Texas Commission on Environmental Quality Response to Public Comments Received on the November 2015 Proposed Tri- and Tetramethoxysilanes Development Support Document

The public comment period for the August 2015 Proposed Development Support Document (DSD) for tri- and tetramethoxysilanes ended in November 2015. The Silicones Environmental, Health, and Safety Center (SEHSC) of the American Chemistry Council submitted comments on November 10, 2015. The Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by the SEHSC to provide technical comments on the proposed DSD for tri- and tetramethoxysilanes. 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. A summary of comments from the SEHSC 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.

1. General Comments

Comment No. 1:

The SEHSC commented that the acronyms for LOAEL and NOAEL should be changed throughout the document to NOAEC and LOAEC for inhalation studies to indicate concentrations not levels. Also, add the acronyms and definitions for NOAEC and LOAEC to the list of Acronyms and Abbreviations.

TCEQ Response:

The TCEQ appreciates the SEHSC's comment. The DSD was not revised based on this comment. The TCEQ believes the acronyms for LOAEL and NOAEL as defined in Acronyms and Abbreviation Section of the TCEQ (2012) Guidelines to Develop Toxicity Factors (TCEQ Guidelines) are appropriate.

Comment No. 2:

The SEHSC commented that all of the methoxysilanes are highly water soluble and have very low partition coefficients, but only trimethoxysilane (TMS) and tetramethoxysilane (TetMS) have been identified as Category 1 vapors, while methyltrimethoxysilane (MTMS), vinyl trimethoxysilane (VTMS) and 3-Chloropropyltrimethoxysilane (CPTMS) were classified as Category 3 vapors. It further commented that, according to Section 3.9.1 Default Dosimetry Adjustments for Gases of the TCEQ (2012) Guidelines, if the classification is supposed to be based on the physical/chemical parameters, then all of the methoxysilanes should be categorized the same.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. The TCEQ agrees that based the water solubility and partition coefficients, all of the methoxysilanes can be considered Category 1 gases. However, when conduct dosimetric adjustments for gases from animal-to-human exposure, besides to the physical/chemical parameters, the toxicokinetic properties and default mode assumptions are used to determine chemicals' gas category (see Table 3-4 of the TCEQ Guidelines). TMS and TetMS dissolve in water rapidly while MTMS, VTMS, and TetMS dissolve in water much slower that TMS and TetMS. The critical effects identified for TMS and TetMS are respiratory effects (a POE effect) and were considered Category 1 vapors. The critical effects identified for MTMS, VTMS, and TetMS, however, are systemic effects and thus, were considered Category 3 vapors.

Comment No. 3

The SEHSC commented that there exists a large database of study information available on TMS under REACh and should be reviewed.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The toxicological information for TMS reported in the reference (ECHA) was also included in the OECD SIDS reports (OECD 2007 and 2008) as well as in the AEGLs report (NRC 2012). The TCEQ reviewed the ECHA toxicological information provided by the SEHSC and determined not to revise the derived ReVs and ESLs for TMS. Nevertheless, the reference has been added to the DSD as ECHA (2015a).

Comment No. 4

The SEHSC commented that there exists a large database of study information available on TetMS under REACh and should be reviewed.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The toxicological information for TetMS reported in the reference (ECHA), except one 5-d subacute animal study, was also reviewed by NRC (2012). The 5-d subacute animal study has been added to the DSD (Section 3.3.2.2); although the ECHA indicates that this study did not meet current guideline for repeated dose toxicity testing. The TCEQ reviewed the ECHA toxicological information provided by the SEHSC and determined not to revise the derived ReVs and ESLs for TetMS. Nevertheless, the reference has been added to the DSD as ECHA (2015b).

Comment No. 5

The SEHSC commented that there exists a large database of study information available on MTMS under REACh and should be reviewed.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The toxicological information for MTMS reported in the reference (ECHA) was also reviewed by OCED (2009a). The TCEQ has reviewed both the ECHA (2007) and OECD (2009a) toxicological information in the proposed DSD and thus, the derived ReVs and ESLs for TetMS are not revised.

Comment No. 6

The SEHSC commented that there exists a large database of study information available on CPTMS under REACh and should be reviewed.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The toxicological information for CPTMS reported in the reference (ECHA) was also reviewed by OCED (2006). The TCEQ reviewed the ECHA toxicological information provided by the SEHSC and determined not to revise the derived ReVs and ESLs for TetMS. Nevertheless, the reference (ECHA) has been added to the DSD as ECHA (2015c).

2. Specific Comments

2.1 Trimethoxysilane

Comment No. 7:

The SEHSC suggested that the following physical/chemical data be revised for TMS:

- Solubility in water: 1,000,000 mg/L; very soluble (OECD)
- Boiling Point: 84 ^{o}C at 1013 hPa
- Hydrolysis Half-Life: <0.3 min at pH 7 and 25 ^{o}C

TCEQ Response:

The suggested physical/chemical data for TMS has been revised accordingly (Table 3 Physical and Chemical Data for Trimethoxysilanes).

Comment No. 8:

The SEHSC commented that a value of "90" is stated (Section 3.3.1.4.3 Line 27) for the total UF. However, it appears that the total would be "180" if the UFs are indeed 10, 3, and 6.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The total UFs value has been corrected from 90 to 180.

Comment No. 9:

The SEHSC commented that the critical effect for the acute ReV and ESL is stated to be based on respiratory effects, however the text on pages 11 (TMS) and 14 (TetMS) state the POD is based on body weight loss. The table and text are inconsistent.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. As described in Section 3.3.1.2, the results of the MPI Research (1998) key study concluded that the 30-min NOAEL (for group man body weight losses during the first post-exposure week) in rats is less than 158 ppm, but greater than 72 ppm. MPI Research (1998) indicated that the results of mean body weight losses were not dose-dependent (i.e., effect was observed in the 158, 181 and 243 ppm groups but not in the 206 ppm group) and the exposure

duration was only 30 min. Thus, the 30-min NOAEL for mean body weight losses was not appropriately used to derive toxicity factors (Page 11). The target organ for toxicity was the respiratory tract; there were no other systemic findings of toxicity. A higher NOAEL of 181 ppm for red lung discoloration on multiple lobes, a better endpoint, was also identified from the key study. The NOAEL of 181 ppm, however, is higher than the 4-h LC_{50} of 60 ppm (male rats) (Section 3.3.1.1). The TCEQ conservatively used the lowest NOAEL of 72 ppm instead of 181 ppm as the POD to derive the acute ReV and ESL for TMS. Since the target organ for toxicity in this study was the respiratory tract, respiratory tract effect was considered critical effects for the selected POD.

As described in Section 3.3.2, no acute studies for 1 day or less were available other than lethality studies and thus, no acute ReV and ESL were derived for TetMS. The ^{acute} ESL for TetMS was set based on the acute ESL for TMS. Accordingly, the acute critical effect was assumed to be respiratory effects in rats as for TMS (Table 1).

Comment No. 10:

The SEHSC commented that instead of using a surrogate, TetMS, to derive chronic ESL for TMS, the NOAEL of 0.5 ppm for TMS identified from both the 90-day study data (Bushy Run Research Center 1995) and 28-day study data (Dow Corning 1980, cited as Breckenridge et al. 1980 in the DSD) could have been used to derive the chronic toxicity factors following the same approach as is used for TetMS. Specifically, the SEHSC suggested that the well-conducted 28-day sub-chronic toxicity study should be considered for use to derive chronic toxicity factors for TMS.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. As described in Section 4.3.1, the results of the 28-d study indicated that the time- and dose-response for TMS is steep. As described in Section 3.3.1.3.2, the level of 0.5 ppm was also a free-standing 90-d NOAEL identified from the Bushy Run Research Center (1995) study. However, OCED (2007) indicates that the 90-d free-standing NOAEL would be at least 0.5 ppm (Section 4.3.1.1). The TCEQ believes that the 28-d NOAEL of 0.5 ppm was considered conservative for the derivation of a chronic ReV for the following reasons. Nevertheless, the 28-day study (Dow Corning 1980, cited as Breckenridge et al. 1980 in the DSD) has been added to Section 4.3.1.2.

