Texas Commission on Environmental Quality Response to Public Comments Received on the May 28, 2010 Proposed n-Butyl Acetate Development Support Document

The public comment period for the May 2010 Proposed Development Support Document (DSD) for n-butyl acetate (n-BA) ended in August 2010. The American Chemistry Council's Oxo Process Panel ("ACC Panel") submitted comments. The Toxicology Division (TD) of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by ACC to provide technical comments on the proposed DSD for n-BA. The goal of the TD and 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. A summary of comments from ACC is provided below, followed by TCEQ responses. The full comments are provided in Appendix 1. Comments on issues that suggest changes in the DSD are addressed whereas comments agreeing with TCEQ's approach are not. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

Upon further review, the DSD has been revised. The acute ReV and ESL for n-BA have been revised by lowering the total uncertainty factor (UF) from 30 to 20 to the human equivalent concentration point of departure (POD_{HEC}). A lower UF_L of 2, instead of 3, has been applied for extrapolation from a lowest-observed-adverse-effects level (LOAEL) to a no-observed-adverse-effects level (NOAEL) based on the fact that the irritation to eyes and respiratory tract rated by all of the subjects who participated in the key acute study (Iregren et al. 1993) was very minimal. The acute ReV and ESL have been revised from 4,800 and 1,400 ppb to 7,400 and 2,200 ppb, respectively.

In regard to the chronic ReV and ESL, the subchronic LOAEL identified by Bernard et al. (1996) has been corrected from 550 to 500 ppm. Furthermore, the chronic ReV and ESL have also been revised by lowering the total UF from 300 to 100 to the chronic POD_{HEC}. A lower UF_{Sub} of 1, instead of 3, has been applied for extrapolation from subchronic to chronic because the subchronic effects found in the key study are concentration dependent and metabolites of n-BA do not accumulate, and chronic effects would not be expected to differ significantly from subchronic effects. Accordingly, the chronic ReV and ESL have been revised to 130 and 39 ppb, respectively

American Chemistry Council's Oxo Process Panel ("ACC Panel") (Appendix 1)

1. The ACC Panel Urges TCEQ to Reevaluate the Health-based acute ReV and acute ESL Methodology

Comment No.1 (Page 2):

The ACC Panel commented that TCEQ used a total UF of 30 to derive the acute ReV from a LOAEL for findings of very minimal irritation to eyes and respiratory tract. The total UF is too large. The ACC Panel indicated that the authors of the key study (Iregren et al. 1993) note that all of the subjects rated n-BA as a "very slight irritation" when rating on categorical scales in

their study. Thus, using such a large uncertainty factor on such a minimal finding can lead to unfounded results.

TCEQ Response:

The DSD has been revised using a lower total UF of 20 (a UF_L of 2 instead of 3 for extrapolation from a LOAEL to a NOAEL, a UF_H of 10 for human variability, and a UF_D of 1 for database uncertainty) to derive acute ReV from a LOAEL for findings of very minimal irritation to eyes and respiratory tract. The TD agrees that the irritation to the eyes and respiratory tract rated by all of the tested subjects was very minimal. Therefore, a lower UF_L of 2, based on the geometric mean (1.7, rounded to 2) of a UF_L of 1 (NOAEL) and 3 (LOAEL for mild and transient effects), was used for extrapolation from a LOAEL to NOAEL (see Section 3.1.8 Adjustments of the POD_{HEC} of the revised n-BA DSD). The revised acute ReV and ESL have been increased to 7,400 and 2,200 ppb, respectively.

Comment No.2 (bottom of Page 2 through Page 3):

The ACC Panel further commented that the proposed acute ReV and ESL for n-BA are much lower than levels that could easily be present in the fresh fruit aisle of a local supermarket. ACC indicated that n-BA levels of between 105 and 585 ppm were routinely recorded as the fruit ripened. A 500 ppm n-BA level has been proposed to provide "sufficient aroma" for the sale of apples and therefore could easily be present in warehouses for apple.

