Tri- and Tetramethoxysilanes

Trimethoxysilanes (CAS Registry Numbers):

- Trimethoxysilane (2487-90-3)
- Methyltrimethoxysilane (1185-55-3)
- Vinyltrimethoxysilane (2768-02-7)
- 3-Chloropropyltrimethoxysilane (2530-87-2)

Tetramethoxysilane (CAS Registry Numbers):

- Tetramethoxysilane (681-84-5)

Prepared by
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Tiffany Bredfeldt, Ph.D.
Roberta L. Grant, Ph.D.
Toxicology Division
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<th>Definition</th>
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<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>AEGL</td>
<td>Acute Exposure Guideline Levels</td>
</tr>
<tr>
<td>AIHA</td>
<td>American Industrial Hygiene Association</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CPTMS</td>
<td>3-chloropropyltrimethoxysilane</td>
</tr>
<tr>
<td>DSD</td>
<td>development support document</td>
</tr>
<tr>
<td>ESL</td>
<td>Effects Screening Level</td>
</tr>
<tr>
<td>acute ESL</td>
<td>acute health-based Effects Screening Level for chemicals meeting minimum database requirements</td>
</tr>
<tr>
<td>acute ESL&lt;sub&gt;generic&lt;/sub&gt;</td>
<td>acute health-based Effects Screening Level for chemicals not meeting minimum database requirements</td>
</tr>
<tr>
<td>chronic ESL&lt;sub&gt;generic&lt;/sub&gt;</td>
<td>chronic health-based Effects Screening Level for chemicals not meeting minimum database requirements</td>
</tr>
<tr>
<td>chronic ESL&lt;sub&gt;threshold(nc)&lt;/sub&gt;</td>
<td>chronic health-based Effects Screening Level for threshold dose response noncancer effects</td>
</tr>
<tr>
<td>DAF</td>
<td>dosimetric adjustment factor</td>
</tr>
<tr>
<td>ET</td>
<td>extrathoracic</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practices</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HEC</td>
<td>human equivalent concentration</td>
</tr>
<tr>
<td>HQ</td>
<td>hazard quotient</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect-level</td>
</tr>
<tr>
<td>LOEL</td>
<td>lowest observed effect level</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>μg</td>
<td>microgram</td>
</tr>
<tr>
<td>Acronyms and Abbreviations</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>µg/m³</td>
<td>micrograms per cubic meter of air</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>mg/m³</td>
<td>milligrams per cubic meter of air</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MMS</td>
<td>monomethoxysilane</td>
</tr>
<tr>
<td>MOA</td>
<td>mode of action</td>
</tr>
<tr>
<td>MTMS</td>
<td>methyltrimethoxysilane</td>
</tr>
<tr>
<td>n</td>
<td>number</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect-level</td>
</tr>
<tr>
<td>NOEL</td>
<td>no-observed-effect-level</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>POD</td>
<td>point of departure</td>
</tr>
<tr>
<td>POD(_{\text{ADJ}})</td>
<td>point of departure adjusted for exposure duration</td>
</tr>
<tr>
<td>POD(_{\text{HEC}})</td>
<td>point of departure adjusted for human equivalent concentration</td>
</tr>
<tr>
<td>ppb</td>
<td>parts per billion</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>ReV</td>
<td>reference value</td>
</tr>
<tr>
<td>RGDR</td>
<td>regional gas dose ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Sprague-Dawley</td>
</tr>
<tr>
<td>TB</td>
<td>tracheobronchial</td>
</tr>
<tr>
<td>TCEQ</td>
<td>Texas Commission on Environmental Quality</td>
</tr>
<tr>
<td>TD</td>
<td>Toxicology Division</td>
</tr>
<tr>
<td>TetMS</td>
<td>tetramethoxysilane</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethoxysilane</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
</tr>
<tr>
<td>UF(_H)</td>
<td>interindividual or intraspecies human uncertainty factor</td>
</tr>
<tr>
<td>Acronyms and Abbreviations</td>
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</tr>
<tr>
<td>----------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>UF_A</td>
<td>animal to human uncertainty factor</td>
</tr>
<tr>
<td>UF_Sub</td>
<td>subchronic to chronic exposure uncertainty factor</td>
</tr>
<tr>
<td>UF_L</td>
<td>LOAEL to NOAEL uncertainty factor</td>
</tr>
<tr>
<td>UF_D</td>
<td>incomplete database uncertainty factor</td>
</tr>
<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>VP</td>
<td>vapor pressure</td>
</tr>
<tr>
<td>VTMS</td>
<td>vinyltrimethoxysilane</td>
</tr>
</tbody>
</table>
Chapter 1 Summary Tables

Tables 1 and 2 provide a summary for air permitting of short- and long-term health-based values from an evaluation of acute and chronic exposures to some selected tri- and tetramethoxysilanes. No data on welfare values (odor and vegetation) were found so no odor-based or vegetation-based values were derived. The tri- and tetramethoxysilanes are not considered to be carcinogens so only chronic ReVs were developed. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Tables 3-5 provide summary information on the physical/chemical properties of the tri- and tetramethoxysilane group members listed in Tables 1 and 2.

Table 1 Short-Term Health-Based Values for Selected Tri- and Tetramethoxysilanes

<table>
<thead>
<tr>
<th>Chemical</th>
<th>1-h Acute ReV (a)</th>
<th>1-h Acute ESL</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoxysilane</td>
<td>1,200 µg/m(^3) (250 ppb)</td>
<td>360 µg/m(^3) (75 ppb) (b)</td>
<td>Critical Effect: Respiratory effects in rats</td>
</tr>
<tr>
<td>Tetramethoxysilane</td>
<td>--- (c)</td>
<td>360 µg/m(^3) (c)</td>
<td>Critical Effect: Data not sufficient to derive chemical-specific values. Surrogate to trimethoxysilane: respiratory effects in rats.</td>
</tr>
<tr>
<td>Methyltrimethoxysilane</td>
<td>22,000 µg/m(^3) (4,000 ppb)</td>
<td>6,700 µg/m(^3) (1,200 ppb) (b)</td>
<td>Critical Effect: Minimal urinary bladder epithelial hyperplasia in rats.</td>
</tr>
<tr>
<td>Vinyltrimethoxysilane</td>
<td>3,000 µg/m(^3) (500 ppb)</td>
<td>910 µg/m(^3) (150 ppb) (b)</td>
<td>Critical Effect: Maternal toxicity (decreased body weight gain) in pregnant rats.</td>
</tr>
<tr>
<td>3-Chloropropyltrimethoxysilane</td>
<td>8,900 µg/m(^3) (1,100 ppb)</td>
<td>2,700 µg/m(^3) (330 ppb) (b)</td>
<td>Critical Effect: Based on free-standing NOAEL: absence of general, maternal, and reproductive and developmental toxicity in rats</td>
</tr>
</tbody>
</table>

