From: [redacted]
To: Carpenter, Thomas
Cc: Brennan, Thomas; Johnston, Khanna
Subject: RE: LyondellBasell oral-comment to 9-26-2018 Chartered SAB review of ETBE and TBA report
Date: Friday, September 28, 2018 11:17:20 AM
Attachments: LyondellBasell Oral-Written Comment to Chartered SAB 9-26-2018.pdf

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Tom,

Pleased find attached a written version of the brief oral comment that would have been presented on behalf of LyondellBasell at the Chartered SAB review of the CAAC reviews of the ETBE and TBA IRIS documents. LyondellBasell fully understands that the busy agenda of the Chartered SAB did not allow the late request to provide oral comment, but is very much appreciative of the kind offer in your email below to submit the oral comment as a written document for formal provision to the Chartered SAB members and placement in the SAB ETBE/TBA docket.

LyondellBasell believes the oral comment will be of value to the Chartered SAB as it assists the CAAC in completion of its peer review of the ETBE and tBA IRIS reviews. LyondellBasell also apologizes for the slight delay in this submission which was due to need for formal written submissions to the agency to undergo LyondellBasell document review and approval.

Thank you and regards,

Jim Bus

James S. Bus Ph.D., DABT, Fellow ATS
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From: Carpenter, Thomas <Carpenter.Thomas@epa.gov>
Sent: Wednesday, September 26, 2018 11:03 AM
To: [redacted]
Cc: Brennan, Thomas <Brennan.Thomas@epa.gov>; Johnston, Khanna <Johnston.Khanna@epa.gov>
Subject: RE: Request to offer oral comment at 9-26-2018 Chartered SAB review of ETBE and TBA

report

Dr. Bus,
My apologies, we will not be able to add you to the registered speakers list to provide oral comments to the SAB on todays call. The deadline was last week and we have filled our available time on both the agenda items and anticipate we will need all our alloted time for the SAB discussions. Please feel free to submit written comments that we will pass along to Board members and post on our web page.

Regards,

Thomas Carpenter
Designated Federal Officer / Sr. Biologist
US EPA Science Advisory Board, MC 1400R
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Washington DC 20460
ph 202 564 4885 Fax 202 565 2098

From: James Bus [redacted]
Sent: Wednesday, September 26, 2018 9:34 AM
To: Carpenter, Thomas <Carpenter.Thomas@epa.gov>
Subject: Request to offer oral comment at 9-26-2018 Chartered SAB review of ETBE and TBA report

Tom,

If it is at all possible, I am requesting an opportunity to provide public oral comment to the Chartered SAB review of the ETBE and TBA CAAC SAB reports on behalf of LyondellBasell. At this time I am not sure if such comment will be needed, and if it is it will be focused on a brief clarification comment regarding report conclusions. If comments are not necessary, I will decline when called on.

I apologize for the late request in that I only learned of the meeting yesterday.

Thank you and regards,

Jim Bus

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Written clarifying comment submitted to EPA Chartered SAB reviewing the EPA CAAC evaluation reports of the EPA IRIS Toxicological Assessments of ETBE and tBA, September 26, 2018.

James S. Bus PhD, DABT, ATS, Exponent, Inc. on behalf of LyondellBasell

LyondellBasell thanks the CAAC and Chartered SAB for their efforts in reviewing the ETBE and tBA IRIS Toxicological Assessments.

The draft Executive Summary of the CAAC report dated August 30, 2018, states (p.4, l.12-15) that "[t]he SAB *concludes* [emphasis added] it is unlikely that performing a quantitative assessment of the data on ETBE liver carcinogenicity would be useful for "providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities"". However, this clear conclusive statement is followed (p.4, l.43-44) by the apparent contradictory statement that "[n]o consensus, however, was reached regarding the EPA's calculation of inhalation unit risk (IUR) for ETBE." If there was clear agreement that "performing a quantitative assessment" [i.e., calculation of an IUR] was "unlikely" to be 'instructive" of understanding cancer risks, hazards or research priorities, then SAB appears to have had consensus that calculation of an IUR for ETBE was not warranted. But yet, the report states that "no consensus" was reached on calculation of an IUR for ETBE.

