Response to Public Comments Received on the T*ert*-Butyl Alcohol Draft Development Support Document

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Response to Comments

March 10, 2023

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Response to Public Comments Received on the September 15, 2022 Proposed tert-Butyl Alcohol Development Support Document

The public comment period on the draft Development Support Document (DSD) for tert-butyl alcohol (TBA) ended December 16, 2022. The agency received comments on the draft DSD from a private citizen and from LyondellBasell. The TCEQ appreciates the effort put forth to provide comments on the draft DSD for TBA. The goal of the TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. Comments are provided below, followed by TCEQ responses.

Comments from a private citizen

Comment: I don't know why Texas is suddenly doing a study about this one other places have already said it's a really bad for people and the environment.

Do you really think using a gasoline additive is okay to put into cosmetics and food flavoring?

I am totally against its use.

Response: Thank you for your comments. The purpose of the proposed Development Support Document is to describe the derivation of a concentration of *tert*-butyl alcohol that is safe in air. While the document does include information on uses of *tert*-butyl alcohol, the request for comments is regarding the derivation of the health-protective concentrations of this chemical in air. The United States Food and Drug Administration (FDA) regulates cosmetics and food flavorings. Please see the links to the appropriate pages of the FDA website for additional information.

FDA regulates cosmetics:

https://www.fda.gov/cosmetics/cosmetics-laws-regulations/fda-authority-over-cosmetics-how-cosmetics-are-not-fda-approved-are-fda-regulated

FDA regulates food flavorings:

https://www.fda.gov/food/food-ingredients-packaging/overview-food-ingredients-additives-colors

Comments from LyondellBasell

Comment 1: Assessing human relevance of toxicological findings in animals for TBA is challenging, and we commend TCEQ's efforts in drafting this DSD. We offer comments to support refinement to this important document.

Response: TCEQ appreciates the effort of LyondellBasell in providing such comments for our consideration.

Comment 2: p.3, Table 2, Notes for Chronic $ReV_{threshold(nc)}$: It would be useful to indicate extrapolation was based on PBPK modeling, e.g., "PBPK-based oral route to inhalation route extrapolation."

Response: TCEQ has added the following footnote, "a. Based on route-to-route extrapolation (i.e., oral-to-inhalation route) using physiologically based pharmacokinetic (PBPK) modeling."

Comment 3: p.5, 2.2.2 Uses: Based on the description of TBA uses in the EPA IRIS (EPA, 2021), this section describes the large numerical volumes of TBA used in the manufacture of the fuel oxygenates MTBE and ETBE. However, TCEQ is referred to earlier comments offered by LyondellBasell regarding TCEQ's request for TBA toxicity data (LyondellBasell comments to TCEQ, October 16, 2020, also referencing July 13, 2016 comments to EPA regarding the draft IRIS TBA Toxicological Review; both attached here in Appendix A) noting that US production of TBA is almost entirely directed to limited site and tightly controlled fuel oxygenate production.

Response: TCEQ appreciates this comment. However, no reference was provided and this type of information is secondary to the primary purpose of the DSD, which is to document the derivation of toxicity factors. Therefore, no revision was made but this comment will appear in the public comment record posted on the TCEQ DSD website for the final TBA DSD.

Comment 4: The draft DSD derivations of the 1-hr acute ReV, ^{acute}ESL and IOAEL values are appropriately based on a high-quality subacute study (NTP, 1997; 6 hr/day, 5 days/week, total 12 exposures) in which ataxia, hyperactivity and hypoactivity were observed with a NOAEL (POD) of 450 ppm and a LOAEL of 900 ppm. The derived health values follow TCEQ internal guidance for derivation of toxicity factors, and the selected neurotoxicity-based endpoint will be health protective of other toxicity endpoints observed at higher POD doses.

Response: TCEQ appreciates this comment acknowledging the protectiveness of the acute ReV.