\(a\) Methoxysilanes are not monitored for by the TCEQ’s ambient air monitoring program

\(b\) Based on the acute ReV multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

\(c\) Data not sufficient to derive specific values. Surrogate to trimethoxysilane.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 2 Long-Term Health-Based Values for Selected Tri- and Tetramethoxysilanes

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Chronic ReV</th>
<th>chronic ESL-threshold(nc)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoxysilane</td>
<td>--- c</td>
<td>13 µg/m³ c</td>
<td>Critical Effect: Data not sufficient to derive chemical-specific values. Surrogate to TetMS: upper respiratory tract, bronchiolar, and inflammatory lesions in rats</td>
</tr>
<tr>
<td>Tetramethoxysilane</td>
<td>44 µg/m³ (7 ppb)</td>
<td>13 µg/m³ (2.1 ppb) b</td>
<td>Critical Effect: Upper respiratory tract, bronchiolar, and inflammatory lesions in rats</td>
</tr>
<tr>
<td>Methyltrimethoxysilane</td>
<td>370 µg/m³ (66 ppb)</td>
<td>110 µg/m³ (20 ppb) b</td>
<td>Critical Effect: Increased incidence of grossly observed urinary bladder calculi along with the kidney dilation in rats</td>
</tr>
<tr>
<td>Vinyltrimethoxysilane</td>
<td>600 µg/m³ (99 ppb)</td>
<td>180 µg/m³ (30 ppb) b</td>
<td>Critical Effect: Urinary bladder and kidney systemic effects in rats</td>
</tr>
<tr>
<td>3-Chloropropyltrimethoxysilane</td>
<td>120 µg/m³ (15 ppb)</td>
<td>12 µg/m³ (1.5 ppb) b</td>
<td>Critical Effect: Histopathologic changes in the urinary bladder/kidneys in rats</td>
</tr>
</tbody>
</table>

a Methoxysilanes are not monitored for by the TCEQ’s ambient air monitoring program

b Based on the chronic ReV multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

c Data not sufficient to derive specific values. Surrogate to tetramethoxysilane.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 3 Physical and Chemical Data for Trimethoxysilanes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trimethoxysilane</th>
<th>3-Chloropropyltrimethoxysilane</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C₃H₁₀O₃Si</td>
<td>C₆H₁₃ClO₃Si</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>122.22</td>
<td>198.72</td>
<td>AIHA, Chemical Book</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
<td>Liquid</td>
<td>AIHA, Chemical Book</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Clear</td>
<td>AIHA, Chemical Book</td>
</tr>
<tr>
<td>Odor</td>
<td>Ester</td>
<td>---</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>CAS Registry Number</td>
<td>2487-90-3</td>
<td>2530-87-2</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Synonyms</td>
<td>TMS</td>
<td>CPTMS, 3-(Trimethoxysilyl) propyl</td>
<td>AIHA, Chemical Book</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>1,000,000 mg/L; very soluble</td>
<td>650,000 mg/L at 25 °C</td>
<td>OECD</td>
</tr>
<tr>
<td>Log K&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>-1.22</td>
<td>0.56</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Density (water = 1)</td>
<td>0.96</td>
<td>1.07</td>
<td>OECD</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>57 mm Hg 20 °C</td>
<td>0.39 mm Hg at 25 °C</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Melting Point</td>
<td>-114 °C</td>
<td>-50°C</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>84 °C at1013 hPa</td>
<td>196 °C at1013 hPa</td>
<td>AIHA, OECD</td>
</tr>
<tr>
<td>Hydrolysis Half-Life</td>
<td>&lt;0.3 min at pH 7 and 25 °C</td>
<td>53.3 min at pH 7 and 25 °C</td>
<td>OECD; Kallas et al. 1991</td>
</tr>
<tr>
<td>Conversion Factors</td>
<td>1 ppm = 5.0 mg/m³</td>
<td>1 μg/m³ = 0.12 ppb</td>
<td>AIHA, Toxicology Division</td>
</tr>
<tr>
<td></td>
<td>1 mg/m³ = 0.2 ppm</td>
<td>1 ppb = 8.13 μg/m³</td>
<td></td>
</tr>
</tbody>
</table>
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 4 Physical and Chemical Data for Trimethoxysilanes (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Methyltrimethoxysilane</th>
<th>Vinyl trimethoxysilane</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C₄H₁₂O₃Si</td>
<td>C₅H₁₂O₃Si</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>136.22</td>
<td>148.23</td>
<td>ChemSpider</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
<td>Liquid</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Color</td>
<td>Clear</td>
<td>Light yellow</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Odor</td>
<td>---</td>
<td>Fruity</td>
<td></td>
</tr>
<tr>
<td>CAS Registry Number</td>
<td>1185-55-3</td>
<td>2768-02-7</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Synonyms</td>
<td>MTMS; Trimechoxy(methyl)silane</td>
<td>VTMS, Trimehoxyvinylsilane; Trimehoxyethylene</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>29000 mg/L</td>
<td>5.043 x 10⁵ mg/L</td>
<td>OECD</td>
</tr>
<tr>
<td>Log $K_{ow}$</td>
<td>-0.67</td>
<td>0.32</td>
<td>OECD</td>
</tr>
<tr>
<td>Density (water = 1)</td>
<td>0.955 at 20°C</td>
<td>0.97</td>
<td>ChemicalBook</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>80.1 mm Hg at 20 °C</td>
<td>11.9 mm Hg at 25 °C</td>
<td>OECD</td>
</tr>
<tr>
<td>Melting Point</td>
<td>&lt; -77°C</td>
<td>-97°C</td>
<td>OECD</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>102 °C at 1013hPa</td>
<td>123 °C at 1013hPa</td>
<td>OECD</td>
</tr>
<tr>
<td>Hydrolysis half life</td>
<td>2.2 h at pH7 and 25 °C</td>
<td>&lt; 2.4 h at pH7 and 25 °C</td>
<td>OECD</td>
</tr>
<tr>
<td>Conversion Factors</td>
<td>1 μg/m³ = 0.18 ppb</td>
<td>1 μg/m³ = 0.17 ppb</td>
<td>Toxicology Division</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 5.57 μg/m³</td>
<td>1 ppb = 6.06 μg/m³</td>
<td></td>
</tr>
</tbody>
</table>
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 5 Physical and Chemical Data for Tetramethoxysilane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tetramethoxysilane</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C₄H₁₂O₄Si</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>155.22</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Color</td>
<td>Clear</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Odor</td>
<td>Faint, ester-like</td>
<td>AIHA 2007</td>
</tr>
<tr>
<td>CAS Registry Number</td>
<td>681-84-5</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Synonyms</td>
<td>TetMS; Tetramethyl silicate; Tetramethyl orthosilicate</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Hydrolyzes</td>
<td>AIHA 2007</td>
</tr>
<tr>
<td>Log Kₜₜₐₜₜ</td>
<td>-1.93</td>
<td>ChemIDPlus</td>
</tr>
<tr>
<td>Density (water = 1)</td>
<td>1.03 at 20 °C</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>10 mm Hg</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Melting Point</td>
<td>-2 °C</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>121°C</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td>Hydrolysis half life</td>
<td>rapid</td>
<td>Kallos et al. 1991</td>
</tr>
<tr>
<td>Conversion Factors</td>
<td>1 μg/m³ = 0.16 ppb</td>
<td>ACGIH 2007</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 6.23 μg/m³</td>
<td></td>
</tr>
</tbody>
</table>
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 6 Structures of Trimethoxysilanes and Tetramethoxysilane