LyondellBasell concurs with the draft CAAC conclusion (p.4, l.25-27) that "[t]he SAB *agrees* that the Saito *et al*. (2013) study [the ETBE inhalation chronic toxicity study] is well-conducted and well-reported. However, with a statistically significant increase in tumors at the high dose only, the Saito *et al*. (2013) data *are not sufficiently robust to provide a meaningful quantitative estimate of human cancer risk* for ETBE" [emphases added]. Consistent with this CAAC conclusion, LyondellBasell has noted in previous public comment on the draft ETBE IRIS that the 5000 ppm high-dose ETBE exposure group not only clearly exceeded an MTD as represented by an approximate 25% loss in body weight, but also was distinctly above metabolic saturation of ETBE (see Appendix A, LyondellBasell Public Comments, October 31, 2016, p.6-9). EPA Cancer Risk Assessment Guidelines (EPA, 2005) explicitly caution that "interpretation of carcinogenicity study results is *profoundly* affected by study exposure conditions, *especially by inappropriate dose selection* [emphases added; EPA, 2005, p. 2-16]", and then states that doses causing body weight losses of greater than 10% and/or saturation of detoxification mechanisms are "signs of treatment-related toxicity associated with an excessive high dose (EPA, 2005, p.2-17). Thus, both of these key high-dose observations reinforce the CAAC conclusion that the high-dose ETBE liver tumor data "are not sufficiently robust to provide a meaningful quantitative estimate of human cancer risk for ETBE."

2) The available information supports a conclusion that ETBE is not a human liver cancer concern.

A statistically significant increase in the incidence of hepatocellular adenomas was observed only in male F344 rats, and was limited to the highest dose tested of 5000 ppm following chronic inhalation exposure (0 500, 1500, and 5000 ppm, 104 weeks; 6 hr/day; 5 days/week) (Saito et al., 2013). Importantly, inhalation toxicokinetic studies have demonstrated that the metabolism of ETBE in rats is saturated at inhalation exposures ≥ 1750 ppm. ETBE saturated metabolism and ensuing nonlinear toxicokinetics are readily evidenced by an increase in the percentage of exhaled volatile organics at 1750 and 5000 ppm exposures that was associated with a concurrent decrease in the percent of radioactivity excreted into urine at these same exposures (see Table B-6, Supplemental Information, citing Sun and Beskitt, 1995; Borghoff, 1996; not cited in draft IRIS is inhalation toxicokinetic report of Borghoff and Asgharian (1996). Borghoff and Asgharian (1996) reported that the percentages of the absorbed dose eliminated as exhaled volatiles recovered in exhaled air or as radioactivity recovered in urine of male and female F344 rats up to 48 hr following single nose-only exposures to ^{14}C-ETBE was as follows:

Mean Percent Eliminated (4 rats/group)

Elimination Pathway	500 ppm	1750 ppm	5000 ppm
Male Exhaled Volatiles	28	41	51
Male Urine	59	53	45
Female Exhaled Volatiles	32	52	64
Female Urine	59	41	30

The limitation of the hepatic tumor response to the toxicokinetically-saturated and high-exposure only test dose indicates that the liver tumor response is not quantitatively relevant to humans based on the observation that real-world human exposures to ETBE are substantially less than the likely onset of the inflection point of nonlinear toxicokinetic behavior at approximately 1750-2000 ppm ETBE. Thus, humans are not chronically exposed to these extremely high concentrations of ETBE in which metabolism is saturated. The ACGIH has set an occupational Threshold Limit Value (TLV®) of 25 ppm ETBE (ACGIH, 2015), however, actual breathing zone exposures of

Japanese gasoline station workers and fuel tank drivers have been reported as less than 0.1 ppm (Eitaki et al., 2011).