- The 4-h LC_{50} (60 ppm) for TMS is similar to the 4-h LC_{50} (63 ppm) for TetMS indicating the relative potency of these methoxysilanes would be equipotent.

- The 28-d NOAEL (10 ppm) for TetMS is much higher than the 28-d or 90-d NOAEL (0.5 ppm) for TMS.

- The 90-d free-standing NOAEL of 0.5 ppm was not used to derive chronic toxicity factors for TMS (Section 4.3.1.1). Likewise, the 28-d NOAEL of 0.5 ppm was not used to derive chronic toxicity factors either for TMS.

- For these reasons, a chronic ReV was not derived for TMS and the chronic ESL for TetMS will be used as surrogate for TMS to derive a chronic ESL.

2.2 3-Chloropropyltrimethoxysilane

Comment No. 11:

The SEHSC suggested that the following physical/chemical data be revised for CPTMS:

- Solubility in water: 650,000 mg/L at 25 ^{o}C, very soluble
- Density: 1.07
- Boiling Point: 196 ^{o}C at 1013 hPa
- Log Kow: 0.56
- Hydrolysis Half-Life: 53.3 min at pH 7 and 25 ^{o}C

TCEQ Response:

The suggested physical/chemical data for CPTMS has been revised accordingly (Table 3 Physical and Chemical Data for Trimethoxysilanes).

Comment No. 12:

The SEHSC suggested that the Table Number 4 be changed to Table Number 3 since the table is a continuation of Table 3 on the previous page.

TCEQ Response:

The TCEQ appreciates the SEHSC's suggestion. The DSD was not revised based on these comments. Table 3 is for trimethoxysilane group while Table 4 is for tetramethoxysilane. The SEHSC's further suggestions for renumbering subsequent table numbers (Table 4 to 8) are not changed either.

2.3 Methyltrimethoxysilane

Comment No. 13:

The SEHSC suggested that the following physical/chemical data be revised for MTMS:

Vapor Pressure: 80.1 mm Hg at 20 ^{o}C
Melting Point: <-77 ^{o}C (OECD and CSR)
Boiling Point: 102 ^{o}C at 1013 hPa (OECD and CSR)
Hydrolysis Half-life: 2.2 hrs at pH 7 and 25 ^{o}C

TCEQ Response:

The suggested physical/chemical data for MTMS has been revised accordingly (Table 3 Physical and Chemical Data for Trimethoxysilanes).

Comment No. 14:

The SEHSC commented that there is also an oral reproductive/developmental study available for MTMS and could be included in Section 3.3 (Page 8) in addition to VTMS and CPTMS.

TCEQ Response:

The TCEQ appreciates the SEHSC comments. MTMS has been added to Section 3.3 line 30 of the DSD: "…several methoxysilanes (VTMS, CPTMS and MTMS where systemic effects were observed)…"

2.4 Vinyl trimethoxysilane

Comment No. 15:

The SEHSC suggested that the following physical/chemical data be revised for VTMS:

- Log Kow: 0.32 (The SIAP incorrectly identifies the log Kow as 0.032; the appropriate value of 0.32 is provided in the SIAR and Dossier)
- Vapor Pressure: 11.9 mm Hg at 25 ^{o}C (an error was made in the units here; 5.93 hPa = 11.9 mm Hg)
- Boiling Point: 123 ^{o}C at 1013 hPa
- Hydrolysis Half-life: <2.4 h at pH 7 and 25 ^{o}C

TCEQ Response:

The suggested physical/chemical data for VTMS has been revised accordingly (Table 3 Physical and Chemical Data for Trimethoxysilanes).

2.5 Tetramethoxysilane

Comment No. 16:

The SEHSC suggested that the vapor pressure for TetMS be revised to 10 mm Hg at 20 oC or 13 mm Hg at 25 oC (measured value).

TCEQ Response:

The suggested vapor pressure for TetMS has been revised accordingly (Table 4 Physical and Chemical Data for Tetramethoxysilane).

Comment No. 17:

The SEHSC commented that in Section 3.3.2.1, the citation for a 4-h GLP nose-only inhalation study (Dow Corning Corp. 1992) should be (Dow Corning Corp. 1982) as the lethality study was conducted in 1982.

TCEQ Response:

The citation of Dow Corning Corp. 1992 has been revised to Dow Corning Corp. 1982 (Section 3.3.2.1).

Comment No 18:

The SEHSC commented that review of studies submitted under REACh will provide sufficient data to support derivation of the acute ReV and ESL values based on studies with TetMS.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. The inhalation LC_{50} study conducted by Dow Corning Corp. 1992 was not appropriate to derive an acute ReV according to the TCEQ Guidelines (TCEQ 2012). As described in Section 3.3.2, very limited data are available from animal studies involving TetMS. No acute studies for 1 day or less were available other than lethality studies, although a 5-d inhalation study (ECHA 2015b) was available. The 5-d subacute inhalation animal study as reviewed and submitted under REACh (ECHA 2015b) was not used either to develop acute toxicity values. As described in Section 3.3.2.2, although a NOAEL and LOAEL of 5 and 12 ppm, respectively, were identified from this study. ECHA (2015b) indicates that this study did not meet current guideline for repeated dose toxicity testing. Therefore, the identified 5-d NOAEL of 5 ppm was not used to develop acute toxicity values.

2.6 Page 6:

Comment No 19:

The SEHSC suggested that the formula for MTMS (C4H12O3Si) be added to Table 3.

TCEQ Response:

The formula for MTMS has been included in Table 3.

2.7 Section 3.2 Mode of Action (MOA) Analysis and Dose Metric (Page 7-8):

Comment No 20:

The SEHSC commented that the explanation that whether acute and/or chronic inhalation exposure to methoxysilanes causes respiratory damage (site of contact effects) or nephrotoxicity (systemic effects) is determined by their rate of hydrolysis excludes the premise that the effects seen in the kidney and/or urinary bladder are actually local (not systemic) effects. There is evidence that inhalation and oral exposure to silanes can produce histopathological effects (epithelial hyperplasia) in the urinary bladder which may not always be considered a systemic effect, but rather a direct contact effect. Given that the critical effect noted for several methoxysilanes in the derivation of acute/chronic ReV Values and 1-h $^{Acute}ESL$ and $^{chronic}ESL_{threshold}$ values is based on urinary bladder/kidney effects, please consider how an explanation of local vs systemic effects would influence these derivations.

TCEQ Response:

The TCEQ appreciates that SEHSC may have a different opinion on the choice of terms to describe the MOAs and adverse effects caused by methoxysilane inhalation. In this case, the intention of the TCEQ is to highlight that some effects happen at the site of contact, the respiratory tract, where as other effect require that the methoxysilanes be absorbed or transported into the body, distributed, metabolized, and excreted at least in part in urine. While we agree that direct contact with the bladder or kidneys would be required to elicit aforementioned effects, the methoxysilanes still went through absorption, distribution, and metabolism to reach the site of injury. These MOA steps do not necessarily inform the derivations from the perspective that the TCEQ does not perform a dosimetric adjustment unless extensive information is known about these steps (i.e., PBPK modeling). Thus, this discussion is primarily focused upon highlighting

MOAs and critical effects that occur with different durations of exposure to specific methoxysilanes. It also is integral to selection of surrogates for interpolation across structurally related methoxysilanes where data regarding a specific duration of exposure may be missing.

2.8 Page 9:

Comment No 21:

The SEHSC suggested that the following be changed:

- line 3: The half-life at pH 7 and 25°C is < 0.3 min, and
- line 30: and 243 ppm needs to be revised.

TCEQ Response:

The suggested changes have been incorporated accordingly.

2.9 Page 10-11:

Comment No 22:

The SEHSC suggested that the following be changed:

- Pg 10, line 14: were observed in all groups during
- Pg 10, line 15: in Group 4 (158 ppm) and
- Pg 11, line 2: observed in the 158 and 243 ppm groups but not in the 181 and 206 ppm groups
- Pg 11, lines 3-4: losses should not be used instead of losses was not appropriately used
- Pg 11, lines 9-10: (Section 3.3.1.1): the low-end level of 72 ppm (nominal concentration) was identified as the NOAEL based on mean body weight loss and was used as a POD to derive acute toxicity factors

TCEQ Response:

The DSD has been changed accordingly.