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Formula</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoxysilane</td>
<td>TMS</td>
<td>C₃H₁₀O₃Si</td>
<td><img src="image" alt="TMS Structure" /></td>
</tr>
<tr>
<td>3-Chloropropyltrimethoxysilane</td>
<td>CPTMS</td>
<td>C₆H₁₅ClO₃Si</td>
<td><img src="image" alt="CPTMS Structure" /></td>
</tr>
<tr>
<td>Methyltrimethoxysilane</td>
<td>MTMS</td>
<td></td>
<td><img src="image" alt="MTMS Structure" /></td>
</tr>
<tr>
<td>Vinyltrimethoxysilane</td>
<td>VTMS</td>
<td>C₅H₁₂O₃Si</td>
<td><img src="image" alt="VTMS Structure" /></td>
</tr>
<tr>
<td>Tetramethoxysilane</td>
<td>TetMS</td>
<td>C₄H₁₂O₄Si</td>
<td><img src="image" alt="TetMS Structure" /></td>
</tr>
</tbody>
</table>

a Structures obtained from ChemSpider
Chapter 2 Major Sources and Uses

Alkoxy silanes (RnSiOR(4-n)) are widely used in coatings industries as adhesion promoters, crosslinkers, and hydrophobes. The most typical alkoxy moieties (OR) are methoxy and ethoxy which highly react with various forms of hydroxyl groups and release methanol (MeOH) and ethanol (EtOH) (Witucki 1993). Methoxysilanes are used for coatings, adhesion promoters, crosslinkers, and water scavengers. For example, trimethoxysilane is used as an intermediate in the production of organofunctional silanes (AIHA 2007) and tetramethoxysilane is used in coating the screens of television picture tubes (ACGIH 2007).

Methoxysilanes are not monitored for by the TCEQ’s ambient air monitoring program, so currently no ambient air data from TCEQ (i.e., peaks, annual averages, trends, etc.) are available to assess methoxysilane concentrations in Texas ambient air.

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

Methoxysilanes are clear, colorless liquids. Like other alkoxy silanes, methoxysilanes generally have sweet fruity odors that become less apparent as the molecular weight increases (NRC 2012). The methoxysilanes category, based on the number of methoxy groups, includes mono-, di-, tri-, and tetramethoxysilanes. They are structural analogs and are in the organic silane family. Methoxysilanes undergo hydrolysis in the presence of water (Kallos et al., 1991). The hydrolysis half-life varies among methoxysilanes from seconds to hours. The stability of individual methoxysilanes is dependent on chemical substitution (i.e., organic substitution, steric bulk of such groups, electronegativity or electropositivity) (Arkles et al., 1992; Brinker, 1988). The hydrolysis products, MeOH and silanols, are expected based on the chemical structure of methoxysilanes at an equal ratio of numbers of methoxy groups to numbers of silanols. For example, dimethoxydimethylsilane (DMDMS) hydrolyzes quickly (i.e., half-life of < 0.6 h) to form 2 moles of MeOH and 1 mole of dimethylsilanediol (OECD 2010). Depending on the pH and concentration of the substance, the alkysilanols may condense to form oligomers and polymers (Arkles et al., 1992; Brinker, 1988). Other physical/chemical properties of methoxysilanes can be found in Tables 3 to 5.

3.2 Mode of Action (MOA) Analysis and Dose Metric

The observed intrinsic toxicity of methoxysilanes is likely due to a mixture of the parent molecule and the hydrolysis products MeOH and silanols and to a lesser degree the polymerization products (OECD 2008, 2009a). Acute inhalation toxicities for some methoxysilanes are similar to those for MeOH (i.e., respiratory irritation and cellular damage) (refer to MeOH DSD TCEQ 2014a). However, the relative toxicities of methoxysilanes are greater than MeOH. Trimethoxysilane (TMS) and tetramethoxysilanes (TetMS) are extremely irritating to the mucous membranes of the eye and respiratory tract (AIHA 2007, ACGIH 2007). Toxicities of TMS and TetMS are higher than those of other trimethoxysilanes [e.g.,
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

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vinylmethoxysilane (VTMS), methyltrimethoxysilane (MTMS)) and MeOH. Available LC₅₀ data indicate the toxicities of the various tri- and tetramethoxysilanes, relative to MeOH, are as follows:

\[ \text{TMS} \geq \text{TetMS} >>> \text{VTMS} > \text{MTMS} >>> \text{MeOH} \]

TMS hydrolyzes quickly to yield 3 moles of MeOH and 1 mole of silanetriol. The high toxicity of TMS might be related to some form of silicate or other oxygen-containing silicon reaction product during hydrolysis in addition to MeOH release (Tamura et al. 1968 and Rop 1979; as cited in AIHA 2007).

Methoxysilanes (e.g., tri- and tetramethoxysilanes) can cause respiratory damage and nephrotoxicity after inhalation exposure in animals. The MOA for nephrotoxicity is unclear, but both the respiratory toxicity (i.e., lesions) and nephrotoxicity (i.e., calculi and renal dilation) are assumed to be relevant to human health. Based on an analysis of the adverse health effects of the tri- and tetramethoxysilanes, the type of health effect observed (respiratory versus systemic effects) may depend on the hydrolysis half-life. The shorter the hydrolysis half-life (minutes), respiratory effects may occur due to the hydrolysis products whereas if the hydrolysis half-life is longer (i.e., hours), systemic effects such as nephrotoxicity may occur due to the parent compound.

Since available inhalation studies for the methoxysilanes are based on animals exposed to the parent chemicals and not the hydrolysis products MeOH and silanols, exposure concentration of the parent chemicals will be used as the default dose metric.

### 3.3 Health-Based Toxicity Factors

Chemical-specific inhalation and/or oral toxicity data (animal studies, lethality studies, and chemical knowledge) are available for a few members of the trimethoxysilanes [TMS, MTMS, VTMS, and 3-chloropropyltrimethoxysilane (CPTMS)] and tetramethoxysilane (TetMS). Only the inhalation toxicity data were used to develop respective inhalation toxicity factors. The majority of animal data available were for subacute/subchronic exposure durations. The derivation of toxicity factors for each of these methoxysilanes were listed separately below.