In recent years several comprehensive reviews have emphasized that rodent carcinogenicity responses restricted to high test doses may have questionable human health hazard and risk

relevance. Thus, high-dose specific saturation of metabolic processes, including toxicokinetics, may result in transition to novel MOA unique to those high dose levels and which are not related to alternative MOA operating at lower animal doses and substantially lower real-world human exposures (Foran et al., 1997; Slikker et al., 2004a,b; Barton et al., 2006; Carmichael et al., 2006; Doe et al., 2006). Consistent with the above expert reviews, the EPA Cancer Risk Assessment Guidelines (2005) have emphasized that changes in toxicokinetics with increasing dose may result *"…in important differences between high and low dose levels in disposition of the agent or generation of its active forms. These studies play an important role in providing a rationale for dose selection in carcinogenicity studies."* Thus, data indicating onset of dose-dependent toxicokinetic nonlinearities should be an important consideration in potential selection of doses for rodent bioassays, and conversely, in interpretation of tumor findings noted above the threshold of nonlinear pharmacokinetics.

The above EPA guidance regarding consideration of toxicokinetics in selection of doses in rodent chronic toxicity/carcinogenicity bioassays is also fully consistent with recent OECD guidance (OECD, 2012). OECD has emphasized that:

> "*Available toxicokinetic data (ADME) should* ***always*** *[emphasis added] be taken into account when selecting dose levels for a chronic toxicity or carcinogenicity study… Many toxicokinetic processes influencing absorption, distribution, elimination and metabolic activation or detoxication may become saturated at higher doses, resulting in systemic exposures to parent compound or metabolites that would not be expected in the real life human exposures for which risk assessments are needed.*"

Equally, or perhaps even more importantly, however, the OECD guidance has clearly articulated that toxicity, including tumors, observed above the threshold for onset of nonlinear toxicokinetics has questionable quantitative health relevance to human hazard in that such high doses are viewed as equivalent to exceeding a Maximum Tolerated Dose determined by conventional body weight and/or other evidence of toxicity (OECD, 2012):

> "*Although top dose selection based on identification of inflection points in toxicokinetic nonlinearity may result in study designs that fail to identify traditional target organ or body weight effects, it must be appreciated that metabolic saturation in fact represents an equivalent indicator of biological stress. In this case, the stress is evidenced by appearance of non-linear toxicokinetics rather than appearance of histological damage, adverse changes in clinical chemistry, haematology parameters or decrease in body weight gain."*

Use of toxicokinetic data to provide a data-informed selection of the appropriate top dose in animal toxicity tests has recently been described as a Kinetically Derived Maximum (KMD) dose selection strategy (Saghir et al., 2012). The KMD dose selection strategy specifically emphasizes that toxicokinetic data, when available, can and should be used as an alternative to conventional top dose selection strategies based on Maximum Tolerated Dose (MTD). KMD considerations are specifically designed to proactively avoid generation of animal toxicity findings that ultimately have limited if any value to identification of true human health hazards

and risks. The KMD approach also has great value for reducing significant laboratory and animal resources (including reduction in unnecessary animal suffering) that otherwise might be applied to further explore the potential (or lack of) health relevance of toxicity findings observed at MTD doses where a KMD approach could have been used as a maximum dose-equivalent alternative.

The rat toxicokinetic data described above indicates ETBE would have been a reasonable candidate for a KMD-based dose selection strategy for the chronic inhalation bioassay reported by Saito et al. (2013). Application of both EPA and OECD guidance recommendations to strongly consider toxicokinetic data in bioassay dose selection would have justified a top inhalation exposure dose of 1500-1750 ppm for the chronic rat ETBE inhalation bioassay. Had such a KMD strategy been employed in the design of the Saito et al. (2013) bioassay, and which would have been in complete compliance with current OECD and EPA guidance for dose selection in rodent toxicity and carcinogenicity bioassays, the end result would have been that the rat hepatocellular tumors would not have emerged as a significant, if any, cancer concern.