TCEQ Response:

The DSD was not revised based on this comment. The TD does appreciate ACC's comments. While the TD acknowledges levels of n-BA present in the fresh fruit aisle of a local supermarket may be high, the levels only present in the indoor environment. The ReVs and ESLs, however, are set to assess the protectiveness of chemical-specific emissions present in the outdoor atmosphere. The TD will always consider the background concentrations from outdoor ambient air, but not from the indoor air, when developing ReVs and ESLs for specific chemicals. The proposed ReVs and ESLs are much higher than the background ambient air concentrations of n-BA resulting from emissions from United States industrial and chemical waste disposal sites (see Chapter 2 of the DSD for n-BA).

Comment No.3 (bottom of Page 3 through Page 4):

The ACC Panel questioned why an additional hazard quotient (HQ) of 0.3 required deriving the acute ESL from acute ReV. The ACC Panel commented that the acute critical effects (mild local irritation) caused by n-BA, which is considered only concentration dependent, will not lead to accumulative or aggregate adverse outcome. There is no need to derive the acute ESL from acute REV using an additional hazard quotient (HQ) of 0.3 in consideration of cumulative and aggregate exposure. ACC further suggested that the acute ReV and acute ESL for n-BA both be the same at 4,800 ppb.

TCEQ Response:

The DSD was not revised based on this comment. Nevertheless, the acute ReV and ESL for n-BA have been increased to 7,400 and 2,200 ppb, respectively. In general, the ReV is used for air monitoring whereas the health-based ESL, which is 70% lower than the ReV, is used in air permitting. As described in Section 1.6 of the 2006 TCEQ ESL Guidelines, ESLs are used to

assess the protectiveness of chemical-specific emission rate limits for facilities undergoing permit reviews. Evaluations are conducted by comparing the modeled worst-case air concentrations to the respective ESLs to determine the potential for adverse effects for emissions from a proposed facility. ESLs are guideline concentrations, not ambient air standards.

Air concentrations of chemicals collected in air monitoring samples represent emissions from multiple chemicals and from different facilities and sources (i.e., can be both cumulative across chemicals and aggregate across sources and time). For review of air monitoring data, the health-based ReV is appropriate. For review of air permit applications, site-wide modeled concentrations for one chemical at a time are evaluated. The impacts from multiple chemicals or from different sites are not included. Therefore, for air permitting, an ***additional buffer***, i.e., a HQ of 0.3, is applied to the acute or chronic ReV to calculate the acute and chronic ESLs. Please refer to the May 2010 documents entitled- "Uses of Effects Screening Levels (ESLs) and Air Monitoring Comparison Values (AMCVs)" and "AMCV Fact Sheet" for details (Available at http://www.tceq.state.tx.us/implementation/tox/AirToxics.html#amcv).

2. MOA Analysis and Dose Metric

Comment No.4 (bottom of Page 4 through Page 5):

The ACC Panel commented that the nasal lesions found in rat's olfactory epithelium resulting from n-BA subchronic exposure are due to several species-specific factors. ACC indicated that rats are obligate nose-breathers and have higher levels of carboxyesterase activity within their olfactory epithelium when compared to humans. This allows for a greater production of acetic acid within those cells from the hydrolysis of n-BA and subsequent degeneration of those cells. Specifically, ACC cited that Norris et al. (1993) found rats absorb and metabolize 40-65% of the inhaled ethyl acetate within the upper respiratory tract prior to the vapor even reaching the lung. This is in contrast to humans where 50% of an inhaled dose of n-BA is exhaled unchanged. ACC suggested that the DSD for n-BA should acknowledge that rats have such a unique susceptibility to these lesions in the mode of action (MOA) discussions. It further indicated that since humans are much less susceptible to these lesions, the critical effect (degeneration of olfactory epithelium) is of little relevance to human health and thus, the UF_A for extrapolating from rats to human should be less than one (1).

