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Document Control Office
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Draft Toxicological Review of Ethyl Tertiary Butyl Ether - External Review Draft, May 2017

Dear Sir or Madam:

The American Petroleum Institute (API) respectfully submits comments for consideration by the U.S. Environmental Protection Agency (EPA) Science Advisory Board Chemical Assessment Advisory Committee in their review of the EPA Integrated Risk Information System (IRIS) Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE). API commends the Agency for providing opportunities for public comment on this important assessment, and for convening the October 26, 2016 Public Science Meeting on this topic. We participated in the 2016 Public Science Meeting and provided comments to the Agency on the previous Public Comment Draft of this assessment. API believes that a number of key aspects of the ETBE assessment can be further improved, as discussed in the attached comments.

American Petroleum Institute Comments

on

EPA Draft Toxicological Review of **Ethyl Tertiary Butyl Ether** - External Review Draft, May 2017

U.S. Environmental Protection Agency
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1220 L Street, NW, Washington DC 20005
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Comments on EPA Draft Toxicological Review of **Ethyl Tertiary Butyl Ether** - External Review Draft, May 2017

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Comments on EPA Draft Toxicological Review of **Ethyl Tertiary Butyl Ether** - External Review Draft, May 2017

I. Introduction and Summary

The American Petroleum Institute (API) respectfully submits these comments for consideration by the U.S. Environmental Protection Agency (EPA) Science Advisory Board Chemical Assessment Advisory Committee in their review of the EPA Integrated Risk Information System (IRIS) Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE). API is a national trade association representing all facets of the oil and natural gas industry, which supports 9.8 million U.S. jobs and 8 percent of the U.S. economy, and provides most of the nation's energy. API's more than 625 members include large integrated companies, as well as exploration and production, refining, marketing, pipeline, and marine businesses, and service and supply firms.

API's members are involved in all major points of the chemical supply chain—from natural gas and crude oil production, to refinery production of fuels and other products, to service companies using chemicals. API and its members are dedicated to continuous efforts to meet chemical management responsibilities while economically developing energy resources and supplying high quality products and services. API recognizes the responsibility to work with other industries, the public, government, and nongovernmental organizations to achieve sound management of chemicals.

API commends the Agency for providing opportunities for public comment on this important assessment, and for convening the October 26, 2016 Public Science Meeting on this topic. API participated in the 2016 Public Science Meeting and provided comments to the Agency on the previous Public Comment Draft of this assessment.

API believes that a number of key aspects of the ETBE assessment can be further improved. Chief among these are the cancer classification, the cancer risk quantification, and the critical endpoint chosen for noncancer risk assessment. Attention by the Advisory Committee to these aspects of the review is requested in finalizing the ETBE toxicological review.

API's major comments, which are further discussed in the remainder of this document, are as follows.

- The available animal data for ETBE do not provide evidence suggestive of potential human carcinogenicity by all routes of exposure.

- The very high doses studied in the chronic cancer bioassays of ETBE, including maximum achievable doses in the oral studies and levels exceeding metabolic saturation in the chronic inhalation study, should be a consideration in deciding the cancer classification for ETBE.

- The Agency's use of the single high dose inhalation data point at an excessive dose to support dose response analysis and extrapolation of low dose cancer risk estimates to humans by all routes of exposure is inappropriate and inconsistent with Agency guidelines.

- The rodent kidney effects of ETBE exposure chosen for characterizing potential human risk are rodent specific, are not relevant to humans, and should not be used as a basis for EPA's noncancer risk assessment of ETBE.

II. Noncancer Kidney Toxicity

Charge Question 3a: "*The draft assessment identifies kidney effects as a potential human hazard of ETBE. EPA evaluated the evidence, including the role of α2u-globulin and chronic progressive nephropathy, in accordance with EPA guidance (U.S. EPA, 1991). Please comment on whether this conclusion is scientifically supported and clearly described.*"

<u>Comment</u>

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.