Comment 5: The draft DSD includes a database uncertainty factor (UF_D) of 3. The rationale for this UF_D in section 3.1.3.4. should be strengthened in the following manner. Include an additional sentence in the descriptive paragraph that states that minimal effects were observed at otherwise toxic dose levels in the postnatal developmental toxicity study. This sentence is the concluding statement in section 3.1.1.3.2 of the draft DSD. The sentence is correct and consistent with conclusions made both by US EPA IRIS and authors of the study (Nelson et al. 1991).

Response: Following careful consideration, TCEQ added similar language to the justification of the UF_D of 3.

Comment 6: In addition, the NOAEL derived from Nelson et al. (1991) in section 3.1.1.3.2 of the draft DSD should be corrected to be 2,000 ppm. As the draft DSD states in section 3.1.1.3.2, Nelson et al. (1991) analyzed brain regions for several neurotransmitters and incorporated multiple tests of motor activity, motor coordination, and cognitive behavior including schedule controlled operant behavior. Although this study is considered of "low quality" because the two

concentrations of TBA were run at different times, Nelson et al. (1991) ran a concurrent control group for each concentration and appropriately compared the test data against its own concurrent control. Additionally, the Nelson et al. study included a large number of endpoints including multiple parameters from several motor and cognitive/operant behaviors as well as neurochemical analyses of multiple neurotransmitters in different brain areas.

EPA's Guidelines for Neurotoxicity Risk Assessment emphasize the importance of considering patterns of effects rather than individual statistical significance (EPA, 1998). Based on the lack of consistent patterns, Nelson et al. (1991) concluded that TBA "does not appear to produce remarkable behavioral or neurochemical deviations in offspring" at either exposure level, including the highest 4,000 ppm exposure concentrations that produced maternal and systemic toxicity. Thus, although there were a few scattered statistically significant findings at 2,000 ppm, there were no adverse findings at this dose level and a conservative NOAEL for this study is 2,000 ppm. We note that the methods section of the Nelson et al. (1991) publication refers to previous publications for further details that strengthen the reliability of this study. Evaluation of these and other papers by the same authors increases confidence that this laboratory was experienced in conducting the same battery of behavioral tests following inhalation exposures to several alcohols. As a result, the existing database is stronger than its characterization in the draft DSD and indicates that further studies are unlikely to identify a more sensitive endpoint or a lower POD. Consequently, the draft DSD should expand its discussion in both 3.1.1.3.2 and 3.1.3.4 to strengthen the justification for the UF_D of 3, which is conservatively protective.

Response: The draft DSD acknowledged in Section 4.1.1.3 that, "In the postnatal development study (Nelson et al. 1991) the authors concluded that "the small number of statistically significant behavioral and neurochemical effects did not provide evidence of a dose-effect relationship or discernible pattern of effects" and that "the few effects were likely of little or no biological significance". Moreover, the exposures to the two concentrations of TBA evaluated (2000 and 4000 ppm) were not run concurrently thereby making comparisons between the exposure concentrations inappropriate…" This latter factor complicates the evaluation of dose-response, which was "not consistently evident for the findings" as stated in the draft DSD. Furthermore, "it is not known what the NOAEL or LOAEL was for males exposed for 6 weeks because there was no mention of comparison to control males".

The effects that were observed cannot be so easily dismissed as having no adverse or biological significance, particularly because the study conduct was not amenable to the evaluation of effect patterns and/or dose-response. Based on these considerations, the TCEQ has more clearly caveated the LOAEL [*emphasis added*] in Section 3.1.1.3.2, stating that "the TCEQ considers ≥ 2000 ppm as a *tentative* LOAEL in pups (maternally and/or paternally exposed) and a NOAEL in pups cannot be confidently identified." This is in agreement with the statement in Section 3.1.1.3.2, "The authors suggest that more investigations be conducted." No changes were made to the justification for the UF_D of 3, however, as it is more than sufficiently justified with the added revision pursuant to the above comment.