2.10 Section 3.3.1.1 (Page11):

Comment No 23:

The SEHSC suggested that the following sentence (lines 9-10) be used:

"The low-end level of 72 ppm (nominal concentration) was identified as the NOAEL based on mean body weight loss and was used as a POD to derive acute toxicity factors."

TCEQ Response:

The suggested sentence has been incorporated accordingly (Section 3.3.1.1).

2.11 Page 12:

Comment No 24:

The SEHSC suggested that the following sentence (lines 23-25) be used:

"The NOAEC from this 4-week inhalation study was 0.5 ppm, with a LOAEC of 5 ppm based on body weight, organ weight, clinical pathology (bronchitis and bronchiolitis), and histopathologic observations."

TCEQ Response:

The sentence has been changed as below (Section 3.3.1.3.2):

"Based on the body weight, organ weight, clinical pathology, histopathologic observations, and deaths, OECD (2007, 2008) concluded that the NOAEL and LOAEL from this study appeared to be 0.5 and 5 ppm, respectively."

Comment No 25:

The SEHSC suggested that the following sentence (lines 29-30) be used:

"A NOAEC of 0.2 ppm and a LOAEC of 1 ppm were identified based on weight loss, increased lung weight, clinical pathology (laryngitis and bronchopneumonia), and necropsy/histopathologic observations."

TCEQ Response:

The suggested sentence (lines 29-30) has been incorporated accordingly (Section 3.3.1.3.3).

2.12 Page 14:

Comment No 26:

The SEHSC commented that, as described on Page 14, lines 2-3, while it is true that no guideline-specific reproductive or developmental studies have been conducted with TMS, an evaluation of reproductive organs is available from two repeated-dose toxicity studies: a 9-d and 90-d inhalation studies conducted by Bushy Run Research Center in 1994 and 1995, respectively.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The 90-d study (Bushy Run Research Center 1995) has already been described in Section 4.3.1 and a free-standing NOAEL for effects including reproductive effects in this study was determined to be 0.5 ppm. Nevertheless, "a 90-d inhalation study conducted for TMS (Bushy Run Research Center 1995)" has been added to sentence (lines 2-3) accordingly. For the 9-d inhalation study as indicated by the SEHSC (Bushy Run Research Center 1994, as cited), while the one surviving male animal exposed to 5 ppm for 9 d was observed to have increased testes weight (absolute and relative to body weight); the relative testes weight (as a percentage of brain weight) for this one animal was decreased. Interpretation of the results for this one high dose male animal must be performed with caution due to the small number of animals (one) and its moribund condition. For these reasons, the 9-d reproductive effects study was not included in the DSD.

Comment No 27:

The SEHSC suggested add the following text to line 32:

- exposure over 5 ½ weeks. All animals exposed at 45 ppm either died or were killed during the 28-day study. No effects were observed in any rats exposed at 0, 1, 5, or 10 ppm.

TCEQ Response:

The suggested text has been added accordingly (Section 3.3.2.3).

Comment No 28:

The SEHSC suggested that lines 34-35 be revised as follows:

"exposure to 30 ppm. Males exposed at 15 ppm had only a decrease in total protein. No microscopic lesions were found in the respiratory tract or ocular epithelium of rats exposed at 1, 5, or 10 ppm."

TCEQ Response:

The text has been revised accordingly (Section 3.3.2.3).

2.13 Page 15:

Comment No 29:

The SEHSC commented that the text (lines 1-4) confuses the findings reported for the upper respiratory tract and the eyes. It recommended revise the text as:

"..inflammation and ocular lesions showed minimal acute keratitis with no epithelial desquamation in 4/20 rats. Upper respiratory tract lesions were more severe at 30 and 45 ppm and included ulceration, desquamation and inflammation of the respiratory epithelium, with a large amount of exudate in the nasal cavity. At 30 and 45 ppm, ocular lesions included desquamation of the central corneal epithelium; effects were moderate to severe at 30 ppm and severe at 45 ppm. Signs of toxicity appear to be dose-dependent. A NOAEC of 10 ppm and a LOAEC of 15 ppm based on minimal acute upper respiratory tract inflammation and minimal ocular keratitis were identified from this subacute study."

TCEQ Response:

The text has been revised accordingly (see Section 3.3.2.3).

Comment No 30:

The SEHSC suggested that to add the following text to lines 30:

"As a result of clinical observations and reduced body weights, animals from the 8000 ppm group were sacrificed by exposure day 9 and 3/5 females in the 4000 ppm group were sacrificed by exposure day 13. In these animals, gross pathological observations included calculi in the urinary bladders of several animals along with kidney discoloration, dilation and calculi. Histopathological evaluation of the urinary bladders containing calculi showed hyperplasia and

inflammation in all cases with widespread urinary bladder necrosis in one male and three females. Gross necropsy was performed on all remaining animals with organ weights and histopathology conducted on selected tissues. There was a statistically significant change in organ weights over the treatment groups for female adrenal glands (increased), lungs (increased) and thymus (decreased), and in kidney weights (increased) for males."

TCEQ Response:

The suggested text has been added accordingly (section 3.3.2.3).

Comment No 31:

The SEHSC suggested that to add the following text to lines 34:

Minimal urinary bladder epithelial hyperplasia, "but with no histopathological findings in any tissue at this level," was

TCEQ Response:

The suggested text "but with no histopathological findings in any tissue at this level," has been added accordingly (Section 3.3.2.3).

2.14 Page 16, line 13:

Comment No 32:

The SEHSC commented that the TCEQ provide justification for the conclusion that MTMS is a Category 3 vapor. It indicated that according to the TCEQ 2012 Guidelines, Category 3 gases are "poorly water soluble" and "are relatively insoluble in water". The physical/chemical data for MTMS indicate that it is highly water soluble (solubility in water = 290,000 mg/L; log Kow = -0.67). Again, according to the guidance document a water solubility value > 10,000 mg/L is classified as very soluble and a log Kow value < 1 is classified as highly soluble in water (hydrophilic).

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. Refer to Response to Comment No. 2.

2.15 Page 16, line 30 to Page 17, line 1:

Comment No 33:

The SEHSC commented that while it is true that no guideline-specific reproductive or developmental studies have been conducted with MTMS, a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) has been conducted via gavage in rats (Dow Corning Corporation 2005).

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The aforementioned Dow Corning Corporation (2005) gavage study has been added to Section 3.3.3.3.3 Adjustment of POD_{HEC} accordingly. The oral study was also included in Section 3.3 (Refer to Response to Comment No. 14).

2.16 Page 17-19:

Comment No 34:

The SEHSC commented that the OECD TG 403 study was conducted in compliance with GLP, so the sentence on Page 17, line 21 should be deleted.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The text (Page 17, line 21) has been revised accordingly (Section 3.3.4.1).

Comment No 35:

The SEHSC commented that what are the limitations to using a developmental toxicity study to derive the acute ReV for VTMS (Page 17, line 22 – Page 18, line 14)?

TCEQ Response:

The TCEQ appreciates the SEHSC's comment. The DSD was not revised based on these comments. While the 1993 reproductive/developmental toxicity study (as cited in ECHA 2011) was used as key study to derive acute ReV, the POD was based on a NOAEL of 25 ppm for maternal toxicity (decreased body weight gain). The NOAEL was lower than the NOAEL of 100 ppm for delayed developmental effects identified from the key study. The NOAEL (25 ppm) for maternal toxicity was also lower than a NOAEL of 150 ppm identified from a 9-d subacute supporting study (Section 3.3.4.3). Therefore, the SEHSC's concerns of the limitations, if any, to using a developmental toxicity study are not applicable for the derivation of the acute ReV for VTMS.

Comment No 36:

The SEHSC suggested adding one sentence - "Prior to their death several clinical abnormalities (e.g., periocular wetness, corneal opacity, blepharospasm, periurogenital area wetness, loss of coordination, hypoactivity, breathing difficulties, and an unkempt appearance) were observed." after "exposure." (Section 3.3.4.3, Page 18, line 20).