Reproductive or developmental toxicity studies are not available for all methoxysilanes, although available oral and inhalation reproductive/developmental studies on several methoxysilanes (VTMS, CPTMS and MTMS where systemic effects were observed) as well as the chlorosilanes or the acetoxysilanes group indicate silanes are not reproductive/developmental toxicants. MeOH is not considered a reproductive/developmental toxicant (TCEQ 2012).
3.3.1 Trimethoxysilane (TMS)

TMS is a clear colorless liquid with an ester-like odor (AIHA 1997). It undergoes rapid hydrolysis in water; the half-life at pH 7 and 25°C is < 0.3 min. Hydrolysis of TMS is expected to produce 3 moles of MeOH and 1 mole of silanetriol (Kallos et al. 1991, OECD 2007). Limited data are available regarding the toxicity of the chemicals in either humans or laboratory animals (NRC 2012). No acute reproductive or developmental toxicity studies have been conducted with TMS. Systemic effects only occur at high concentrations. The vapors are extremely irritating to the mucous membranes of the eye and respiratory tract (AIHA 2007).

3.3.1.1 Inhalation LC\textsubscript{50} Studies

A GLP LC\textsubscript{50} study was conducted by Union Carbide (ECHA 2015a; OECD 2008; Nachreiner and Dodd 1988, as cited in NRC 2012). Five male and five female Sprague-Dawley (SD) rats were exposed to TMS at concentrations of 68, 155, 342, or 643 ppm for 1 hour (h) or 19, 39, 71, or 166 ppm (analytical concentration) for 4 h.

- The 1-h LC\textsubscript{50} was 161 ppm for males, 146 ppm for females with an average value of 154 ppm for both sexes.
- The 4-h LC\textsubscript{50} was 81 ppm for males, 42 ppm for females with an average value of 60 ppm for both sexes.

There were no significant differences in LC\textsubscript{50} values between male and female rats.

3.3.1.2 Key Inhalation Animal Study (MPI Research 1998)

A study was conducted following GLP (following USEPAOTS 798.1150) that used groups of 5 male and 5 female SD rats exposed to TMS for 30 min (MPI Research 1998, as cited in OECD 2008, ECHA 2015a) at target concentrations of 100 and 200 ppm (Groups 1 and 2, respectively), and 175, 150, or 225 ppm (groups 3, 4, and 5, respectively). The animals were observed for a 14-d post exposure period, and then sacrificed.

Since TMS hydrolyses rapidly, hydrolysis most likely occurred within the experimental chamber. Therefore, both TMS and MeOH in the experimental chamber were analyzed. Since animals are exposed to TMS, MeOH, and silanols within the experimental chamber, the use of nominal concentrations would be more representative of the parent chemical, TMS, and is preferred. The corresponding nominal and analytical concentrations are summarized in Table 6. The nominal concentrations of TMS for Groups 1-5 were 72, 206, 181, 158, and 243 ppm, respectively. MPI Research (1998) used nominal concentrations to describe the Point of Departure (POD) or no observed adverse effect level (NOAEL).

MeOH production, used as a measurement of the hydrolysis of the parent chemical, appeared to be slight to moderate based on visual inspection of the GC chromatograms for Groups 1 and 2,
when compared to Groups 3, 4, and 5. MeOH concentrations were measured for Groups 3, 4, and 5, with the respective mean values being 76, 26, and 83 ppm (Table 6).

**Table 7 Summary of Exposure Regimes and Corresponding Nominal and Analytical Concentrations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Target (ppm)</th>
<th>Nominal (ppm)</th>
<th>Analytical (ppm)</th>
<th>MeOH (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>72</td>
<td>45</td>
<td>Slight to moderate</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>206</td>
<td>132</td>
<td>Slight to moderate</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>181</td>
<td>178</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>158</td>
<td>105</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>225</td>
<td>243</td>
<td>232</td>
<td>83</td>
</tr>
</tbody>
</table>

This study was judged to be valid with restrictions (OECD 2008), since the exposure duration was 30 min. Criteria evaluated for treatment effect during the study period were clinical signs, body weights, eye examinations, and gross necropsy findings and mortality (i.e., histopathology of the nasal region was not conducted).

The only mortalities that occurred during the conduct of this study were a single male in Group 2 (206 ppm) that died on post-exposure day 11 and a single male and female in Group 5 (243 ppm) that each died on post-exposure day 6. Group mean body weight losses were observed (with 2 exceptions: Group 1 and 2 females) during the first post-exposure week, and enhanced group mean body weight gains were observed in all groups during the second post-exposure week. However, a decrease in mean body weight gain was observed in Group 4 (158 ppm) and Group 5 (243 ppm) in females after the 14-d post-exposure period. At necropsy after the 14-d post exposure period, the tissues from most males and females of all groups were within normal limits (i.e., no abnormal necropsy observed). Five animals from the two highest exposure groups (Groups 2 and 5, 206 and 243 ppm, respectively) exhibited mild to moderate red lung discoloration on multiple lobes.

Based on the results of this study, MPI Research concluded that the 30-min NOAEI (for group mean body weight losses during the first post-exposure week) in rats is less than 158 ppm (LOAEL) (nominal concentration), but greater than 72 ppm (nominal concentration). The target organ for toxicity was the respiratory tract; there were no other systemic findings of toxicity.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

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However, the results of mean body weight losses were not dose-dependent (i.e., effect was observed in the 158 and 243 ppm groups but not in the 181 and 206 ppm group) and the exposure duration was only 30 min. Thus, the 30-min NOAEL (>72 and < 158 ppm) for mean body weight losses should not be used to derive toxicity factors. The results of mild to moderate red lung discoloration on multiple lobes observed in the 206 and 243 ppm groups, however, showed that red lung discoloration was a better endpoint. Thus, the level of 181 and 206 ppm were considered a NOAEL and LOAEL, respectively, for red lung discoloration on multiple lobes. The NOAEL of 181 ppm, however, is higher than the 4-h LC₅₀ of 60 ppm (male rats) (Section 3.3.1.1). For these reasons, the low-end level of 72 ppm (nominal concentration) was identified as the NOAEL based on mean body weight loss and was used as the POD to derive acute toxicity factors. Since the target organ for toxicity in this study was the respiratory tract, respiratory tract effect was considered critical effects for the selected POD.

3.3.1.3 Supporting Subacute Studies

Three additional subacute inhalation studies (5-d, 9-d and 4-week) are reported below, although the MPI Research (1998) acute study for 30 min is preferred over subacute studies for the development of a 1-h ReV based on TCEQ guidelines (TCEQ 2012). However, these subacute studies indicate that the time- and dose-response for TMS is steep (see Section 3.3.1.3.2 and 3.3.1.3.3). The 5-d study indicated that rats, mice, and hamsters have similar dose-response and adverse respiratory effects after exposure to TMS. ECHA (2015a) and OECD (2008) provide information on other studies that were judged to be of lower quality or did not provide useful information, so these studies are not discussed in this DSD.