Comment 7: p.18, 4.1: The draft DSD follows TCEQ guidance in its selection of the increased absolute kidney weight reported at the 15-month interim-sacrifice of female rats in a 2-year drinking water study (key study, NTP, 1995) as the appropriate (but highly conservative) POD for derivation of chronic health values. As required by TCEQ guidance, this endpoint had the overall lowest POD associated with all other kidney endpoints considered, and thus reflects the first observed response of the overall dose-dependent spectrum of kidney responses (Table 6: increased absolute kidney weight in a 13 week inhalation study; increased suppurative inflammation, transitional epithelial hyperplasia or severity of CPN in the 2-year drinking water study).

Response: TCEQ appreciates this comment.

Comment 8: The draft DSD appropriately excludes consideration of male rat nephropathy in selection of the key endpoint because it is clearly associated with overlays of both α2u-globulin and CPN modes of action (MOA). The α2u-globulin mode is accepted by EPA as a mode of action lacking qualitative human relevance and thus male rat kidney toxicity induced by TBA is not viewed as relevant to human risk.

Response: TCEQ appreciates this comment.

Comment 9: p.25, top, "The renal findings in female rats were considered appropriate for derivation of a chronic ReV because: (1) the MOA for CPN is currently unknown; (2) there is no consensus that the exacerbation of CPN observed in rats is not relevant to humans; and (3) potential human relevance of the renal findings observed in female rats cannot be excluded.": A substantial body of toxicological literature views naturally occurring rat CPN and exacerbation of CPN by xenobiotics as lacking qualitative human relevance because CPN has no human clinical correlate (Hard and Khan, 2004; Hard et al., 2009; Hard et al., 2012; Hard et al., 2013; Hard et al., 2019; more details are found in LyondellBasell comments to TCEQ, October 16, 2020). Thus, the draft DSD should further clarify and emphasize that selection of the female rat kidney endpoint is highly conservative given its questioned qualitative relevance to human health non-cancer and cancer risks.

Response: TCEQ acknowledges that selection of the female rat kidney endpoint is conservative in the face of uncertainty regarding its relevance to human health. The following text was added to Section 4.1.2 to emphasize this, "In light of the conflicting evidence regarding the relevance of CPN to humans (see Appendix 2), the use of female rat kidney endpoint data is a conservative choice to ensure the protection of public health in the face of uncertainty."

Comment 10: Importantly, as described by Hard et al. (2013; this paper is not cited/reviewed in the draft DSD; LyondellBasell comments to TCEQ, October 16, 2020), a mode of action has been proposed for CPN and its exacerbation by xenobiotics resulting in low-grade (mostly adenomas) and incidence renal tumors. These investigators emphasized that mode of action analyses do not require a detailed understanding of the underlying and more precise mechanism(s) of CPN, but rather require only that "…the key event be identified as increased CPN with its associated

increase in tubular cell proliferation." Thus, the draft DSD should note that a CPN-based mode of action has indeed been proposed.

Response: TCEQ has added such a reference to Hard et al. (2013) to Section 4.2.1 of the DSD (*Carcinogenic Weight of Evidence and Hazard Assessment*).

Comment 11: Although a substantial body of literature has indicated that chemically-induced exacerbation of CPN is not qualitatively relevant to human risk, Hard et al. (2013) also observes that "regulatory/authoritative bodies have generally not specifically addressed the role of CPN in the MoA for renal tumors." The draft DSD also refers to an EPA commissioned pathology consultation with NIEHS that included a charge of addressing the human relevance of TBA-induced exacerbation of CPN (NIEHS, 2019, provided as Appendix D of EPA IRIS, 2021). The NIEHS consultation response to EPA described the opinion of a single, but reputable, pathologist (JC Seely) who had multiple CPN-based publications and concluded:

> "The etiology of CPN is unknown and represents a complex disease process in rats. Given the fact that there is no definitive pathogenesis for this multifactorial disease process, it cannot be fully ruled out that chemicals which exacerbate CPN in rats may have the potential to exacerbate disease processes in the human kidney."