The conclusion that the 5000 ppm inhalation exposure concentration was an excessively high test concentration in rats is further evidenced by the observation that Saito et al. (2013) reported that male and female body weights were significantly decreased to 75 and 78%, respectively, of controls at the terminal 104-week sacrifice. This severe weight loss exceeds the 10% body weight loss recommended for achievement of a Maximum Tolerated Dose. The potential that excessive toxicity was uniquely associated with the high-dose 5000 ppm exposure condition under which nonlinear toxicokinetics were apparent is further evidenced by the observation that male and female terminal body weights were a non-statistically significant 94 and 91% of controls, respectively, in next lower 1500 ppm ETBE exposure. In addition, the significantly increased incidence of preneoplastic eosinophilic and basophilic liver foci was limited to the 5000 ppm treatment group, indicating that tumorigenic responses would be unlikely at the 1500 ppm mid-dose. These findings further indicate that the high-dose specific ETBE male rat liver tumors were secondary to use of an excessively high top bioassay dose.

Increased liver tumors were observed only in male rats following inhalation exposure to 5000 ppm, and occurred only under conditions of distinctly nonlinear toxicokinetics.
OECD and EPA guidance indicate that adverse responses, including tumorigenicity, observed under such high-dose specific conditions are not quantitatively relevant to human cancer hazards or risks. Given the limited tumorigenic response (single species, single sex, tumors limited to a human-irrelevant metabolically-saturating high dose), the discussion of the choice of potential hazard descriptors should include an assessment of

the appropriateness for the choice of the *not likely to be carcinogenic to humans* descriptor. In particular, the *Preamble to IRIS Toxicological Reviews* specifically notes that this descriptor is justified when "…convincing evidence that effects are not likely by a particular exposure route *or below a defined dose* [emphasis added]" is available.

It is important to note that the inflection point for onset of nonlinear ETBE toxicokinetics is likely between ETBE exposures of 1500- 2000 ppm (Borghoff and Asgharian, 1996, Borghoff et al., 2016). In contrast, human occupational and general environmental exposures are considerably below this inflection point dose. ETBE has not been in commercial use in the United State for approximately 15 years, and the US Geological Survey (2006) has reported ETBE was detected in only 0.5% of public wells at approximately 0.2 µg/L (domestic wells had less frequent ETBE detection). However, ETBE is currently blended as a fuel oxygenate in Europe and Japan (Eitaki et al., 2011). ETBE has been estimated at a maximum environmental air concentration of 0.0091 ppm in Japan (JPEC, 2008), and mean occupational 8 hr-TWA exposures of 0.08 and 0.04 ppm have been reported for gasoline station workers and gasoline tanker drivers, respectively (Eitaki et al., 2011). The substantial disparity between the onset of nonlinear toxicokinetics in animals and real-world human exposures supports the conclusion that the rat liver tumors are not a quantitatively relevant response for human hazard and risk evaluation.

Toxicokinetic considerations relevant to liver toxicity and tumors

The section of the draft assessment does not describe the interpretative implications of the finding that liver tumors were only observed at an inhalation dose level exhibiting nonlinear toxicokinetic behavior. As implied by the title of this section of the draft assessment, such data should be a key consideration in the overall MOA evaluation. Importantly, in the Supplementary Information provided for the draft assessment it is stated that: "A review of the data demonstrating the percentage of recovered radiolabel via various routes of elimination demonstrate, in the rat and mouse, a pattern indicative of metabolic saturation occurring at inhaled concentrations above 4,180 mg/m^3 [1000 ppm]" (p. B-19). This key conclusion is not carried over to the main draft assessment document. The IRIS Supplementary Information cites Sun and Beskitt (1995) and a preliminary study of Borghoff (1996) as evidence for saturation of ETBE metabolism. This information should be supplemented with the more comprehensive study of Borghoff and Asgharian (1996) demonstrating dose-dependent onset of nonlinear toxicokinetics in rats and mice.