kidney effects in rats should be considered a hazard relevant to humans (Page 1 line 41).

- The SAB also recommends that EPA consider the use of another parameter, such as . . . exacerbation of nephropathy, besides urothelial hyperplasia, as a surrogate for ETBE non-cancer kidney effects. . . .The EPA could also consider other indicators besides suppurative inflammation and transitional epithelial hyperplasia as indicators of kidney effects for TBA [than chronic progressive nephropathy] or provide better justification for their choice (Page 1 line 47 to Page 2 line 5)

- For non-cancer effects, the SAB agrees that non-cancer toxicity at sites other than the kidney should not be used as the basis for deriving an oral reference dose (RfD) or inhalation reference concentrations (RfC) for ETBE or TBA. Nearly all of the possible effects at these sites occurred at much higher exposure levels than did effects observed on the kidney (Page 2 line 7)

- Regarding non-cancer kidney outcomes, the SAB did not reach consensus regarding the oral reference dose for non-cancer kidney outcomes from exposure to ETBE (Page 2 line 12)

The draft SAB report conclusion that an RfD and RfC based on other organ toxicity should not be derived contradicts the conclusion reached by some SAB members that the kidney is not relevant to humans. It is not appropriate to dismiss use of alternative non-kidney endpoints simply because they occurred at higher doses than kidney (e.g., p.24, l.7-11), and particularly so

when there is a clear lack of consensus of the human relevance of the kidney lesions. This approach of deriving organ/system specific RfD/RfC values is consistent with guidance in the Preamble to IRIS toxicological reviews. A failure to recommend derivation of RfD/RfC values using endpoints other than kidney may otherwise inappropriately and non-transparently bias values derived from kidney alone as being scientifically justified.

Similarly, the suggestion to consider the use of other kidney parameters or blood (serum) levels as surrogate for ETBE and TBA non-cancer kidney effect, besides urothelial hyperplasia, to derive the non-cancer RfD/RfC values is inconsistent with the lack of consensus on the human relevance of kidney outcomes. As outlined in detail in LyondellBasell's comments submitted July 31, 2017 on both ETBE and TBA, the only pathological processes identifiable in the rat kidney following exposure to ETBE and TBA are α2u-globulin nephropathy and exacerbation of CPN, both of which are not relevant to humans.

The SAB accepted the EPA conclusion that the data for ETBE do not fulfil all of the established criteria for an α2u-globulin MOA (3.3.1.1. ETBE, page 21, para 1). The EPA considers the database is insufficient to conclude that ETBE is an inducer of α2u-globulin nephropathy in male rats, and that other MOA could be operative and relevant to human hazard assessment. The EPA view that the histological sequence induced by ETBE in the male rat kidney has numerous data-gaps is a misleading exaggeration. The SAB should be aware of the following: Subacute studies with ETBE recorded the presence of hyaline droplets, and one report by a group of experts in renal pathology described the droplets as having angular profiles characteristic of α2u-globulin protein (Cohen et al, 2011). Granular casts were observed by this independent group in a subacute study that the SAB considered was well-conducted. It should be noted here that formation of granular casts implies cell loss and degeneration. Granular casts occur from luminal accumulation of droplet-laden degenerate proximal convoluted tubule cells testifying to the occurrence of tubule cell exfoliation and death. Cell proliferation in male rat proximal tubules was observed at 1, 4 and 13 weeks, which provides some evidence of sustained cell proliferation (Medinsky et al, 1999). The EPA took the view that the low, transient increase in female rats at 1 and 4 weeks at the highest dose only, but not sustained to 13 weeks, negated the male finding. Completing this histological sequence, linear mineralization in the renal papilla was reported for male rats and not female rats (Cohen et al, 2011). Although a weak inducer of α2u-g nephropathy, the evidence supporting this category of renal response for ETBE is compelling.