TCEQ Response:

While the TD may not necessarily agree with the comments, the TD does appreciate ACC's comments. The DSD has been revised to acknowledge that the rat's unique susceptibility to the olfactory degeneration lesions and that human may be less susceptible to the olfactory degeneration lesions in the MOA discussions. However, the TD was unable to validate the finding that rats absorb and metabolize 40-65% of the inhaled ethyl acetate within the upper respiratory tract prior to the vapor even reaching the lung from the Norris et al. (1993) study. The TCEQ considers the critical effects noted in rats to be relevant to humans. Thus, the UF_A of 3 for extrapolating from rats to human was not changed to be less than one (1). Nevertheless, the UF_{Sub} of 3 for extrapolation from subchronic to chronic has been revised to 1 because the subchronic effects found in the key study are concentration dependent and metabolites of n-BA do not accumulate, and chronic effects would not be expected to differ significantly from subchronic effects. Accordingly, a revised total UF of 100 instead of 300 was used to set the

chronic ReV and ESL. The chronic Rev and ESLs have been revised to 130 and 39 ppb, respectively.

3. n-BA Should be Treated as a Category 3 Vapor for the purposes of Risk Assessment

Comment No.5 (bottom of Page 5 through Page 6):

The ACC Panel commented that n-BA should be treated as Category 3 vapor, not Category 1 vapor for deriving the POD_{HEC}. ACC suggested that the Category 1 vapor adjustment should be removed due to the lack of relevance of the nasal lesion to human. It indicated that using the Category 1 vapor adjustment ignores what is known about the rat's unique susceptibility to the olfactory degeneration lesions.

TCEQ Response:

The DSD was not revised based on this comment. n-BA is water soluble and the critical effects (minimal to mild necrosis of the olfactory epithelium) observed in rats exposed to n-BA was a point of entry (POE) respiratory effects. According to Section 2.9.1 of the 2006 TCEQ Guidelines, default dosimetric adjustment from animal-to-human exposure for n-BA was also conducted as a Category 1 vapor. However, the TD acknowledges the rat's unique susceptibility to the olfactory degeneration lesions and that human may be less susceptible to the olfactory degeneration lesions.

4. Additional Clarification

Comment No. 6 (Page 6):

The ACC Panel commented that the derived chronic ReV of 48 ppb is most certainly exceeded in any store selling apples. ACC indicated that ambient air levels of n-BA have been reported to be in the low ppm range in areas holding apples that are ripening.

TCEQ Response:

The DSD was not revised based on this comment. Please see Response to Comment No. 2. Nevertheless, the chronic ReV and ESL for n-BA have been increased to 130 and 39 ppb, respectively (see Response to Comment No. 4).

Comment No. 7 (Page 6):

The ACC Panel indicated that the Bernard et al. (1996) key study and David et al. (1998) supporting study are the same study; and the LOAEL identified by the Bernard et al. (1996) was 500 ppm, not 550 ppm as stated in DECOS (2001).

TCEQ Response:

The TD appreciates this clarification. The LOAEL has been corrected to 500 ppm and used to develop the chronic ReV and ESL accordingly (see Section 4.1.2.1 *Bernard et al. (1996)* of the revised n-BA DSD).

APPENDIX 1

American Chemistry Council's Oxo Process Panel ("ACC")

Comments Regarding the TCEQ Development Support Document for n-Butyl Acetate ESL Values

August 31, 2010

Via email

Toxicology Section, MC 168
Texas Commission on Environmental Quality
12100 Park 35 Circle, Bldg. F
Austin, TX 78753

Re: Development Support Document, Proposed May 28, 2010: n-Butyl Acetate, CAS Registry Number: 123-86-4"

Dear Sir or Madam:

The American Chemistry Council's Oxo Process Panel[1] ("the Panel") appreciates the opportunity to provide the Texas Commission on Environmental Quality (TCEQ) with these comments on their proposed development support document (DSD) for effects screening levels (ESL) for n-butyl acetate. The Panel understands the importance of ESLs in providing TCEQ with guidance to protect human health and welfare. The Panel considers the Draft DSD for n-butyl acetate to be scientifically sound on several issues, and demonstrates the diligence of TCEQ's effort to develop supportable values. However, TCEQ was overly conservative on a few key scientific issues which affect the acute ReV and ESLs for n-butyl acetate. Therefore, the Panel offers the following comments below for TCEQ's consideration.

[1] The "Oxo Process" refers to an industrial synthesis process which is used to produce alcohols and related oxygenated compounds. The Panel members include BASF Corporation, Celanese Limited The Dow Chemical Company, and Eastman Chemical Company.