TCEQ Response:

The suggested sentence has been added accordingly.

Comment No 37:

The SEHSC suggested adding the following text - "Prior to sacrifice, rats of the 750 ppm group had markedly increased water intake, with a concomitant increase in urine volume and a decrease in urine specific gravity. Hematuria and mild hematologic (decreases in hemoglobin concentration (5.7% in males, 2.5% in females) and hematocrit (5.4% in males, 3.0% in females) in both sexes; a 4% decrease in erythrocyte count in males only) alterations were also observed." after "150 ppm rat." (Section 3.3.4.3, Page 18, line 23).

TCEQ Response:

The suggested text has been added accordingly (Section 3.3.4.3).

Comment No 38:

The SEHSC suggested adding one sentence- "At necropsy, treatment-related lesions were observed in the 1500 ppm group only and consisted of discoloration of the kidneys, corneal and lenticular opacities, brain hemorrhage, perinasal encrustation, and blood-tinged urine in the bladder." after "value." (Section 3.3.4.3, Page 18, line 26).

TCEQ Response:

The suggested sentence has been added accordingly.

Comment No 39:

The SEHSC commented that the TCEQ provide justification for the conclusion that VTMS is a Category 3 vapor (Page 19, line12). It indicated that according to the TCEQ 2012 Guidelines, Category 3 gases are "poorly water soluble" and "are relatively insoluble in water". The physical/chemical data for VTMS indicate that it is highly water soluble (solubility in water = 5.043 x 105 mg/L; log Kow = -0.32). These parameters indicate that VTMS is water soluble.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. Please refer to Response to Comment No. 2.

2.17 Page 21:

Comment No 40:

The SEHSC suggested that the sentence (line 16-17) - "Gross necropsies for adrenal glands, kidneys, liver, and urinary bladder were performed on all rats." be revised as "Gross necropsies were performed on all rats.

TCEQ Response:

The sentence (line 16-17) has been revised accordingly (Section 3.3.5.3).

Comment No 41:

The SEHSC commented that the purpose of the following sentence (line 33-35) is not clear: "Since the critical effect is unknown, adjustments as a Category 3 vapor (for possible systemic effects (i.e., reproductive/developmental) and as a Category 1 vapor (for possible respiratory effects) were considered." It further commented that the TCEQ was looking at the effects (site of contact vs. systemic) and then trying to justify placing the chemical in a specific category. What is the justification for considering that CPTMS could be a Category 3 vapor? The physical/chemical data for CPTMS indicate that it is highly water soluble (solubility in water = 650,000 mg/L; log Kow = 0.56). Both parameters demonstrate that CPTMS is water soluble.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. As described in Response to Comment No. 2., the TCEQ agrees that based the water solubility and partition coefficients, CPTMS can be considered Category 1 gases. However, when conduct dosimetric adjustments for gases from animal-to-human exposure, besides to the physical/chemical parameters, the toxicokinetic properties and default mode assumptions are

used to determine chemicals' gas category (see Table 3-4 of the TCEQ Guidelines). Because the critical effect is unknown for the acute key study, i.e., lack of general and reproductive or developmental toxicity (RCC Ltd 2005, Section 3.3.5.2). Additionally, the critical effect is also unknown for the 2-week subacute supporting study, i.e., no treatment-related effects were observed at gross necropsy (Dow Corning Corporation 1990a, Section 3.3.5.3). Therefore, both Category 1 and 3 gas were considered for dosimetric adjustments. As indicated in Section 3.3.5.4.2, the POD_{HEC} were identical to the POD_{HEC} derived for systemic effects. The resulting subacute POD_{HEC} derived for the respiratory tract, if any, was equal to the POD_{HEC} derived for systemic effects.

2.18 Page 25, Line 15:

Comment No 42:

The SEHSC commented that what is the purpose of the IOAEL? It indicated that the IOAEL does not appear in the TCEQ guidance document. It further commented that since the proposed acute IOAEL values for methoxysilanes were determined from different study regimens and durations, it is unclear exactly how these values could be relevant for comparison.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. The IOAEL did appear in the TCEQ (2012) Guidelines (Section 3.13 Identification of Inhalation Observed Adverse Effect Levels, Page 106-110). The IOAELs are provided for informational purposes only. That is, to communicate to agency risk assessors, risk managers, the public, and other groups the air concentrations and exposure conditions (e.g., magnitude, frequency, duration) associated with observed adverse effect levels based on available dose-response data and to put into perspective corresponding health-protective values (e.g., interval between effect levels and the ReV).

While the available LOAELs for methoxysilanes were identified from different study regimens and durations, animal-to-human dosimetric adjustments were performed to determine their respective $LOAEL_{HEC}$ values. Both the proposed acute and chronic IOAELs for the methoxysilanes were set at their respective $LOAEL_{HEC}$ values determined from animal studies. Therefore, the proposed IOAELs for methoxysilanes would be considered relevant for comparison.

2.19 Section 4.2:

Comment No 43:

The SEHSC commented that the sentence (Page 26, Line 18) - " The hydrolysis rate is important to the MOA due to the fact that it dictates the chemical species actually inhaled and subsequently distributed and metabolized in the body." isn't as clear as stated in the report. The SEHSC indicated that it is possible to deliver unreacted parent compound to the animals even with substances with short hydrolysis half-lives such as TMS.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. The TCEQ concurs with the SEHSC that it is possible to deliver unreacted parent

compound to the animals even with substances with short hydrolysis half-lives such as TMS. The TCEQ, however, believes that the aforementioned sentence regarding the hydrolysis rate is important to the MOA is valid. As described in Section 3.2, the shorter the hydrolysis half-life, respiratory effects may occur due to the hydrolysis products whereas if the hydrolysis half-life is longer, systemic effects such as nephrotoxicity may occur due to the parent compound.

2.20 Page 27-29:

Comment No 44:

The SEHSC commented that it is an inaccurate way to assess the overall relative potential inhalation toxicity of TMS and TetMS using their 4-h LC_{50} values (Page 27, line 36).

TCEQ Response:

The TCEQ does not agree with the SEHSC's comment. The use of LC_{50} values was not the only way to assess the overall relative potential toxicity of TMS and TetMS. In fact, when a category/read-across approach is used in consideration of setting a generic ESL, factors such as chemical/physical properties, structure-activity relationship, toxicity data, critical effects, and MOA for TMS and TetMS are all considered (Refer to Section 4.3.1).

Comment No 45:

The SEHSC commented that why the 28-d inhalation toxicity study with TMS (Breckenridge et al. 1980) was not used for the derivation of a chronic ESL, but rather to use the 28-d inhalation toxicity study from an analogous material, TetMS (Page 27-28, Section 4.3.1).

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. The explanation for not using both the 90-d study data (Bushy Run Research Center 1995) and 28-d study data (Dow Corning 1980(cited as Breckenridge et al. 1980 in the DSD) has been addressed in Response to Comment No 10.

Comment No 46:

The SEHSC suggested that the sentence (Page 28, lines 21-22) be revised as: "A NOAELC of 10 ppm and a minimal LOAEL of 15 ppm for minimal acute inflammation in the nasal region and keratitis of the ocular epithelium were identified from this subacute/subchronic study."

TCEQ Response:

The sentence has been revised accordingly (Section 4.3.2.1).

Comment No 47:

The SEHSC suggested delete "bronchiolar inflammatory lesions" from the sentence (Page 28, lines 26-27). It further suggested add "keratitis of the ocular epithelium" to the sentence. The SEHSC suggested that the sentence (Page 29, lines 16-17) be revised accordingly.

TCEQ Response:

Both sentences (Page 28, lines, 26-27 and Page 19, lines 16-17) have been revised accordingly (Section 4.3.2.2.1 and 4.3.2.2.3).

2.21 Page 30:

Comment No 48:

The SEHSC suggested that the following sentence be added to the end of line 9: "Ten additional rats/sex were included in the control and high dose groups and exposed to MTMS for 90 d, followed by a 28-d recovery period without exposure to MTMS."

TCEQ Response:

The sentence has been added accordingly (Section 4.3.3.1).