3.3.1.3.1 Dow Corning Corp. 1981

The following information was taken directly from NRC (2012)

In a repeat exposure study, Sprague-Dawley (BR) rats, (ICR) BR mice, LVG (SYR) hamsters, and New Zealand White rabbits were exposed to trimethoxysilane at concentrations of 0, 10, 25, or 50 ppm for 7 h/day for 5 consecutive days, with a 14-day observation period post exposure (Dow Corning Corp. 1981). Five animals per sex were used in the studies with rats, mice, and hamsters, and two animals per sex were used in the study with rabbits. Table 7-6 presents the mortality data for this study. The investigators calculated 5-day LC₅₀ values of 13, 14, 72, and 1 ppm for the rats, mice, hamsters, and rabbits, respectively. The report stated that the rabbits could have had a preexisting viral condition that was exacerbated under study conditions, thus resulting in high mortality. The laboratory had experienced this scenario in other studies with rabbits from the same supplier. All animals had similar clinical signs of gasping, depression, and nasal discharge (see Table 7-7 in NRC (2012)). In the animals that died, lung congestion, atelectasis, and hemorrhage were observed; however, raw data were not provided. The study
author reported that the animals killed at the end of the observation period had the same effects, but they were less severe.

TABLE 7-6 Mortality Results in Dow Corning Corp. (1981) Study of Trimethoxysilane (from NRC 2012)

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Rats</th>
<th>Mice</th>
<th>Hamsters</th>
<th>Rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/10</td>
<td>0/10</td>
<td>0/10</td>
<td>0/2</td>
</tr>
<tr>
<td>10</td>
<td>3/10</td>
<td>5/10</td>
<td>0/10</td>
<td>2/2</td>
</tr>
<tr>
<td>25</td>
<td>9/10</td>
<td>4/10</td>
<td>3/10</td>
<td>2/2</td>
</tr>
<tr>
<td>50</td>
<td>10/10</td>
<td>10/10</td>
<td>3/10</td>
<td>2/2</td>
</tr>
</tbody>
</table>

The Dow study is reliable with restrictions (OECD 2008) since the calculation of 5-d LC$_{50}$ data is unusual. The reported concentrations were analytical concentrations. The value of the Dow study is that it indicated rats and mice had similar 5-d LC$_{50}$ values (i.e., 13 versus 14 ppm), whereas hamsters had a higher LC$_{50}$ value (72 ppm). The TCEQ concluded that the rabbit LC$_{50}$ data were not reliable.

3.3.1.3.2 Breckenridge et al. 1980

In a GLP 4-week study conducted by the Dow Chemical, ten SD rats/sex/exposure level were exposed 7 h/d, 5 d/week, for 4 weeks to TMS at concentrations of 0, 0.5, 5, or 10 ppm (Breckenridge et al. 1980, as cited in OECD 2008, NRC 2012). In rats exposed to 10 ppm, 20/20 had bronchitis and bronchiolitis upon histopathological examination compared to 0/20 in the 0.5 ppm group and controls. During weeks 2 and 3 of treatment, 60% of the high-concentration animals died and 40% of the mid-concentration animals died by the end of the fourth week. No mortalities occurred in the control or low-dose groups. Exposure in the high dose group was terminated at day 21 and the survivors were immediately sacrificed due to the high mortality levels. High- and mid-dose animals exhibited lung congestion, generalized weakness, and a statistically significant decrease in body weight and food consumption while the low-dose group was comparable to controls and showed no clinical signs. Histopathologic examination was performed on the 0, 0.5, and 10 ppm groups only. All 20 rats in the 10-ppm group had bronchitis and bronchiolitis, whereas none of the rats in the 0.5 ppm and control groups exhibited these effects. Hematology results showed a concentration-dependent increase in the RBC, hematocrit and hemoglobin values in the 5 and 10 ppm groups and a concentration-dependent decrease in the white blood cells in most of the treated animals. 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.
3.3.1.3 Union Carbide (1991)
Union Carbide (1991) conducted an inhalation study exposing Fisher 344 rats to 0, 0.2, 1, or 5 ppm TMS vapor for 6 h/d for 9 d over an 11-d period. In the 5 ppm group, 14/15 males and 12/15 females died between days 8 and 12. A NOAEL of 0.2 ppm and a LOAEL of 1 ppm were identified based on weight loss, increased lung weight, clinical pathology (laryngitis and bronchopneumonia), and necropsy/histologic observations. No signs of systemic toxicity were observed and histopathological changes were seen only in the respiratory tract.

3.3.1.4 Summary of Derivation of Acute ReV and acute ESL

3.3.1.4.1 POD and Critical Effect
The NOAEL of 72 ppm based on a 30-min exposure rat study (MPI Research 1998) was used as the POD to derive the acute ReV and acute ESL for TMS. The critical effects occurred in the respiratory tract. There was not enough information provided by OECD 2008 on the MPI Research (1998) study to determine the specific region of the respiratory tract that was affected.

3.3.1.4.2 Dosimetric Adjustments
The POD of 72 ppm was then adjusted from 30-min exposure to 1-h exposure concentration using Haber’s rule as modified by ten Berge (1986) with a chemical-specific value of “n”=1.45 which was derived by Nachreiner and Dodd (1988, as cited in NRC 2012).

\[
POD_{ADJ} = C_2^n = (C_1)^n \times (T_1 / T_2)
\]

\[
C_2 = (72 \text{ ppm})^{(1.45)} \times (0.5 \text{ h/1 h})
\]

\[
C_2 = [(72 \text{ ppm})^{(1.45)} \times (0.5 \text{ h/1 h})]^{1/1.45}
\]

\[
C_2 = 44.64 \text{ ppm}
\]

The POD_{ADJ} of 44.64 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). TMS was considered a Category 1 vapor (respiratory effects, a portal-of-entry (POE) effect). However, it is not clear if respiratory effects occurred in the extrathoracic (ET) region, the tracheobronchial region, or the pulmonary region since only gross necropsy findings were reported, not histopathology from the nasal region. Therefore, the most conservative regional gas dose ratio (RGDR) for these three regions was chosen (i.e., the RGDR of one for the ET region (TCEQ 2014b)). Therefore, the POD_{ADJ} was adjusted from an animal concentration to a POD_{HEC} using a default value of one as RGDR for the ET region (TCEQ 2014b). The resulting POD_{HEC} is 44.64 ppm.