API commends the Agency for identifying kidney effects reported in rats following exposure to ETBE and its metabolite tertiary-butyl alcohol (TBA) as a key science topic for discussion during the June 2016 IRIS Public Science Meeting. Since rat kidney effects have been cited as critical effects in the Agency's assessment of both chemicals, API strongly encourages the peer reviewers to consider comments submitted in response to this review of ETBE alongside those received in response to EPA's review of TBA. API specifically endorses the written comments provided and source materials identified on this topic by Dr. Samuel Cohen following the June 2016 Public Science Meeting, which can be found in the TBA docket[1], and by Dr. Marcy Banton in response to EPA's Public Comment Draft for ETBE, which can be found in the ETBE docket[2]. These materials support the view that rat kidney effects of ETBE exposure are inappropriate for characterizing potential human risk. As with ETBE's primary metabolite TBA, the ETBE-induced kidney findings observed in repeated exposure rat studies are associated with MOAs (α2u-globulin nephropathy and CPN) that are not relevant to humans. As stated by Dr. Banton, the draft assessment's selection of urothelial hyperplasia as the key endpoint for derivation of the oral reference dose (RfD) and inhalation reference concentration (RfC) is not valid because the type of transitional cell hyperplasia observed in various chronic studies of ETBE is not a manifestation of chemically-induced renal toxicity, but a component of advanced chronic progressive nephropathy, a spontaneous disease process of rats that is not relevant to humans.

The relevance of specific pathology, e.g. transitional cell hyperplasia, appearing in concert with rat kidney CPN is thus a key issue for consideration by the peer reviewers. In the absence of pathology distinct from that associated with CPN in the rat, API believes exacerbation of a disease process acknowledged as not occurring in humans is an inappropriate basis for human risk assessment. Acknowledging that rat CPN does not occur in humans, but then differentiating exacerbation of CPN as relevant to human health, remains unsupported in the absence of specific pathology differentiating the underlying disease processes.

It is also noteworthy that the Agency states their evaluation of the rat kidney effects, including the role of α2u-globulin and chronic progressive nephropathy, was conducted in accordance with EPA guidance (U.S. EPA, 1991). The effort that has been focused on this topic in the intervening 26 year period since the 1991 EPA guidance document begs the question of whether an evaluation structured in accordance with the 1991 guidance adequately reflects the current state of the science on this topic. Attention by the peer reviewers to this fundamental question is requested.

[1] Comment submitted by Samuel M. Cohen, Department of Pathology & Microbiology, University of Nebraska Medical Center. Available at: https://www.regulations.gov/document?D=EPA-HQ-ORD-2013-0111-0039
[2] Comment submitted by Marcy I. Banton, PhD, Senior Manager, Global Toxicology and Chemical Control, LyondellBasell. Available at: https://www.regulations.gov/document?D=EPA-HQ-ORD-2009-0229-0064

III. Oral Reference Dose for Noncancer Outcomes

Charge Question 3c: "*Section 2.1 presents an oral reference dose of 5x10–1 mg/kg–day, based on urothelial hyperplasia in male rats (Suzuki et al., 2012). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative data set or approach would be more appropriate, please outline how such data might be used or how the approach might be developed.*"

Comment

As discussed above, the rodent kidney effects of ETBE exposure are inappropriate for characterizing potential human risk and should not be used as a basis for EPA's noncancer risk assessment of ETBE. Dose-response assessment conducted for the purposes of extrapolating risks from these findings to humans is inappropriate.

IV. Inhalation Reference Concentration for Noncancer Outcomes

Charge Question 3d: "*Section 2.2 presents an inhalation reference concentration of 9 x 100 mg/m3, based on urothelial hyperplasia in male rats (Saito et al., 2013). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative data set or approach would be more appropriate, please outline how such data might be used or the approach might be developed.*"

Comment

Consistent with the comments above that the rodent kidney effects of ETE exposure are inappropriate for characterizing potential human risk and should not be used as a basis for EPA's noncancer risk assessment of ETBE, dose-response assessment conducted for the purposes of extrapolating risks from these findings to humans is inappropriate.