CPN exacerbation by chemicals as a mode of action for renal neoplasia proved to be a major controversial topic within the SAB. The lack of consensus appeared to focus on the disagreement concerning whether CPN should be considered as a "cluster of renal changes", that is as a diagnostic entity, or whether the individual components of CPN could also occur separately from CPN and be individually affected by the test articles. It must be emphasized here that that CPN is a diagnostic entity as recommended by various Societies of Toxicologic Pathology (Frazier et al. 2012). CPN represents a consistent combination of lesions and it is this consistent pattern of lesions and pattern of development that characterizes the disease entity of CPN. Thus, when a chemical

exacerbates CPN, it is exacerbating this consistent combination of individual lesions and not just one of them. This MOA does not occur in humans and should not be used to derive an RfD or RfC as recommended by some members of SAB (Hard et al. 2009).

In summary, the report dealing with the kidney findings was confusing, because of the number of contradictory statements. Furthermore, there was no clear message concerning the known scientific data for the MOAs under consideration. Given the frequency of disagreements among members of the SAB concerning kidney effects and MOAs for those kidney effects, it is important that any final documents on ETBE and TBA highlight this lack of SAB consensus.

We suggest that the SAB include Tier 1 recommendations to (a) strengthen the arguments supporting the lack of human relevance of the kidney lesions in the sections on hazard identification and dose-response; and (b) include derivation of RfD and RfC values for both a kidney and non-kidney endpoint.

### *4. PBPK modeling is a scientifically preferred approach to develop the cancer unit risk*

LyondellBasell agrees with the SAB that "The SAB strongly supports EPA's application of the PBPK model in the dose-response characterization of ETBE and TBA as an appropriate way to incorporate science using state-of-the-art methods." [Executive Summary, page 2, Lines 5-6, Toxicokinetic modeling.] as well as the following recommendations:

- "The SAB noted that the overall presentation of the PBPK modeling should be more cohesive, clear, and transparent." [Executive Summary, Page 2, line 8-9.]
- "Instead of using a default method to calculate the human equivalent dose, the SAB recommended an ETBE and TBA model parameterization for humans be created using the published human PBPK model of Nihlen and Johanson (1999) and data in Amberg et al., (2000)." [Executive Summary, Page 2, lines 9-11.]

LyondellBasell disagrees with the SAB that "In future modeling efforts, the EPA could assess whether fits to data would benefit from consideration of capacity-limited blood binding of ETBE or sex differences in metabolism." [Executive Summary, Page 2, lines 13-15]

- In the ETBE-TBA rat PBPK model described by Salazar et al., (2015), a description for a reversible sequestration of TBA in blood was described which would be reflective of a reversible protein binding. Although Salazar et al. felt that this was needed to better predict TBA blood data following iv administration of TBA, the model fits to the same data described by Borghoff et al. (2016) were similar or improved without this description compared to those described by Salazar et al. (2015).

LyondellBasell supports the SAB's comment that there is concern for the dose metric selected as stated that "The SAB finds the choice of the rate of metabolism of ETBE to be a reasonable dose metric; however, it is not recommended for extrapolation from inhalation to oral routes of administration of ETBE." [Executive summary, Page 2 lines 18-19].

- The selection of the dose metric should be re-evaluated by the agency (rate of ETBE metabolism vs free liver concentration) prior to a final decision of whether to use it as a dose-metric since it is not clear from the SAB comments how their recommendations would change the model's predictions and its use for extrapolation.

LyondellBasell disagrees with the following statement "The SAB concludes that the oral slope factor chosen is scientifically supported for both ETBE and TBA. [Executive summary, Page 4, line 34]

- ETBE is not carcinogenic when tested in drinking water at its limit of water solubility, and the inhalation exposure concentration (5000 ppm) that causes liver tumors results in systemic ETBE dose levels that would not be physically attainable from drinking water exposures. As such derivation of an oral slope factor for ETBE is not necessary. Previous comments in this submission suggest that the SAB assessment of the oral cancer slope factor derivation as being "scientifically supported" may be a reflection of only that EPA used correct methodology that was generally consistent with EPA guidance policy. However, it appears the SAB has determined that, because of the unique overall circumstances of the dose-response and nature of tumor responses for ETBE and TBA, derivation of IUR or oral cancer slope factor values were not justified.