3.3.1.4.3 Adjustment of POD_{HEC}
The POD_{HEC} was then used to derive the acute ReV and ESL by applying the following UF_s, with total UF_s = 180:
• a UF$_H$ of 10 for intraspecies variability,

• a UF$_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,

• a UF$_D$ of 6 was used. Most animal studies were conducted in rats, although the Dow Corning (1981) study indicated differences in adverse health effects and mortality between species were not great. There were no significant differences between male and female rats in LC$_{50}$ studies. There were no acute reproductive/developmental studies available for TMS, but a 90-d inhalation study conducted for TMS (Bushy Run Research Center 1995), and oral and inhalation studies conducted for other methoxysilanes, chlorosilanes or acetoxy silanes do not indicate the silane groups are reproductive/developmental toxicants. MeOH is not considered a reproductive/developmental toxicant (TCEQ 2014). In addition, TMS produced mainly respiratory effects and not systemic effects, which indicates systemic absorption is minimal. A UF$_D$ of 6 was used because the time- and dose-response for TMS is steep, although the NOAEL selected as a POD was conservative (Section 3.3.1.2). Confidence in the database is considered low to medium.

\[
\text{Acute ReV} = \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_D)} = \frac{44.64 \text{ ppm}}{(10 \times 3 \times 6)} = 0.248 \text{ ppm} = 250 \text{ ppb (rounded to two significant figures)}
\]

The acute ESL of 75 ppb (360 µg/m$^3$) for TMS was set based on the acute ReV of 250 ppb (1,200 µg/m$^3$) multiplied by a HQ of 0.3. Refer to Table 7 for summary information.

### 3.3.2 Tetramethoxysilane (TetMS)

TetMS is expected to undergo rapid hydrolysis in water to produce 4 moles of MeOH and 1 mole of silanetriol (Kallos et al. 1991). Very limited data are available from animal studies involving TetMS (NRC 2012). No acute studies for 1 day or less were available other than lethality studies, although a 5-d inhalation study (ECHA 2015b) and a well-conducted 28-d repeat dose inhalation study (Kolesar et al. 1989) was available. These studies, however, were not used to develop an acute value, although the studies are described below (Section 3.3.2.2 and 3.3.2.3). No data is available on developmental/reproductive toxicity of TetMS in laboratory animals.

#### 3.3.2.1 Inhalation LC$_{50}$ Study

Ten male SD rats/dose were exposed to 31, 50, or 88 ppm TetMS for 4 h in a GLP nose-only inhalation study (Dow Corning Corp. 1982, as cited in ECHA 2015b and NRC 2012). Mortality occurred at 50 and 88 ppm. By day 7 post-exposure, 9/10 rats exposed to 88 ppm died, and 3/10 exposed to 50 ppm died. The 4-h LC$_{50}$ was 63 ppm.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methylenebis(trimethoxysilane) (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

3.3.2.2 Subacute Animal Study (ECHA 2015b)

ECHA (2015b) reports a 5-d subacute inhalation study conducted in 1985 (the investigators were not reported). In this study, ten SD rats/sex/group were exposed to TetMS at 5 (±1), 12 (±1), 20 (±3) ppm (analytical concentration) 6 h/d for 5 d. The results showed that the only significant adverse effect, lung hemorrhage, was observed in the mid- and high-dose groups. At the mid-dose 14 of 20 animals had minor lung hemorrhages, and one animal had moderate lung hemorrhages. In the highest dose 17 of 20 animals had minor to severe lung hemorrhages (10 had moderate to severe hemorrhages). A NOAEL and LOAEL of 5 and 12 ppm, respectively, were identified from this study. ECHA (2015b), however, indicates that this study did not meet current guideline for repeated dose toxicity testing. Furthermore, the identified 5-d NOAEL of 5 ppm is lower than a 28-d NOAEL of 10 ppm reported by Kolesar et al. (1989) (see Section 3.3.2.3 below). Therefore, the identified 5-d NOAEL of 5 ppm was not used to develop acute toxicity values.

3.3.2.3 Subchronic Animal Study (Kolesar et al. 1989)

In a subchronic inhalation study, Kolesar et al. (1989) exposed ten SD rats/sex/group to TetMS at 0, 1, 5, or 10 ppm (Phase 1) and 0, 15, 30, or 45 ppm (Phase 2) 6 h/d, 5 d/week for 28 d of exposure over 5½ weeks. All rats exposed to 45 ppm TetMS either died or were sacrificed during the 28-d study. No treatment-related effects were observed in rats exposed at 0, 1, 5, or 10 ppm. The results showed that a statistically significant difference was observed in food consumption, body weight, and hematologic and clinical parameters in those exposed to 30 ppm. Males exposed at 15 ppm had only a decrease in total protein. No microscopic lesions were found in the respiratory tract of rats or ocular epithelium at 1, 5, or 10 ppm. However, at ≥ 15 ppm (Phase 2), respiratory tract and corneal lesions were observed. At 15 ppm, there were nasal changes in 2/20 rats, and there were ocular lesions (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 NOAEL of 10 ppm and a LOAEL of 15 ppm based on minimal acute upper respiratory tract inflammation and minimal ocular keratitis were identified from this subacute study.

28-d NOAEL of 10 ppm for TetMS was not used to develop an acute value, since it was overly conservative and there was an acceptable acute 30-min inhalation study available for TMS. TetMS is similar to TMS. Both are rapidly hydrolyzed, have similar physical/chemical properties (Tables 3 and 5), produce respiratory effects, and have similar LC50 data (TMS is 60 ppm and TetMS is 63 ppm). For these reasons, an acute ReV was not derived for TetMS. The acute ESL for TMS will be used as surrogate for TetMS to develop an acute ESL.
3.3.2.4 Generic acute ESL\textsubscript{generic} \hfill  

The acute ESL of 360 µg/m\textsuperscript{3} for TetMS was set based on the acute ESL of 360 µg/m\textsuperscript{3} for TMS. Refer to Table 7 for summary information.

3.3 Methyltrimethoxysilane (MTMS) \hfill  

MTMS undergoes hydrolysis in water; the half-life at pH 7 and 25°C is 2.2 h (Kallos et al. 1991, OECD 2009a). The hydrolysis is expected to produce 3 moles of MeOH and 1 mole of methylsilanol. No reproductive or developmental toxicity studies have been conducted with MTMS.

3.3.3.1 Inhalation LC\textsubscript{50} Study \hfill  

The acute inhalation 6-h LC\textsubscript{50} value of > 7,605 ppm (42.1 mg/L) for rats was determined in a reliable study conducted according to a test appropriate protocol (OECD TG 403), and in compliance with GLP (ECHA 2007, OECD 2009a).

3.3.3.2 Key Inhalation Animal Study (ECHA 2007) \hfill  

In a range finding study, conducted using the appropriate OECD guidelines, and in compliance with GLP, groups of 5 rats/sex were exposed by whole body MTMS vapor inhalation for 6 h/d for 14 d at target concentrations of 0, 400, 800, 4,000, and 8,000 ppm (European Chemicals Agency, ECHA 2007). Body weights were reduced in females in the 4,000 and 8,000 ppm groups and males in the 8,000 ppm group. Decreased food consumption was reported for males (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. Clinical chemistry evaluations indicated a significant increase in cholesterol levels for the 4,000 ppm females and for alanine aminotransferase, urea nitrogen, glucose, and total protein for the 4,000 ppm males. Centrilobular or panlobular hepatocellular hypertrophy was also present in 4/5 males 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 observed in one female from the 800 ppm exposure group. A NOAEL of 400 ppm and minimal LOAEL of 800 ppm for minimal urinary bladder epithelial hyperplasia were identified from this subacute range finding study. The NOAEL of 400 ppm was used as POD to derive acute toxicity factors.
3.3.3.3 Summary of Derivation of Acute ReV and acute ESL

3.3.3.3.1 POD and Critical Effect
The NOAEL of 400 ppm was selected as the subacute POD to derive the acute ReV and acute ESL for MTMS. The critical effect is minimal urinary bladder epithelial hyperplasia.