V. Cancer Modes-of-Action in Rat Liver

Charge Question 4a: "*As described in section 1.2.2, the draft assessment evaluated the roles of the receptor pathways PPARα, PXR, and CAR in ETBE tumorigenesis in male rats. The analysis, conducted in accordance with EPA's cancer guidelines (U.S. EPA, 2005), considered the liver tumors in male rats to be relevant to human hazard identification. Please comment on whether this conclusion is scientifically supported.*"

Comment

The mode of action (MOA) of ETBE high dose male rat liver tumors following inhalation exposure is of questionable relevance to human risk assessment given the excessive doses used in the rat study. The Draft Review concludes that a mode of action for the high dose male rat liver tumors could not be established, and in the absence of information to indicate otherwise, the liver tumors induced by ETBE are considered to be relevant to humans. In public comments submitted to the docket, the Japan Petroleum Energy Center (JPEC), who conducted much of the available MOA research for ETBE, stated that the high dose liver tumors are likely associated with centrilobular hypertrophy resulting from microsome proliferation and increased synthesis of microsomal cytochrome P450 enzymes, generation of ROS, and promotion of spontaneously initiated hepatocytes. Interpretations from the JPEC research program differ from those of EPA and conclude that the mode of action for ETBE high dose liver tumors in male rats is unlikely to be relevant to humans. API encourages the peer reviewers to pay special attention to the JPEC comments on this aspect of the ETBE assessment, which can be found in the docket[3].

In response to earlier comments submitted on this topic, EPA added Table 1-13 to the Draft Review, which groups and summarizes evidence related to the ten key characteristics of carcinogens based on the criteria of Smith et al. (2015). This analysis provides at best a weak association with carcinogen characteristics, providing evidence for only a single characteristic, metabolism to acetaldehyde. No evidence was found for five characteristics and evidence was judged inadequate or equivocal for the remaining four characteristics. With regard to acetaldehyde as a determinant of the mode of action for the high dose male rat liver tumors, EPA states that existing data are inadequate to conclude that ETBE induces liver tumors via acetaldehyde-mediated mutagenic MOA. Further comments on this topic are provided below in our response to Charge Question 4b.

A key question becomes how to properly assess relevance to humans in this situation, when an MOA has not been established, available data do not indicate a mutagenic MOA, and there is limited evidence of carcinogenicity as discussed below in response to Charge Question 4b. Are the excessive dose aspects of the male rat liver tumor response properly weighted in EPA's review? API encourages the peer reviewers to pay particular attention to this aspect of the assessment.

[3] Comments submitted by Japan Petroleum Energy Center. Available at: https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=PS&D=EPA-HQ-ORD-2009-0229

VI. Cancer Characterization

Charge Question 4b: "*As described in sections 1.2.1, 1.2.2, 1.2.5 and 1.3.2, and in accordance with EPA's cancer guidelines (U.S. EPA, 2005), the draft assessment concludes that there is suggestive evidence of carcinogenic potential for ETBE by all routes of exposure, based on liver tumors in male F344 rats via inhalation and on promotion of liver, colon, thyroid, forestomach, and urinary bladder tumors in male rats via oral exposure. Does the classification give appropriate weight to the results from initiation–promotion studies? Please comment on whether this cancer descriptor is scientifically supported. If another cancer descriptor should be selected, please outline how it might be supported.*"

<u>Comment</u>

API believes that the available animal data for ETBE do not provide evidence suggestive of potential human carcinogenicity by all routes of exposure. API encourages the peer reviewers to pay special attention to all aspects of this unusual dataset, including the following points.

- The very high doses studied in the chronic cancer bioassays of ETBE, including maximum achievable doses in the oral studies and levels exceeding metabolic saturation in the chronic inhalation study, should be a consideration in deciding the cancer classification for ETBE. See further discussion of this point in the response to Charge Question 4e below.

- Evidence of carcinogenic potential of ETBE in chronic cancer bioassays is quite limited. The carcinogenic potential of ETBE has been studied in chronic rat bioassays via inhalation, drinking water and gavage exposure. Evidence of tumorigenicity is:
    - limited to almost entirely benign tumors (one carcinoma) in a single tissue, liver;
    - limited to males only;
    - limited to inhalation exposure; and
    - limited to the highest exposure concentration, which saturated metabolic processes, and which exceeded the recommended maximum dose for a single acute inhalation exposure by standard test guidelines.

- Chronic oral cancer bioassays (drinking water and gavage) were negative at the maximum achievable dose. In the case of the chronic drinking water bioassay, the highest concentration that could be tested was 10,000 ppm. ETBE has water solubility values of approximately 2,300 ppm at 20 deg C (REACH registration), 2640 ppm at 25 deg C (EPISuite WSKOW estimate from Log Kow), and 12,000 ppm at 20 deg C (Evans and Edlund, 1936, as cited in EPISuite). So the bioassay concentration of 10,000 ppm can reasonably be considered the maximum exposure that can be achieved by the drinking water route. Animals in the chronic gavage study were administered doses up

to approximately twice the intake levels achieved in the drinking water study; these higher doses also produced no evidence of carcinogenicity. These high dose considerations should be weighted in the cancer classification decision. API notes, in this regard, that the Agency's 2005 Carcinogen Risk Assessment Guidelines indicate that more than one descriptor can be used when an agent's effects differ by dose or exposure route.