LyondellBasell agrees with the SAB that "The SAB concludes that the NTP (1995) TBA drinking water study is not suitable for developing an IUR. Concerns include the lack of biological relevance due to the magnitude of the high dose, the lack of a mouse TBA PBPK model and the possibility of nonlinear metabolism kinetics at that dose. The SAB also has concerns as to whether modeling a single positive concentration would produce a meaningful oral slope factor." [Executive summary, Page 4 Line 45-46, page 5, lines 1-3].

- However, the same justification could be made for ETBE, besides the fact that there is an ETBE PBPK model, inhalation exposure to ETBE at high exposure concentration causes a liver tumor response at a concentration that results in nonlinear metabolism. Also, ETBE, like TBA would result in modeling a single positive concentration.

5. ***LyondellBasell agrees with SAB's suggestion to consider maternal toxicity and high dose toxicity in evaluation of developmental and reproductive outcomes.***

The SAB is to be applauded for suggesting to the EPA that they include maternal systemic toxicity endpoints when evaluating reproductive and developmental outcomes. The IRIS documents were incomplete in summarizing the maternal toxicity endpoints. The SAB is also to be applauded for recommending to the EPA that the description of "minimal effects at otherwise toxic dose levels" be applied to male and female reproductive toxicity endpoints for ETBE rather than describing the evaluation as "inadequate evidence" since there is a plethora of data for these endpoints (Page 25, lines 25-27 and 31-33).

REFERENCES

Borghoff SJ and Asgharian B. (1996). Ethyl tertiary-Butyl Ether (ETBE): Pharmacokinetic Study in Male and Female CD-1 Mice After Single Inhalation Exposure and Male and Female F-344 Rat; After Single and Repeated Inhalation Exposure. Final Report, Chemical Industry Institute of Toxicology, RTP, NC. Sponsor ARCO Chemical Company, Newton Square, PA.

Cohen SM, Hard GC, Regan K, Seely J, and Bruner R (2011). Pathology Working Group review of selected histopathologic changes in the kidneys of rats assigned to toxicology and carcinogenicity studies of ethyl *tertiary* butyl ether (ETBE). Report to Lyondell Chemical Company, Houston, TX, on Japan Bioassay Research Center Studies No: 0665 and 0691.

Eitaki Y, Kawai T and Omae K. (2011). Exposure assessment of ETBE in gas station workers and gasoline tanker truck drivers. J. Occup. Health. 53:423–431.

EPA. (1998). Health Effects Test Guidelines. OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity. EPA 712-C-98-212, August, 1998.

EPA. (2005). Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F, March, 2005.

Frazier KS, Seely JC, Hard GC, Betton G, Burnett R, Nakatsuji S, Nishikawa A, Durchfeld-Meyer B and Bube A. (2012). Proliferative and non-proliferative lesions of the rat and mouse urinary system. Toxicol. Pathol. 40 (Suppl. 4):14S-86S.

Hard GC, Johnson KJ, and Cohen SM (2009). A comparison of rat chronic progressive nephropathy with human renal disease – implications for human risk assessment. Crit. Rev. Toxicol. 39: 332-346.

McGregor D. (2006). Methyl tertiary-butyl ether: studies for potential human health hazards. Crit. Rev. Toxicol. 36:319-58.

Medinsky MA, Wolf DC, Cattley RC, Wong B, Janszen DB, Farris GM, Wright GA and Bond JA. (1999). Effects of a thirteen-week inhalation exposure to ethyl tertiary butyl ether on Fischer-344 rats and CD-1 mice. Toxicol. Sci. 51**:** 108-118. Erratum, Toxicol. Sci. (2006) 94: 441.

OECD. (2009). OECD Guideline for the Testing of Chemicals. Combined Chronic Toxicity/Carcinogenicity Studies. OECD 453, Adopted: 7 September 2009.

Travlos GS, Hard GC, Betz LJ and Kissling GE. (2011). Chronic progressive nephropathy in male F344 rats in 90-day toxicity studies: Its occurrence and association with renal tubule tumors in subsequent 2-year bioassays. Toxicol. Pathol. 39: 381-389.