3.3.3.3.2 Dosimetric Adjustments
The subacute POD of 400 ppm was adjusted from a 6-h exposure to a 1-h exposure concentration using Haber’s rule as modified by ten Berge (1986) with a default value of “n”=3 (TCEQ 2012).

\[
C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} \\
= [(400 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3} \\
= 726.848 \text{ ppm} = \text{POD}_{\text{ADJ}}
\]

The POD_{ADJ} of 726.848 ppm was then adjusted to POD_{HEC}. MTMS was considered a Category 3 vapor (systemic effects), so the POD_{ADJ} was adjusted to POD_{HEC} using the following equation:

\[
\text{POD}_{\text{HEC}} = \text{POD}_{\text{ADJ}} \times [(\text{Hb/g})_A / (\text{Hb/g})_H]
\]

Since the measured blood/air partition coefficients in the rat ((Hb/g)_A) and human ((Hb/g)_H) for MTMS are not available, a default value of one is used as the dosimetric adjustment factor (DAF) (i.e., (H b/g)_A/(H b/g)_H) (TCEQ 2012). The resulting subacute POD_{HEC} is equal to the POD_{ADJ} of 726.848 ppm.

3.3.3.3.3 Adjustment of POD_{HEC}
The POD_{HEC} was then used to derive the acute ReV and ESL by applying the following UFs, with total UFs = 180:

- a UF_H of 10 for intraspecies variability,
- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- a UF_D of 6 was used because only one study for one animal species was reported. A UF_D of 10 was not used since the study was a two-week GLP study and the LOAEL of 800 ppm was based on minimal urinary bladder epithelial hyperplasia in one female rat, which could be considered the NOAEL. There were no inhalation reproductive/developmental studies but an oral reproductive study was available for MTMS (Dow Corning Corporation 2005, as cited in ECHA 2007). Confidence in the
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methytrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

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database is considered medium to low because only one animal species was used in inhalation bioassays.

\[
\text{Acute ReV} = \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_D)} \\
= \frac{726.848 \text{ ppm}}{(10 \times 3 \times 6)} \\
= 4.038 \text{ ppm} \\
= 4,000 \text{ ppb (rounded to two significant figures)}
\]

The acute ESL of 1,200 ppb (6,700 µg/m³) for MTMS was set based on the acute ReV of 4,000 ppb (22,000 µg/m³) multiplied by a HQ of 0.3. Refer to Table 7 for summary information.

### 3.3.4 Vinyltrimethoxysilane (VTMS)

VTMS undergoes hydrolysis in water; the half-life at pH 7 and 50°C is < 2.4 h (Kallos et al. 1991, OECD 2009b). Hydrolysis of VTMS is also expected to produce 3 moles of MeOH and 1 mole of silanetriol (OECD 2009b). The acute toxicity of VTMS has been studied by the inhalation, dermal and oral routes in rats.

#### 3.3.4.1 Inhalation LC₅₀ Study

The combined 4-h inhalation LC₅₀ in male/female Fischer 344 rats for VTMS is 2,773 ppm (16,800 mg/m³) (ECHA 2011). The study was conducted in accordance with OECD TG 403 and was in compliance with GLP.

#### 3.3.4.2 Key Inhalation Animal Reproductive/Developmental Studies (ECHA 2011)

In a reproductive/developmental toxicity study conducted in 1993, in accordance with USEPA OTS 798.4350 (Inhalation Developmental Toxicity Screen) (ECHA 2011), 25 timed-pregnant CD(R) rats/group were exposed to target concentrations of 0 (control), 25, 100, and 300 ppm VTMS (A-171 Silane) vapor for 6 h/d on gestational days (GD) 6 through 15. The corresponding analytical concentrations were 0, 24.6, 96.7, and 312.0 ppm. The dams were sacrificed on GD 21. The pregnancy rate was equivalent for all groups and ranged from 96 to 100%. No treatment-related mortality occurred during the study. There were no treatment-related effects on gestational body weight, food consumption, or clinical signs. However, on GD 6-9, body weight gain was decreased by 28% and 34% in the 100 and 300 ppm groups, respectively. Macroscopic assessment of the dams and organ weights measured at necropsy did not reveal any treatment-related effects. Assessment of the various reproductive endpoints did not reveal any differences among the groups. A NOAEL and LOAEL of 25 and 100 ppm, respectively, for decrease in body weight gain (i.e., maternal toxicity) were identified.

Fetal examinations indicated no evidence of treatment-related embryolethality or teratogenicity. A slight developmental delay in the 300 ppm group was indicated by an increase in the incidence of delayed skeletal ossification of the anterior arch of the atlas, thoracic centra, interparietal,
metatarsals, and phalanges. A statistical increase in the number of litters at 100 ppm with unossified anterior arch of the atlas was not considered by the authors to be biologically significant because no other endpoints were similarly affected and the incidence (79.2%) was close to that observed in historical controls (29.2-73.9%). Mean fetal body weight/litter were not different among control and treated groups. No exposure-related embryotoxicity or teratogenicity was observed in this study. A NOAEL and LOAEL of 100 and 300 ppm for delayed developmental effects were identified from this study.

The NOAEL and LOAEL of 25 and 100 ppm for maternal toxicity (decreased body weight gain) was lower than the NOAEL and LOAEL of 100 ppm and 300 ppm for developmental effects and thus, was used as the POD to derive acute toxicity factors for VTMS. The analytical concentration for the NOAEL is 24.6 ppm.

3.3.4.3 Supporting Animal Study (ECHA 2011)

In a subacute inhalation range-finding study conducted in 1986 (ECHA 2011), Fischer-344 rats, 20/sex/dose, were exposed for 6 h/d, 5 d/week, for 9 d of exposure to vapor of VTMS at target concentrations of 0 (control), 150, 750, or 1,500 ppm (corresponding analytical concentrations were 0, 153, 746, or 1,484 ppm). All animals in the 1,500 ppm group died during the first 5 d of exposure. Prior to their death several clinical abnormalities (e.g., periocular wetness, corneal opacity, blepharospasm, periurethral area wetness, loss of coordination, hypoactivity, breathing difficulties, and an unkempt appearance) were observed.” after “exposure. Rats in the 750 ppm group had periurethral area wetness and corneal opacities, while rats of the 150 ppm group appeared normal throughout the study. Body weight loss was observed in the 1,500 and 750 ppm groups, and body weight gain was slightly decreased in the 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 and hematologic results were normal in the 150 ppm-exposed rats. Alterations in organ weights in the 750 ppm group were primarily a reflection of body weight losses; however, male absolute kidney weights increased 7% compared to the control mean 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 microscopic lesions included necrotizing rhinitis, necrotizing keratitis, and necrosis of the papillary, tubular, and pelvic regions of the kidneys in rats exposed to 1,500 or 750 ppm of VTMS. Multiple signs of irritation and toxicity were observed in rats exposed to 750 or 1500 ppm. A minimum-effect concentration (slight decrease in body weight gain) was 150 ppm (153 ppm, analytical concentration) and considered the NOAEL.