Despite the above statement, the consulting pathologist responded to the EPA charge question "It has been hypothesized that there is no analog to the CPN process in the aging human kidney. Does this position reflect *consensus in the field of pathology* [emphasis added}?" with the following, seemingly contradictory, statement:

> "Yes, the publication by Hard, Johnson, and Cohen makes a very strong case that the renal development, biological behavior, and morphological spectrum of CPN have no analog in the human kidney and the CPN is a distinct entity in the rat (Hard et al., 2009). Overall, CPN has prominent protein filled dilated tubules, no vascular changes, no immunological or autoimmune basis, and little inflammation which distinguishes CPN from most human nephropathies (Hard et al., 2009). There appears to be nothing in the literature that counters this assumption."

Based in part on the above consultation, EPA IRIS (EPA, 2021) developed its risk assessment (RfD and RfC values) on the assumption that CPN was human relevant; and based on this conclusion, the draft DSD also relies on increased TBA-induced female rat kidney weight as the primary response for derivation of the chronic health values. It is important to note, however, that the strength of the NIEHS consultation is tempered in that it originates from a single pathologist who also clearly states that there is nothing that "counters" the assumption that CPN *lacks* a human clinical disease correlate.

Response: TCEQ appreciates LyondellBasell providing these points and perspective on CPN and increased TBA-induced female rat kidney weight as the primary basis for EPA and TCEQ chronic health values. However, as an example, even if CPN has no analog in the human kidney and CPN is a distinct entity in the rat (from the latter statement), this does not preclude chemicals that

exacerbate CPN in rats from exacerbating other disease processes in the human kidney (from the former statement). No DSD revisions were made pursuant to these comments.

Comment 12: Given the inconsistency of the interpretation of the human relevance of CPN, the draft DSD would benefit from additional amplification of the above discussions identifying the relatively high level of uncertainty associated with the human relevance of rat kidney toxicity (including increased kidney weights in female rats), as part of the constellation of kidney responses inclusive of CPN. Such amplification would provide clarity and further emphasis that reliance on the rat kidney weight response as the basis for the chronic risk values is indeed highly conservative and thus is health protective of other more human relevant responses (e.g., liver toxicity) observed at higher TBA doses.

Response: TCEQ acknowledges that selection of the female rat kidney endpoint is conservative in the face of uncertainty regarding its relevance to human health. The following text was added to Section 4.1.5 to emphasize this, "In light of the conflicting evidence regarding the relevance of CPN to humans (see Appendix 2), the TCEQ's consideration of this and other POD_{HEC} values based on female rat kidney endpoints is a conservative choice to ensure the protection of public health (in the face of uncertainty) against the full spectrum of potential TBA-induced adverse effects."

Comment 13: p.34, 4.2.1: Discussion of TBA-induced mouse thyroid tumors is limited to stating that support for human risk is not "particularly strong" because most observed tumors were "entirely benign." The draft DSD discussion regarding the low concern for the risk relevance of this response would be enhanced if it included observations presented in previous LyondellBasell comments to TCEQ that the incidence of the observed tumors was not statistically significant compared to control, tumors were only observed at a dose that was substantially above the limit dose of 1,000 mg/kg/day for EPA toxicity testing guidelines, and also occurred at a dose likely exceeding toxicokinetic saturation. Because occupational and general population exposures are likely well below the limit dose and doses exhibiting toxicokinetic saturation, tumor findings above such doses lack quantitative mode of action relevance to human risk (LyondellBasell, comments to TCEQ, October 16, 2020).

Response: The above considerations would be more important if TBA were classified as "carcinogenic to humans" or "likely to be carcinogenic to humans", triggering a cancer dose-response assessment and a closer examination of the adequacy and relevance of the dose-response data for assessing human carcinogenic risk. As no dose-response assessment is triggered for TBA under TCEQ guidelines (TCEQ 2015) and the reason for this is clearly explained in the DSD, no revisions were made. This comment will appear in the public comment record posted on the TCEQ DSD website for the final TBA DSD.

Comment 14: p.34, draft DSD conclusion that the "carcinogenic weight of evidence best supports the *suggestive evidence of carcinogenic potential* for TBA": It is unclear how TCEQ concludes the weight of evidence provides the "best support" for "suggestive" evidence of carcinogenicity. Since TCEQ guidance does not appear to specifically address levels of and processes for cancer classification and thus is not positioned to support a conclusion of "best

supports," it would be more accurate if the opening of the sentence were re-worded as something like "Because EPA (2021) has concluded that the carcinogenic weight of evidence best supports…" Such a re-wording would make it clear that TCEQ has not reached an independent position on TBA cancer classification.