Comment No 49:

The SEHSC suggested that the following sentence (lines 13-14) be revised: "calculi in urinary bladder of four males and one female, which persisted only in the recovery group males but was not observed in the recovery group females following the 28-d recovery period."

TCEQ Response:

The sentence has been revised accordingly (Section 4.3.3.1).

Comment No 50:

The SEHSC commented that the paragraph (lines 18-23) should be limited to the findings observed at 2,200 mg/m^3.

TCEQ Response:

The paragraph (lines 18-23) has been revised for the effects observed in the 2,200 mg/m^3 only. Subsequently, the effects observed in the 8,900 mg/m^3 (lines 10-17) have been revised too. Refer to Section 4.3.3.1.

Comment No 51:

The SEHSC commented that the statistically significant increase of 18% weights in female adrenal glands (line 20) should be absolute, *not* relative, weights.

TCEQ Response:

The sentence has been revised to "…of 18% absolute weights..." accordingly (Section 4.3.3.1).

2.22 Page 31:

Comment No 52:

The SEHSC commented that, as noted above in Comment No 32, what is the justification for the conclusion that MTMS is a "Category 3" vapor? According to the guidance document and based on its water solubility and partition coefficient, MTMS would be classified as a Category 1 chemical.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The DSD was not revised based on these comments. Please see Response to Comment No 32 above.

2.23 Page 32, lines 15-19:

Comment No 53:

The SEHSC commented that the key animal study was not a combined repeated-dose/reproductive/developmental toxicity study but a repeated 14-week inhalation study (Section 4.3.4.1). It further commented that the 14-week study should be considered a subchronic, not chronic, study.

TCEQ Response:

The TCEQ appreciates the SEHSC's comments. The key animal study has been revised to a repeated dose inhalation toxicity study accordingly. According to the TCEQ 2012 Guidelines (Section 3.2 Overview for Development of Toxicity Values, Page 44), the exposure duration for 1-3 months, usually a 90-d or 13-week, is considered subchronic, and the exposure duration for longer than 3 months, most commonly a 2-year study is considered chronic in typically used animal species. Therefore, the 14-week (longer than 3 months or 13 week) key study was considered a subchronic, *not* a chronic study.

2.24 Page 33:

Comment No 54:

The SEHSC commented that sentence (line 27) - "No reproductive effects were observed in this study" be replaced with "No significant effects on reproductive organs were observed in this study."

TCEQ Response:

The sentence has been revised accordingly (Section 4.3.4.1).

Comment No 55:

The SEHSC suggested that "(testes, epididymides, prostate (and associated sex glands), uterus, vagina, cervix, ovaries, fallopian tubes, or mammary tissue)" be added to the sentence (line 31) between "….reproductive organs and examined at"

TCEQ Response:

The suggested addition has been incorporated accordingly (Section 4.3.4.1).

Comment No 56:

The SEHSC suggested that the sentence (lines 32-33): "A free-standing NOAEL of 400 ppm for the absence reproductive effects were identified from this study" be deleted as this study was not designed to evaluate reproductive toxicity as an endpoint and therefore, a NOAEL cannot be derived for it.

TCEQ Response:

The sentence (lines 32-33) has been deleted accordingly (Section 4.3.41).

2.25 Page 34:

Comment No 57:

The SEHSC commented that as indicated in Comment No 52 above, the 14-week study (ECHA 2011) was considered a subchronic, not a chronic, study, the SEHSC commented that a UF_{Sub} of 3 be considered appropriate to account for the use of a subchronic study (lines 17-18).

TCEQ Response:

The TCEQ appreciates the SEHSC's comment. The DSD was not revised based on this comment. As stated in Response to Comment No 52, the 14-week study (ECHA 2011) was considered a chronic study. Therefore, a UF_{Sub} of 3 would not be considered.

Comment No 58:

The SEHSC commented that the 14-week repeated dose inhalation toxicity study was not designed to evaluate reproductive or developmental toxicity and thus, inhalation should be deleted from sentence in line 22 ("Reproductive/developmental studies were also conducted for both inhalation and gavage"). It suggested add a gavage reproductive to toxicity study to the text after line 22.

TCEQ Response:

The TCEQ appreciates the SEHSC's comment. The DSD was not revised based on this comment. The last bullet in Section 4.3.4.2.3 (lines 19-23) was to explain the justifications for selecting an uncertainty factor for database completeness (UF_D) of 3. In addition to the 14-week inhalation and oral studies, as described in Section 3.3.4.4.3, reproductive/developmental studies were also conducted for both inhalation and gavage (ECHA 2011). Since the proposed DSD focuses on the derivation of inhalation toxicity factors, the NOAEL of 1000 mg/kg.bw/day for reproductive toxicity identified from an oral gavage study was not added.

2.26 Page 35, line 23:

Comment No 59:

The SEHSC suggested revise the following: "Groups of male and female rats (10/sex/concentration) were…"

TCEQ Response:

The sentence (line 23) has been revised accordingly (Section 4.3.5.1).

2.27 Page 36, lines 3-4:

Comment No 60:

The SEHSC suggested delete the sentence "There were no test article-related microscopic changes in any of the respiratory tract organs or other tissues examined", as it was already reported on the previous page, lines 30-31.

TCEQ Response:

The sentence (lines 3-4) has been deleted accordingly (Section 4.3.5.2).

APPENDIX

The Siliones Environmental, Health, and Safety Center (SEHSC) of the American Chemistry Council

Comments Regarding the TCEQ Development Support Document for Tri- and Methoxysilanes Toxicity Values

American Chemistry Council | SEHSC Silicones Environmental, Health, and Safety Center

November 10, 2015

Via Electronic Submission

Texas Commission on Environmental Quality
Toxicology Division, MC 168
P.O. Box 13087
Austin, TX 78711-3087

RE: TCEQ Development Support Document (DSD) Proposed August 15, 2015 on Tri- and Tetramethoxysilane

Dear Sir or Madam:

In response to the TCEQ call for public comments on the proposed DSD on Tri- and Tetramethoxysilanes, the Silicones Environmental, Health, and Safety Center (SEHSC) of the American Chemistry Council are pleased to submit the enclosed comments for your consideration. SEHSC is a not-for-profit trade sector group whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Center is comprised of North American silicone chemical producers and importers.

Thank you for your consideration of our comments. If you have any questions regarding this submission, please contact me at (202) 249-6197 or karluss_thomas@americanchemistry.com.

Sincerely,

Karluss Thomas
Sr. Director, SEHSC

700 2nd Street NE, Washington, DC 20002 | (202) 249.7000

SEHSC Comments on Texas Commission on Environmental Quality (TCEQ)
(August 15, 2015, proposed) Development Support Document:
Tri- and Tetramethoxysilanes

General Comments:

- NOAEL and NOAEL: These acronyms should be changed throughout the document to NOAEC and LOAEC for inhalation studies to indicate concentrations not levels. Also, add the acronyms and definitions for NOAEC and LOAEC to the list of Acronyms and Abbreviations.

- As noted in the Texas Commission on Environmental Quality (TCEQ) (October 2012) TCEQ Guidelines to Develop Toxicity Factors section 3.9.1 Default Dosimetry Adjustments for Gases, the physical and chemical properties of a chemical such as reactivity and lipid and water solubility influence whether gaseous toxicants affect the respiratory system (POE effects) or more distal organ systems. Table 3-4 provides the gas category scheme including the physical/chemical characteristics, toxicokinetics properties and default model systems. The following summary was provided on pg 84:

  > "Category 1 includes gases that are highly water soluble and undergo rapid, irreversible reactions in the respiratory tract (e.g., hydrogen fluoride, chlorine, formaldehyde, and volatile organic acids and esters). Category 1 gases often exert POE effects. Category 2 includes moderately water-soluble gases that may remain within the respiratory system and/or migrate within the blood to distal organ systems (e.g., sulfur dioxide, xylene, propanol, and isoamyl alcohol). Category 3 includes gases that are relatively insoluble in water (e.g., 1,3-butadiene and dichloromethane). Inhaled Category 3 gases may be toxic to organ systems distal to the respiratory system."