- Tumor promotion results are not equivalent to and should not be weighted more heavily than the negative chronic bioassay results. Tumor promotion studies were conducted by the oral gavage route up to a limit dose of 1,000 mg/kg/day, which was also the high dose in the chronic gavage cancer bioassay. This limit dose is approximately twice the maximum exposure achievable by drinking water and exceeds doses shown to saturate metabolism.

How the tumor promotion results should be weighted as evidence of carcinogenic potential in light of the negative chronic oral bioassays is a key consideration. The Agency cites the tumor promotion results in support of their conclusions regarding human carcinogenicity potential and classification of ETBE as having "*suggestive evidence of carcinogenic potential*" by all routes of human exposure, indicating that the tumor promotion results are weighted more heavily than the chronic rodent bioassays. API believes this is inappropriate and inconsistent with Agency guidelines.

The Draft Review indicates that Agency guidelines do not provide specific recommendations on how to incorporate results from such studies. API notes, however, that the Agency's 2005 Carcinogen Risk Assessment Guidelines (cancer guidelines) (pg. 2-24) do provide comments on the use of tumor initiation-promotion data, stating, in part:

> *The support that these studies give to a determination of carcinogenicity rests on their contribution to the consistency of other evidence about an agent. For instance, benzoyl peroxide has promoter activity on the skin, but the overall evidence may be less supportive. . .These studies also may contribute information about mode of action. It is important to recognize the limitations of these experimental protocols, such as short duration, limited histology, lack of complete development of tumors, or experimental manipulation of the carcinogenic process, that may limit their contribution to the overall assessment. Generally, their results are appropriate as aids in the interpretation of other toxicological evidence (e.g., rodent chronic bioassays), especially regarding potential modes of action. On the basis of currently available information, it is unlikely that any of these assays, which are conducted for 6 months with 15 animals per group, will replace all chronic bioassays for hazard identification.*

Review shows that two quite different tumor promotion protocols were employed in studies of ETBE. A total of three rat studies have been reported, each at doses up to 1000 mg/kg/day. Two studies investigated tumor-promoting effects of ETBE in liver, kidney and urinary bladder using conventional methods following administration of a single initiating agent (Hagiwara et al. 2015; Hagiwara et al. 2013). These studies reported a NOAEL of 500 mg/kg/day for the tumor promoting effects of ETBE. A third study was conducted according to the multi-organ, multi-carcinogen DMBDD model, in which animals were given five different carcinogens for up to four weeks, followed by ETBE at gavage doses of 0, 300 or 1000 mg/kg/day (Hagiwara et al. 2011). In the DMBDD study, ETBE was reported to have tumor promoting potential in some organs at 300 mg/kg/day and more, and in others at 1000 mg/kg/day. Thus, a lower NOAEL was indicated in the multi-organ DMBDD study than was found in the conventional tumor promotion studies. During the October 26, 2016 IRIS Public Science Meeting, questions were raised about the degree to which the multi-organ, multi-carcinogen DMBDD protocol has been fully validated. For example, has the assay been shown to be reliable in differentiating chemicals which have tumor promoting potential from chemicals which do not? To the best of our knowledge, this question remains open, and is relevant to how these results should be employed in the classification of ETBE.

The charge statement by EPA that classification is "based on liver tumors in male F344 rats via inhalation and on promotion of liver, colon, thyroid, forestomach, and urinary bladder tumors in male rats via oral exposure" indicates that the results from all three of the tumor promotion studies are weighted equally in the classification decision by EPA, and that the tumor promotion results are weighted more heavily than the negative results from the chronic oral cancer bioassays. API believe the tumor promotion data are given too much weight by the Agency in their integration of the carcinogenicity information for ETBE. Citing the tumor promotion results as supportive of a cancer concern in the face of multiple negative chronic cancer bioassays conducted at limit doses by the same route of exposure and in the same species seems to be inconsistent with the Agency's cancer guidelines, and this is scientifically inappropriate.