1. **The Panel Urges TCEQ to Reevaluate the Health-based acute ReV and acute ESL Methodology**

The proposed DSD for n-butyl acetate relies on the Iregren, et al., 1993 study information to create a health-based acute ReV and acute ESL of 4800 ppb and 1400 ppb, respectively (section 3.1.9 and table 4) using a total uncertainty factor of 30 from a LOAEL for very minimal irritation to eyes and respiratory tract. These findings correlate with the finding of "sensation of a bad smell". As a result, the authors of this publication questioned whether the subjects were rating the intensity of the smell versus the intensity of perceived irritation (page 739, section titled "Magnitude Estimation"). Furthermore, the authors frequently note within the publication that all of the subjects rated n-butyl acetate as a "very slight irritation" when rating on categorical scales. Using such a large uncertainty factor on such a minimal finding can lead to unfounded results.

One consequence of deriving such a low number (by using such a large uncertainty factor) from findings of "very slight irritation" is that the numbers can be misinterpreted. For example, many fruits (e.g strawberries, apples, apricots, and various kinds of melon) contain n-butyl acetate as a naturally occurring compound in levels up to 2.7 mg/kg. As n-butyl acetate is a volatile compound, off-gassing is a natural consequence of fruit ripening (Gonzalez, et al., 2009, Aubert and Chanforan, 2007, Menager, et al., 2004, Aubert and Bourger, 2004, Villatoro, et al., 2008, Lavilla, et al., 1999, Lopez, et al., 1999, and Jordon, et al., 2001), and ppm levels could easily be present in the fresh fruit aisle of a local supermarket. Indeed, within an apple orchard, n-butyl acetate levels of between 105 and 585 ppm were routinely recorded as the fruit ripened (Vallet and Dorn,

2005). If levels of n-butyl acetate are present in an outside environment such as an apple orchard from fruit ripening, then it is not unreasonable to assume that closed environments such as a grocery store would contain similar levels. In fact, a 500 ppm n-butyl acetate level has been proposed to provide "sufficient aroma" for the sale of apples (Bachmann, 1983) and therefore could easily be present in warehouses for apples. It is difficult to imagine that this could be classified as having a potential health concern for air permitting effects screening levels. After all, n-butyl acetate generated from the off-gassing of apples as they ripen is the same n-butyl acetate that is released into the atmosphere from industrial and consumer activities.

The health-based acute ReV and acute ESL of 4800 ppb and 1400 ppb, respectively (section 3.1.9 and table 4) used a total uncertainty factor of 30 from a LOAEL for very minimal irritation to eyes and respiratory tract (Iregren et al., 1993). The acute ESL of 1400 ppb was then derived using a hazard quotient (HQ) of 0.3. The Guidelines for deriving these values describe the use of hazard quotients as:

> "1.4 Specific Risk Management Objectives (No Significant Risk Levels): In order to ensure consistent protection of human health, chemical-specific ESLs are based on a defined risk management objective of no significant risk. The no significant risk level for an individual chemical is defined as the concentration associated with a hazard quotient (HQ) of 1 and the concentration associated with a theoretical excess lifetime cancer risk of one in 100,000 (1×10^{-5}). This theoretical excess lifetime cancer risk level is consistent with the State of California's No Significant Risk Level (22 CCR §12703). In consideration of cumulative and aggregate exposure, the Toxicology Section (TS) uses an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with a nonlinear dose-response assessment."

Therefore it appears, that the HQ of 0.3 was used "in consideration of cumulative or aggregate exposure" for the type of very slight eye and respiratory tract irritation from

n-butyl acetate exposures to 700 ppm for 4 hours (Iregren et al., 1993). Additionally, the TCEQ DSD also states:

> "3.1.7 Critical Effect and Dosimetric Adjustments: The 4-h LOAEL of 700 mg/m3 for local irritation identified by Iregren et al. (1993) was used as the PODHEC to derive the acute ReV and acuteESL. As indicated in the Iregren et al. (1993) study, the local irritation effects of n-BA are only concentration dependent (see Section 3.1.2), so an exposure duration adjustment from 4 h to 1 h for the 4-h LOAEL was not conducted (TCEQ 2006). Thus, the 4-h LOAEL of 700 mg/m3 was used as a 1-h concentration PODHEC."