Response: TCEQ guidance (TCEQ 2015) incorporates EPA's cancer guidelines (USEPA 2005a,b) by reference and the agency does conduct an independent review of the data under those guidelines, as needed, to determine cancer classification. In the present case, however, this was not needed. Therefore, pursuant to the comment, the referenced sentence now reads, "Because TCEQ concurs with USEPA (2021a) that the carcinogenic weight of evidence best supports the *suggestive evidence of carcinogenic potential* descriptor for TBA, consistent with TCEQ guidelines (TCEQ 2015a), the TD will not perform or adopt a carcinogenic dose-response assessment for TBA."

Comment 15: p.60: See comments above noting Hard et al. (2013) proposed an evidence-based mode of action hypothesis for CPN and chemically-induced exacerbation of CPN as lacking qualitative relevance to human risk because the key events are not observed in human chronic disease.

Response: TCEQ has added a footnote reference for the carcinogenic MOA proposed in Hard et al. (2013) to Appendix 2, which primarily concerns the human relevance of CPN for noncancer effects.

Comment 16: p.61, footnote "b," "The mechanism and/or MOA for chemically exacerbated CPN in rats (as with TBA or ETBE) is unknown, and without an understanding of the key events it is not possible to determine whether or not the underlying processes that occur in rats may also occur in humans (Melnick et al. 2012), much less confidently state that they do not.": The sentence should not infer that knowledge of "mechanism" is necessary to understand CPN health implications, but rather only "MOA." As noted in previous comments above, a mode of action of action has been proposed for chemically-induced CPN exacerbation (Hard et al., 2013), which should be noted and discussed. The draft DSD should also note that the analysis of Melnick et al. (2012) has been substantially challenged as to the reliability of its conclusions (Hard et al., 2013) and that caution is required when suggesting that the Melnick analysis supports a conclusion that "it is not possible to determine whether or not the underlying processes that occur in rats may also occur in humans (Melnick et al. 2012), much less confidently state that they do not."

Response: TCEQ has removed reference to "mechanism" in the referenced sentence and added a footnote reference for the carcinogenic MOA proposed in Hard et al. (2013) to Appendix 2, instead of a full discussion, as Appendix 2 primarily concerns the human relevance of CPN for noncancer effects. The added language reads, "Additionally, exacerbation of CPN, which may not be relevant to humans, has been proposed as an MOA for the development of renal tubule tumors in rats, calling into question the human relevance of these tumors (Hard et al. 2013). The authors of Hard et al. (2013) disagree with and critique various aspects of the Melnick et al.

(2012) review that raised questions regarding the validity of exacerbation of CPN as an MOA for rat renal tumorigenesis."

LyondellBasell References

Hard, G. C. and Khan, K. N. (2004). A contemporary overview of chronic progressive nephropathy in the laboratory rat, and its significance for human risk assessment. Toxicol Pathol 32(2): 171-180.

Hard, G. C., Johnson, K. J., and Cohen, S. M. (2009). A comparison of rat chronic progressive nephropathy with human renal disease-implications for human risk assessment. Crit Rev Toxicol 39(4): 332-346.

Hard, G. C., Betz, L. J., and Seely, J. C. (2012). Association of advanced chronic progressive nephropathy (CPN) with renal tubule tumors and precursor hyperplasia in control F344 rats from two-year carcinogenicity studies. Toxicol Pathol 40(3): 473-481.

Hard, G. C., Banton, M. I., Bretzlaff, R. S., Dekant, W., Fowles, J. R., Mallett, A. K., McGregor, D. B., Roberts, K. M., Sielken, R. L., Jr., Valdez-Flores, C., and Cohen, S. M. (2013). Consideration of rat chronic progressive nephropathy in regulatory evaluations for carcinogenicity. Toxicol Sci 132(2): 268-275.