API also finds the Draft Review document to be inconsistent and therefore unclear about the factors weighted in the classification decision. Section 1.3.2 (page 1-111) states that the conclusion of suggestive evidence of carcinogenic potential for ETBE is "*based primarily on a positive carcinogenic response in the liver at one dose in a single animal study, along with significant increases in focal pre-neoplastic liver lesions and mechanistic data, including the metabolism of ETBE to acetaldehyde in the liver, and the mutagenic and genotoxic effects of acetaldehyde.*"

With regard to this stated concern about acetaldehyde as a contributor to ETBE carcinogenic potential, the results of the chronic bioassays are the best source of data to address this concern, as acetaldehyde exposure via metabolism is an intrinsic property of these studies.

Given that the chronic bioassays of ETBE were conducted at limit doses, weighting acetaldehyde as a separate factor in determining the carcinogen classification is unjustified in our view. It should also be noted that to the extent acetaldehyde's mutagenicity is weighted in the classification decision of ETBE, it is reasonable to expect that this risk would be evident in the existing genotoxicity dataset for ETBE. While EPA considers the genotoxicity dataset for ETBE to be limited, the existing studies of ETBE in Aldh2 competent test systems (as in the negative chronic oral cancer bioassays) do not support EPA's concern for mutagenicity. Therefore, API believes that citing the mutagenic and genotoxic effects of acetaldehyde as a basis for the cancer classification of ETBE is not justified by the available data.

Finally, API notes that the Agency's 2005 Carcinogen Risk Assessment Guidelines (pg. 2-58) indicate that "More than one descriptor can be used when an agent's effects differ by dose or exposure route." API encourages the peer reviewers to give serious consideration to this guidance and whether it could be properly applied to the cancer characterization of ETBE. In this case, the available evidence suggests no carcinogenic potential by the oral route, and no carcinogenic potential below excessive doses by the inhalation route, yet the excessively high dose inhalation data are used as the basis for classifying ETBE carcinogenicity by all routes and at all doses.

VII. Cancer Toxicity Values

Charge question 4c: "*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 quantitative analysis, and whether the Saito et al. (2013) study is suitable for this purpose."

<u>Comment</u>

The Draft Review presents cancer dose response analysis based on the single inhalation data point to define a point of departure for linear extrapolation and estimation of low dose human cancer risk, and extends this approach to also quantify low dose oral cancer risk. The Agency's 2005 cancer guidelines (pg. 3-2) states that such analyses, based on suggestive evidence,

"*generally would not be considered Agency consensus estimates*" and that "*Dose-response assessments are generally not done when there is inadequate evidence*" of carcinogenic potential. These qualifiers are appropriate in the case of ETBE.

Consistent with the position explained earlier regarding insufficient evidence of carcinogenic potential by ETBE of relevance to humans, the Agency's use of the single high dose inhalation data point to support linear dose response analysis and extrapolation of low dose cancer risk estimates to humans by all routes of exposure is inappropriate and inconsistent with Agency guidelines. The approach described in the Draft Review is especially egregious in applying the inhalation results to the oral route of exposure in the face of no evidence of carcinogenicity in two oral cancer bioassays conducted at maximum achievable doses. A more appropriate approach would be acceptance of 6,270 mg/m3 as a NOAEL for tumorigenic effects of ETBE by inhalation in the rat.

VIII. Oral Slope Factor for Cancer

Charge Question 4d: "*Section 2.3 presents an oral slope factor of 1 x 10–3 per mg/kg–day, based on liver tumors in male rats by inhalation (Saito et al., 2013), converted for oral exposure using a toxicokinetic model (Borghoff et al., 2016). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative approach would be more appropriate, please outline how it might be developed.*"

<u>Comment</u>

Chronic oral bioassays were negative at the maximum achievable dose. In the case of the chronic drinking water bioassay, the highest concentration that could be tested was 10,000 ppm. ETBE has water solubility values of approximately 2,300 ppm at 20 deg C (REACH registration), 2640 ppm at 25 deg C (EPISuite WSKOW estimate from Log Kow), and 12,000 ppm at 20 deg C (Evans and Edlund, 1936, as cited in EPISuite). So the bioassay concentration of 10,000 ppm can reasonably be considered the maximum exposure that can be achieved by the drinking water route. Animals in the chronic gavage study were administered doses up to approximately twice the intake levels achieved in the drinking water study; these higher doses also produced no evidence of carcinogenicity. In the face of these definitive negative results by the oral route of exposure, extrapolation of high dose liver tumor response seen in the chronic inhalation study to predict oral cancer risk is inappropriate.