  All of the methoxysilanes are highly water soluble and have very low partition coefficients, but only trimethoxysilane (TMS) and tetramethoxysilane (TetMS) have been identified as Category 1 vapors, while methyltrimethoxysilane (MTMS), vinyl trimethoxysilane (VTMS) and 3-Chloropropyltrimethoxysilane (CPTMS) were classified as Category 3 vapors. If the classification is supposed to be based on the physical/chemical parameters, then all of the methoxysilanes should be categorized the same.

- There exists a large database of study information available on TMS under REACh. Perhaps this database should be reviewed (as is done for other methoxysilanes in this document) to ensure the data that exist there would not influence the derivation of the point of departure (POD), acute reference value (ReV) and effects screening level (ESL). The reference would be http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea02033-b9b0-6e47-e044-00144f67d031/AGGR-6695e063-eb08-433c-9f67-c65da4ff3d6b_DISS-9ea02033-b9b0-6e47-e044-00144f67d031.html#AGGR-6695e063-eb08-433c-9f67-c65da4ff3d6b.

- There exists a large database of study information available on TetMS under REACh. Perhaps this database should be reviewed (as is done for other methoxysilanes in this document) to ensure the data that exist there would not influence the derivation of the POD, acute ReV and ESL. The reference would be http://apps.echa.europa.eu/registered/data/dossiers/DISS-d7f5f034-9d29-0c95-e044-00144f67d031/AGGR-36c630f9-e7fe-47c7-b9a9-3e955dcafd31_DISS-d7f5f034-9d29-0c95-e044-00144f67d031.html#AGGR-36c630f9-e7fe-47c7-b9a9-3e955dcafd31.

- There exists a large database of study information available on MTMS under REACh. Perhaps this database should be reviewed (as is done for other methoxysilanes in this document) to ensure the data that exist there would not influence the derivation of the POD, acute ReV and

ESL. The reference would be http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eadf710-f015-2047-e044-00144f67d031/DISS-9eadf710-f015-2047-e044-00144f67d031_DISS-9eadf710-f015-2047-e044-00144f67d031.html.

- There exists a large database of study information available on (CPTMS) under REACh. Perhaps this database should be reviewed (as is done for other methoxysilanes in this document) to ensure the data that exist there would not influence the derivation of the POD, acute ReV and ESL. The reference would be http://apps.echa.europa.eu/registered/data/dossiers/DISS-9e9bdce7-3813-5f44-e044-00144f67d031/AGGR-24441044-5812-478a-8cc8-a765815e08a1_DISS-9e9bdce7-3813-5f44-e044-00144f67d031.html#AGGR-24441044-5812-478a-8cc8-a765815e08a1.

Specific Comments:

Pg 3: Trimethoxysilane:

- Solubility in water: 1,000,000 mg/L; very soluble (OECD)
- Boiling Point: 84 ^{o}C at 1013 hPa
- Hydrolysis Half-Life: <0.3 min at pH 7 and 25 ^{o}C
- 3.3.1.4.3 Line 27. A value of "90" is stated for the total UF. However, it appears that the total would be "180" if the UFs are indeed 10, 3, and 6.
- Table 1: The critical effect for the acute ReV and ESL is stated to be based on respiratory effects, however the text on pages 11 (TMS) and 14 (Tetramethoxysilane) state the POD is based on body weight loss. The table and text are inconsistent.
- 4.3.1: This section and Table 2 for TMS indicate that the 90-day repeated dose subchronic toxicity study (413 OECD) data are not sufficient to derive the chronic ReV and ESL values for this chemical. A surrogate substance, tetramethoxysilane (TetMS) was used to derive these values. However, it appears as if the 90-day study data are consistent with the 28-day study data for TMS and that these data could have been used to derive the chronic ReV and ESLs following the same approach as is used for tetramethoxysilane. The following supports this perspective:

  The 90-day inhalation study (Bushy Run Res center 1995) is discussed in this section but not found suitable for the purpose as a LOAEL was not derived because there were no adverse effects seen up to the highest dose tested (0.5ppm, NOAEL). It is indicated that the free-standing NOAEL of 0.5 ppm was not informative and did not provide information on the dose-response relationship above NOAEL. Therefore, it was not used to derive the chronic toxicity factors. Texas Guidance (TG442) indicates that chronic experimental exposure data is preferentially used to derive chronic toxicity dose-response estimates, although subchronic data may be used with the potential for additional application of an uncertainty factor to account for the effect of exposure duration. In this regard, a well-conducted 28-day sub-chronic toxicity study is available (Dow Corning, 1980) and should be considered for use to derive chronic toxicity factors. In this study a dose response effect was seen across a dose range of 0.5 – 10 ppm. The NOAEL for this study was determined to be 0.5 ppm and the LOAEL was 5 ppm (based on bronchitis and bronchiolitis). This study appears to be appropriate for consideration and this may impact derivation of a chronic ReV.

Pg 3: 3-Chloropropyltrimethoxysilane:

- Solubility in water: 650,000 mg/L at 25 ^{o}C, very soluble (Note that 65,000 mg/L is the water solubility for the hydrolysis product, 3-chloropropylsilanetriol)
- Density: 1.07
- Boiling Point: 196 ^{o}C at 1013 hPa

- Log Kow: 0.56 (Note: the -1.13 value is the log Kow for the hydrolysis product, 3-chloropropylsilanetriol)
- Hydrolysis Half-Life: 53.3 min at pH 7 and 25 ^{o}C

Pg 4: Change Table number from 4 to 3 since the table is a continuation of Table 3 on the previous page.

Pg 4: Methyltrimethoxysilane:

- Vapor Pressure: 80.1 mm Hg at 20 ^{o}C (= 106.8 hPa at 20 ^{o}C, as measured value noted in OECD and the CSR document)
- Melting Point: <-77 ^{o}C (OECD and CSR)
- Boiling Point: 102 ^{o}C at 1013 hPa (OECD and CSR)
- Hydrolysis Half-life: 2.2 hrs at pH 7 and 25 ^{o}C
- Section 3.3, page 8, line 30. There is reference to VTMS and CPTMS as methoxysilanes with reproductive/developmental tests. MTMS could also be indicated here.

Pg 4: Vinyl trimethoxysilane:

- Log Kow: 0.32 (The SIAP incorrectly identifies the log Kow as 0.032; the appropriate value of 0.32 is provided in the SIAR and Dossier)
- Vapor Pressure: 11.9 mm Hg at 25 ^{o}C (an error was made in the units here; 5.93 hPa = 11.9 mm Hg)
- Boiling Point: 123 ^{o}C at 1013 hPa
- Hydrolysis Half-life: <2.4 h at pH 7 and 50 ^{o}C

Pg 5: Renumber as Table 4

Pg 5: Tetramethoxysilane:

- Vapor Pressure: 10 mm Hg at 20 ^{o}C or 13 mm Hg at 25 ^{o}C (measured value)
- 3.3.2.1: Citation correction: Line 26 referring a 4hr nose-only study (citation should be Dow Corning Corp 1992, cited as NRC 2012). This study was conducted in 1982 and includes both TMS and TetMS. Perhaps review of the studies submitted under REACh will provide sufficient data to support derivation of the acute ReV and ESL values based on studies with TetMS.

Pg 6: Renumber as Table 5

Pg 6: Add the formula for MTMS to the table: $C_4H_{12}O_3Si$

Pgs 7-8, Section 3.2 Mode of Action (MOA) Analysis and Dose Metric:

- The explanation that whether acute and/or chronic inhalation exposure to methoxysilanes causes respiratory damage (site of contact effects) or nephrotoxicity (systemic effects) is determined by their rate of hydrolysis excludes the premise that the effects seen in the kidney and/or urinary bladder are actually local (not systemic) effects. There is evidence that inhalation and oral exposure to silanes can produce histopathological effects (epithelial hyperplasia) in the urinary bladder which may not always be considered a systemic effect, but rather a direct contact effect. Given that the critical effect noted for several methoxysilanes in the derivation of acute/chronic ReV values and 1-h ^{Acute}ESL and $^{chronic}ESL_{threshold}$ values is based on urinary bladder/kidney effects, please consider how an explanation of local vs systemic effects would influence these derivations.