So if the "local irritation effects of n-butyl acetate are only concentration dependent" then "an exposure duration adjustment from 4 h to 1 h for the 4-h LOAEL was not conducted (TCEQ 2006)". If this is true, then why is an additional HQ required to account for "consideration of cumulative or aggregate exposure"? Can mild local irritation that is independent of duration cause cumulative or aggregate adverse effects? Moreover, the Panel does not believe the additional HQ of 0.3 is warranted in this instance since the irritation is only concentration dependent, and each instance of irritation will not lead to a cumulative or aggregate adverse outcome. We suggest that the acute ReV and acute ESL n-butyl acetate both be the same at 4800 ppb.

2. <u>MOA Analysis and Dose Metric</u>

In section 4.1.4, MOA Analysis and Dose metric – The nasal lesions found in the rat olfactory epithelium resulting from n-butyl acetate inhalation exposure are due to several species-specific factors. First, the rat is an obligate nose-breather, while humans can and breathe through both their nose, and mouth. Therefore, inhalation exposure results in a much larger delivered dose to the olfactory epithelium of the rat would then be expected to be delivered to the olfactory epithelium of a human. Secondly, the rat

uses their olfactory senses much more than humans, and consequently, has higher levels of carboxylesterase activity within their olfactory epithelium when compared to humans. This allows for a greater production of acetic acid within those cells from the hydrolysis of the n-butyl acetate and subsequent degeneration of those cells. For example, Norris et al., (1993) found that rats absorb and metabolize 40-65% of the inhaled ethyl acetate (a closely related acetate ester to butyl acetate) within the upper respiratory tract prior to the vapor even reaching the lung. This is in contrast to humans where 50% of an inhaled dose of n-butyl acetate is exhaled unchanged (as stated in the TCEQ document; DECOS, 2001).

The difference in absorption and metabolism is due to the species, not the chemicals in question, since both ethyl acetate and butyl acetate have similar respiratory bioavailabilities in rats (Poet et al., 2002; "Respiratory Bioavailability of a Series of Acetate Esters and Alcohols in Rats", Battelle Northwest National Laboratories). For these reasons, rats have a unique susceptibility to these lesions and MOA discussion should acknowledge this. In addition, the uncertainty factor for extrapolating from rats to humans should be less than 1 since humans are much less susceptible to these lesions by this MOA. Therefore, this critical effect (degeneration of olfactory epithelium) is of little relevance to human health.

3. **N-Butyl Acetate Should be Treated as a Category 3 Vapor for the Purposes of this Risk Assessment**

N-butyl acetate should be treated as a category 3 vapor for the purposes of this risk assessment and the category 1 vapor calculation should be removed due to the lack of relevance of this lesion to humans as discussed herein. The POD of 98.21 ppm from

the category 3 vapor calculation should be used for deriving the POD_{HEC}. Using the category 1 vapor calculation ignores what is known about the rat's unique susceptibility to the olfactory degeneration lesions.

4. Additional Clarification

A chronic ReV of 48 ppb is an interesting number since this value is most certainly exceeded in any store selling apples. Ambient air levels of n-butyl acetate has been reported to be in the low ppm range in areas holding apples that are ripening. Please also note that section 4.1.2.1, Page 13, line 8 – The Bernard et al., 1996 and David et al., 1998 are the same study. The low exposure group in this study was 500 ppm (not 550 ppm as stated in DECOS (2001)).

5. Conclusion

TCEQ was overly conservative on a few key scientific issues which affect the acute ReV and ESLs for n-butyl acetate. As previously discussed, the panel believes that the acute ReV and acute ESL n-butyl acetate both be the same at 4800 ppb. Additionally, n-butyl acetate should be treated as a category 3 vapor for the purposes of this risk assessment and the category 1 vapor calculation should be removed due to the lack of relevance of this lesion to humans as discussed herein.

Again, thank you for the opportunity to provide these comments. If you have any questions, please do not hesitate to contact me at (703) 741-5612 or at Leslie_Berry@americanchemistry.com.

Sincerely,

Leslie Berry

Leslie Berry
Oxo Process Panel Manager,
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Reference List

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