In terms of the oral slope factor calculations provided in the Draft Review, API notes that while the dataset and dose response model remain the same as presented in the 2016 Public Comment Draft, the oral slope factor increased from 9 x 10E-4 in the PCD to 1 x 10E-3 in the ERD. Based on the summary provided in the document this change appears to be related to

differences in how the dose adjustment calculations (inhalation to oral) were performed, although the details are not entirely clear. API encourages the peer reviewers to review the derivation of this value in detail, and to assure that it is proper and clearly described if it remains in the Draft Review.

IX. Inhalation Unit Risk for Cancer

Charge Question 4e: "*Section 2.4 presents an inhalation unit risk of 8 x 10–5 per mg/m3, based on liver tumors in male rats by inhalation (Saito et al., 2013). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative approach would be more appropriate, please outline how it might be developed.*"

Comment

The male rat liver tumors occurred at a very high dose that saturated metabolic processes. The chronic rat inhalation study of ETBE produced almost exclusively benign (one carcinoma) liver tumors only in male rats and only at the unusually high chronic concentration of 20,900 mg/m3. This concentration is above the limit of 20,000 mg/m3 recommended by OECD for acute (single exposure) vapor inhalation studies. The implications of prolonged exposures to such high concentrations need to be carefully considered. Principal among concerns is whether this high exposure level exceeded the animals' metabolic capacity. Information contained in the Draft Review suggests that this is the case. The Draft Review states 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/m3".* The review states separately that *"there are several unpublished reports relevant to the elimination of ETBE following inhalation exposure… Unpublished reports have not gone through the public peer-review process and are of unknown quality. They are included here* [in the Draft Review] *as additional information only".* These statements suggest that information exists to allow consideration of metabolic saturation at the tumorigenic dose in male rats and its possible influence on mechanisms and dose response.

The Agency's cancer guidelines (pg 2-17) speak to excessive doses, stating: "*an excessive high dose may include …. saturation of absorption and detoxification mechanisms…. Studies that show tumor effects only at excessive doses may be compromised and may or may not carry weight, depending on the interpretation in the context of other study results and other lines of evidence. Results of such studies, however, are generally not considered suitable for dose-response extrapolation if it is determined that the mode(s) of action underlying the tumorigenic responses at high doses is not operative at lower doses."*

Evidence that the 20,900 mg/m3 inhalation exposure concentration was an excessively high test concentration in rats is further supported by the fact 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. Male and female terminal body weights were 94% and 91% of controls, respectively, in next lower (6,270 mg/m3) ETBE exposure. In addition, the significantly increased incidence of preneoplastic eosinophilic and basophilic liver foci was limited to the 20,900 mg/m3 treatment group, indicating that tumorigenic responses would be unlikely at the 6,270 mg/m3 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 (per comments submitted to the docket by Dr. Marcy Banton)[4].

Given that the male rat liver tumors observed in the chronic inhalation study of ETBE occurred at an excessively high dose, thorough consideration of the evidence is warranted and a suitable rationale for risk quantitation needs to be established. API believes the Draft Review falls short of providing such a rationale. A mutagenic mode of action is not established for ETBE based on the available genotoxicity data. Conventional tumor promotion studies (by gavage) also indicate effects only at excessive doses (1,000 mg/kg/day). The most reliable evidence for ETBE experimental tumorigenesis indicates a limited effect—almost exclusively benign liver tumors (one carcinoma) at excessive doses in male rats only. Linear low dose extrapolation of these results is inappropriate, as acknowledged in the Agency's cancer guidelines.

A more appropriate approach would be acceptance of 6,270 mg/m3 as a NOAEL for tumorigenic effects of ETBE by inhalation in the rat.

[4] Comment submitted by Marcy I. Banton, PhD, Senior Manager, Global Toxicology and Chemical Control, LyondellBasell. Available at: https://www.regulations.gov/document?D=EPA-HQ-ORD-2009-0229-0064

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