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Pg 9, line 3: The half-life at pH 7 and 25°C is < 0.3 min

Pg 9, line 30: and 243 ppm

Pg 10: Renumber as Table 6

Pg 10, line 14: were observed in all groups during

Pg 10, line 15: in Group 4 (158 ppm) and

Pg 11, line 2: observed in the 158 and 243 ppm groups but not in the 181 and 206 ppm groups

Pg 11, lines 3-4: losses should not be used to

Pg 11, lines 9-10: (Section 3.3.1.1):

- the low-end level of 72 ppm (nominal concentration) was identified as the NOAEL based on mean body weight loss and was used as a POD to derive acute toxicity factors.

Pg 12, lines 23-25:

- The NOAEC from this 4-week inhalation study was 0.5 ppm, with a LOAEC of 5 ppm based on body weight, organ weight, clinical pathology (bronchitis and bronchiolitis), and histopathologic observations.

Pg 12, lines 29-30:

- A NOAEC of 0.2 ppm and a LOAEC of 1 ppm were identified based on weight loss, increased lung weight, clinical pathology (laryngitis and bronchopneumonia), and necropsy/histopathologic observations.

Pg 14, lines 2-3:

- "There were no reproductive/developmental studies available for TMS". While it is true that no guideline-specific reproductive or developmental studies have been conducted with TMS, an evaluation of reproductive organs is available from two repeated-dose toxicity studies, and similar information has been provided below for the other methoxysilanes:

  Three groups of 10 male and 10 female rats with an additional 5 rats/sex in the control and high exposure groups were exposed 6 hours/day, 5 days/week, for 13 weeks to trimethoxysilane at target concentrations of 0.02, 0.1, and 0.5 ppm. The control group (0 ppm) was exposed to filtered air alone. Five animals/sex in the control and 0.5 ppm groups were maintained for a 4-week recovery period. Reproductive organs (testes, epididymis, prostate, seminal vesicles, ovaries, vagina and uterus) were evaluated. There were no test article related effects in any of the reproductive organs at the highest concentration tested (0.5 ppm) after 90 days exposure. [Bushy Run Research Center (1995) Trimethoxysilane Y-4398 (TMS): Ninety-Day Vapor Exposure in Rats. Laboratory Project ID 93N1313. January 6, 1995]

  Three groups of 10 male and 10 female rats were exposed 6 hours/day, 5 days/week, for 9 days to trimethoxysilane vapor at target concentrations of 0.2, 1, and 5 ppm. A control group was exposed to filtered air alone. Five additional animals/sex were in the control and 5 ppm groups for a l4-day recovery group. Testes weights were collected. The one surviving male animal exposed to 5 ppm for 9 days was observed to have increased testes weight (absolute and relative to body weight); the relative testes weight (as a percentage of brain weight) for this one animal was decreased. Interpretation of the results for this one high dose male

animal must be performed with caution due to the small number of animals (one) and its moribund condition. [Bushy Run Research Center (1994) Trimethoxysilane: Nine-Day Vapor Inhalation Study in Rats. Laboratory Project ID 91U0021, September 14, 1994]

Pg 14, line 32, add the following text:

- exposure over 5 ½ weeks. All animals exposed at 45 ppm either died or were killed during the 28-day study. No effects were observed in any rats exposed at 0, 1, 5, or 10 ppm.

Pg 14, lines 34-35, revise as follows:

- exposure to 30 ppm. Males exposed at 15 ppm had only a decrease in total protein. No microscopic lesions were found in the respiratory tract or ocular epithelium of rats exposed at 1, 5, or 10 ppm.

Pg 15, line1- 4:

- As currently written, the text confuses the findings reported for the upper respiratory tract and the eyes. Consider the following revisions: inflammation and ocular lesions showed minimal acute keratitis with no epithelial desquamation in 4/20 rats. Upper respiratory tract lesions were more severe at 30 and 45 ppm and included ulceration, desquamation and inflammation of the respiratory epithelium, with a large amount of exudate in the nasal cavity. At 30 and 45 ppm, ocular lesions included desquamation of the central corneal epithelium; effects were moderate to severe at 30 ppm and severe at 45 ppm. Signs of toxicity appear to be dose-dependent. A NOAEC of 10 ppm and a LOAEC of 15 ppm based on minimal acute upper respiratory tract inflammation and minimal ocular keratitis were identified from this subacute study.

Pg 15, line 30: Add the following information:

- "(week one) and females (weeks one and two) in the 4,000 and 8,000 ppm groups. As a result of clinical observations and reduced body weights, animals from the 8000 ppm group were sacrificed by exposure day 9 and 3/5 females in the 4000 ppm group were sacrificed by exposure day 13. In these animals, gross pathological observations included calculi in the urinary bladders of several animals along with kidney discoloration, dilation and calculi. Histopathological evaluation of the urinary bladders containing calculi showed hyperplasia and inflammation in all cases with widespread urinary bladder necrosis in one male and three females. Gross necropsy was performed on all remaining animals with organ weights and histopathology conducted on selected tissues. There was a statistically significant change in organ weights over the treatment groups for female adrenal glands (increased), lungs (increased) and thymus (decreased), and in kidney weights (increased) for males.

Pg 15, line 34, add the following information:

- and all females of the 4,000 ppm group. Minimal urinary bladder epithelial hyperplasia, but with no histopathological findings in any tissue at this level, was

Pg 16, line 13:

- Provide justification for the conclusion that MTMS is a Category 3 vapor. According to the guidance document "TCEQ Guidelines to Develop Toxicity Factors", October 2012, Revised RG-442, pg 84, Category 3 gases are "poorly water soluble" and "are relatively insoluble in water". The physical/chemical data for MTMS indicate that it is highly water soluble (solubility in water = 290,000 mg/L; log Kow = -0.67). Again, according to the guidance document a water solubility value > 10,000 mg/L is classified as very soluble (pg 46) and a log Kow value < 1 is classified as highly soluble in water (hydrophilic).

Pg 16, line 30 to pg 17, line 1:

- "There were no reproductive/developmental studies available for MTMS." While it is true that no guideline-specific reproductive or developmental studies have been conducted with MTMS, a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) has been conducted via gavage in rats. No adverse effects on reproductive parameters were observed up to the highest dose tested (1,000 mg/kg bw/day). No adverse effects on the development of fetuses were observed up to the highest dose tested. The NOAEL for reproductive and developmental toxicity for MTMS was established at 1000 mg/kg bw/day. [Dow Corning Corporation (2005) Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test for Methyltrimethoxysilane in Sprague-Dawley Rats. Study Number 9896-102. Report No. 2005-I0000-55426.]

Pg 17, line 21:

- The OECD TG 403 study was conducted in compliance with GLP, so the sentence on line 21 should be deleted.

Pg 17, line 22- pg 18, line 14:

- What are the limitations to using a developmental toxicity study to derive the acute ReV for VTMS?

Pg 18, line 20: Add the following information:

- "exposure. Prior to their death several clinical abnormalities (e.g., periocular wetness, corneal opacity, blepharospasm, periurogenital area wetness, loss of coordination, hypoactivity, breathing difficulties, and an unkempt appearance) were observed. Rats in"

Pg 18, line 23: Add the following information:

- "150 ppm rats. Prior to sacrifice, rats of the 750 ppm group had markedly increased water intake, with a concomitant increase in urine volume and a decrease in urine specific gravity. Hematuria and mild hematologic (decreases in hemoglobin concentration (5.7% in males, 2.5% in females) and hematocrit (5.4% in males, 3.0% in females) in both sexes; a 4% decrease in erythrocyte count in males only) alterations were also observed. Urinalysis…"

Pg 18, line 26: Add the following information:

- "value. At necropsy, treatment-related lesions were observed in the 1500 ppm group only and consisted of discoloration of the kidneys, corneal and lenticular opacities, brain hemorrhage, perinasal encrustation, and blood-tinged urine in the bladder. Noteworthy"

Pg 19, line 12:

- What is the justification for identifying VTMS as a Category 3 vapor? As stated previously, according to the guidance document Category 3 gases are "poorly water soluble" and "are relatively insoluble in water". The physical/chemical data for VTMS indicate that it is highly water soluble (solubility in water = 5.043×10^5 mg/L; log Kow = -0.32). These parameters indicate that VTMS is water soluble.

Pg 21, lines 16-17: revise as follows:

- "Gross necropsies were performed on all rats. Body weights"

Pg 21, lines 33-35:

- The purpose of the following sentence is not clear: "Since the critical effect is unknown, adjustments as a Category 3 vapor (for possible systemic effects (i.e., reproductive/developmental) and as a Category 1 vapor (for possible respiratory effects) were

considered." Don't the physical/chemical parameters of a chemical determine which category a chemical belongs in? It appears that you are looking at the effects (site of contact vs. systemic) and then trying to justify placing the chemical in a specific category. What is the justification for considering that CPTMS could be a Category 3 vapor? The physical/chemical data for CPTMS indicate that it is highly water soluble (solubility in water = 650,000 mg/L; log Kow = 0.56). Both parameters demonstrate that CPTMS is water soluble.

Pg 24: Renumber as Table 7

Pg 25, line 15:

- What is the purpose of the IOAEL? It does not appear in the TCEQ guidance document. Lines 25-27 state: "Effects occurred in some animals and represent a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer." The following IOAEL values have been proposed for these chemicals based on the exposure times shown below. The study regimens and durations are very different, so it is unclear exactly how these values could be relevant for comparison.

Chemical	IOAEL	Duration of exposure
TMS	790 mg/m3 (158 ppm)	30 min
TetMS	Inadequate data	
MTMS	4400 mg/m3 (800 ppm)	6 hr/d, 5d/wk, 14 d
VTMS	610 mg/m3 (100 ppm)	GD 6-15
CPTMS	Inadequate data (free-standing NOAEL = 100 ppm)	

Pg 26, section 4.2, Line 18:

- "The hydrolysis rate is important to the MOA due to the fact that it dictates the chemical species actually inhaled and subsequently distributed and metabolized in the body." This isn't as clear as stated in the report. We have shown that it is possible to deliver unreacted parent compound to the animals even with substances with short hydrolysis half-lives such as trimethoxysilane.

Pg 27, line 36:

- The use of a 4-h LC_{50} value in the following sentence "The 4-h LC50 (60 ppm) for TMS is similar to the 4-h LC_{50} (63 ppm) for TetMS indicating the relative potency of these methoxysilanes would be equipotent." is an inaccurate way to assess the overall relative potential inhalation toxicity of two chemicals.

Pg 27-28:

- Chronic evaluation for TMS: The 90-d inhalation toxicity study was not used for the derivation of a ^{chronic}ESL for TMS, but rather the proposal is to use the 28-d inhalation toxicity study from an analogous material, TetTMS. The 28-d inhalation toxicity study with TMS could be used for this derivation. Some details for the 28-d study have been provided on pg 12 (Breckenridge et al., 1980). The NOAEC from this 4-wk inhalation study was 0.5 ppm, with a LOAEC of 5 ppm based on body weight, organ weight, clinical pathology (bronchitis and bronchiolitis), and histopathologic observations. Provide an explanation for why this study with TMS was not used to derive the ^{chronic}ESL value?

Pg 28, lines 21-22: For clarity, suggest the following revisions:

- "A NOAEC of 10 ppm and a minimal LOAEC of 15 ppm for minimal acute inflammation in the nasal region and keratitis of the ocular epithelium were identified from this subacute/subchronic study."

Pg 28, lines 26-27: Consider revisions:

- "The critical effects at the LOAEC of 15 ppm are upper respiratory tract lesions (nasal region) and keratitis of the ocular epithelium.~~bronchiolar inflammatory lesions~~." *(Note: these effects were not seen until 30 ppm)*

Pg 29, lines 16-17: Revision are needed for clarity:

- "The critical effects at the LOAEC…"
  are upper respiratory tract lesions (nasal region) and keratitis of the ocular epithelium,…"

Pg 30, line 9: Add the following sentence to the end of this line:

- "concentrations in ppm were 25, 100, 400 and 1600 ppm. Ten additional rats/sex were included in the control and high dose groups and exposed to MTMS for 90 days, followed by a 28-day recovery period without exposure to MTMS."

Pg 30, lines 13-14: Suggest the following addition:

- "calculi in urinary bladder of four males and one female, which persisted only in the recovery group males but was not observed in the recovery group females following the 28-d recovery period.."

Pg 30, lines 18-23:

- This paragraph should be limited to the findings observed at 2,200 mg/m^3.

Pg 30, line 20:

- There was a statistically significant increase of 18% in the absolute (not relative) adrenal gland weight in females at 2,200 mg/m3.

Pg 31, line 12:

- As noted above in comments for pg 16, what is the justification for the conclusion that MTMS is a "Category 3" vapor? According to the guidance document and based on its water solubility and partition coefficient, MTMS would be classified as a Category 1 chemical.

Pg 32, lines 15-19:

- In a repeated dose inhalation toxicity study ~~a combined repeated-dose/reproductive/developmental toxicity study, in accordance with OECD TG 422~~, *(Note: While no guideline was specified for this study, it definitely was not a repeated dose/reproductive/developmental toxicity screening study conducted in accordance with OECD TG 422*) groups of 20 Fischer 344 rats/sex/concentration were exposed 6 h/d, 5 d/week, for 14 weeks to VTMS (A-171 Silane) vapor at measured concentrations of 0 (control), 60.5, 605 and 2421 mg/m3 (0, 10, 100, or 400 ppm), respectively. This study was considered a subchronic ~~chronic~~ study since it is longer than 3 months (TCEQ 2012). *(Note: A 2-year study (lifetime exposure) is considered to be a chronic study in rats. An exposure duration less than 2 years is a subchronic study.)*

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Pg 33, line 27:

- Replace "No reproductive effects were observed in this study" with "No significant effects on reproductive organs were observed in this study.", as this study was not designed to evaluate reproductive effects.

Pg 33, line 31: suggest the following addition:

- "….reproductive organs (testes, epididymides, prostate (and associated sex glands), uterus, vagina, cervix, ovaries, fallopian tubes, or mammary tissue) examined at"

Pg 33, line 32-33:

- Delete "A free-standing NOAEL of 400 ppm for the absence reproductive effects was identified from this study" because this study was not designed to evaluate reproductive toxicity as an endpoint and therefore, a NOAEC cannot be derived for it.

Pg 34, lines 17-18: The 14-week study is not a chronic study; it is a subchronic study. Revise as follows:

- "A UF_{Sub} of 3 was considered appropriate to account for the use of a subchronic study.~~a UF_{Sub} of 2 instead of 1 was used. The 14-week study (ECHA 2011) was considered a chronic study but it was close to a subchronic 13-week exposure~~,"

Pg 34, line 22: The 14-week repeated dose inhalation toxicity study was not designed to evaluate reproductive or developmental toxicity. Revise as follows:

- "A repeated dose/reproductive/developmental toxicity study was conducted by ~~both inhalation and~~ oral gavage (OECD TG 422). The NOAEL for reproductive toxicity was 1000 mg/kg bw/day for males and 250 mg/kg bw/day for females (based on a reduced number of estrous cases). There were no effects on developmental parameters; the NOAEL for developmental effects was 1000 mg/kg bw/day." [Note that there is also a developmental toxicity study conducted according to EPA OTS 798.4350 in which pregnant rats were exposed to VTMS vapor or filtered air via inhalation for 6 hours/day on gestational days 6-15 at target concentrations of 0 (control), 25, 100 and 300 ppm (ca. 0, 0.15, 0.60 and 1.8 mg/L). The NOAEC for maternal toxicity was 0.15 mg/L based on decreased body weight gain at 0.60 and 1.8 mg/L; the NOAEC for developmental effects was 0.60 mg/L based on evidence of slightly delayed skeletal ossification in fetuses from the 1.8 mg/L group.

Pg 35, line 23: suggested revision:

- "Groups of male and female rats (10/sex/concentration) were…"

Pg 36, lines 3-4:

- Delete the sentence "There were no test article-related microscopic changes in any of the respiratory tract organs or other tissues examined", as it was already reported on the previous page, lines 30-31.

Pg 38: Renumber as Table 8

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