3.3.4.4 Summary of Derivation of Acute ReV and acute ESL

3.3.4.4.1 POD and Critical Effect

The NOAEL of 24.6 ppm identified from the developmental/reproductive study (ECHA 2011) was used as the POD to derive the acute ReV and acute ESL for VTMS. The critical effect is maternal toxicity (decreased body weight gain).

3.3.4.4.2 Dosimetric Adjustments

The NOAEL of 24.6 ppm was based on a reproductive/developmental study. If the critical effect had been a developmental effect, which could involve a critical window of exposure, a duration adjustment would not be conducted (TCEQ 2012). Since the critical effect was general maternal toxicity, a duration adjustment from 6 h to 1 h was conducted. The NOAEL of 24.6 ppm was used as the acute POD to derive the acute toxicity factors for VTMS. The subacute POD of 24.6 ppm was then adjusted from a 6-h exposure to a 1-h exposure concentration using Haber’s rule as modified by ten Berge (1986) with a default value of “n”=3 (TCEQ 2012).

\[ C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(24.6 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3} = 44.701 \text{ ppm} = \text{POD}_{\text{ADJ}} \]

The POD_{ADJ} of 44.701 ppm was then adjusted to a POD_{HEC}. VTMS was considered a Category 3 vapor (systemic effects), so the POD_{ADJ} was adjusted to POD_{HEC} using the following equation:

\[ \text{POD}_{\text{HEC}} = \text{POD}_{\text{ADJ}} \times \left( \frac{(H_b/g)_A}{(H_b/g)_H} \right) \]

Since the measured blood/air partition coefficients in the rat ((Hb/g)_A) and human ((Hb/g)_H) for VTMS were not available, a default value of one was used as the DAF (i.e., (H b/g)_A/(H b/g)_H) (TCEQ 2012). The resulting subacute POD_{HEC} was equal to the POD_{ADJ} of 44.701 ppm.

3.3.4.4.3 Adjustment of POD_{HEC}

The POD_{HEC} was then used to derive the acute ReV and ESL by applying the following UFs, with total UFs = 90:

- a UF_H of 10 for intraspecies variability,
- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- a UF_D of 3 was used because only one animal species was studied. A higher UF_D was not used because inhalation and gavage subacute studies were available (ECHA 2011) and the
critical effect was identified in a repeat-dose subacute study. Reproductive/developmental studies were also conducted for both inhalation and gavage. Confidence in the database is considered medium.

\[
\text{Acute ReV} = \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_D)}
\]

\[
= \frac{44.701 \text{ ppm}}{(10 \times 3 \times 3)} = 0.497 \text{ ppm}
\]

The acute ESL of 150 ppb (910 µg/m³) for VTMS was set based on the acute ReV of 500 ppb (3,000 µg/m³) multiplied by a HQ of 0.3. Refer to Table 7 for summary information.

### 3.3.5 Chloropropyltrimethoxysilane, 3- (CPTMS)

CPTMS undergoes hydrolysis and results in the production of 3 moles of MeOH for each mole of silanetriol. At pH 7 and 25°C, the half-life is 53.3 min (Kallos et al. 1991, OECD 2006, ECHA 2015c). Exposures to CPTMS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis product MeOH, with some potential exposure to trisilanols, and silanol oligomers (OECD 2006).

#### 3.3.5.1 Oral LD\(_{50}\) Study

There is no available acute inhalation lethality data. However, the oral (gavage) LD\(_{50}\) in rats was reported to be > 2,000 mg/kg (OECD 2006, ECHA 2015c).

#### 3.3.5.2 Key Inhalation Animal Study (RCC Ltd 2005)

In a one-generation study (OECD TG 422) by RCC Ltd (2005, as cited in OECD 2006 and ECHA 2015c), CPTMS was administered at 0 (control), 5, 25, and 100 ppm by whole-body vapor inhalation to male rats for 6 h/d for 28 d and to female rats throughout the 14-d pre-pairing, pairing and gestation period until the day 19 post coitum. Neither food consumption nor body weight development was affected by exposure to the test item at any concentration. None of the parameters under investigation during the functional observational battery was considered to be affected by exposure to the test article. During necropsy of F0 parent animals, no exposure-related findings were noted. Mean absolute organ weights, as well as organ/body weight ratios and organ/brain weight ratios, were not affected by exposure to the test article. There were no findings which distinguished CPTMS-treated animals from controls. Exposure to CPTMS up to and including the highest concentration of 100 ppm did not result in any signs of general toxicity due to the exposure.

For reproductive toxicity, parental (P) generation males were sacrificed after they had been treated for 28 days, while P generation females and pups were sacrificed on postnatal day 4. The fertility rate was high, resulting in at least 9 litters per group for evaluation of reproductive effects. There were no treatment-related effects on precoital time, fertility indices, mean duration
of gestation, number of implantations, post-implantation loss, pup survival, or litter size from birth through to scheduled sacrifice on postnatal day 4. No abnormal findings were noted for pups at first litter check or during the first 4 days postpartum. Sex ratios at first litter check and on postnatal day 4 were unaffected by treatment with the CPTMS. Mean pup weights on postnatal day 0 and day 1 were unaffected by treatment with the test article. Mean pup weight development during the first 4 days postpartum was unaffected by treatment with the test article. No treatment-related histopathological findings were observed in the reproductive organs of either sex from the parental generation. The assessment of the integrity of the spermatogenic cycle did not provide any evidence of impaired spermatogenesis. Exposure to CPTMS up to and including the highest concentration of 100 ppm did not result in any signs of reproductive toxicity.

For developmental toxicity, no abnormal findings were noted for pups at first litter check or during the first 4 days postpartum. No treatment-related findings were noted at macroscopic examination of F1 pups. This one generation study in rats concluded that exposure to CPTMS up to and including the highest concentration of 100 ppm (814 mg/m³) did not result in any signs of general, reproductive, or developmental toxicity. A free-standing NOAEL of 100 ppm for a lack of general and reproductive or developmental toxicity was identified from this study.

3.3.5.3 Supporting Animal Study (Dow Corning Corporation 1990a)

In a 2-week subacute inhalation study (Dow Corning Corporation 1990a, as cited in OECD 2006), groups of male and female rats were exposed to CPTMS at target concentrations of 0, 50, 100, and 150 ppm (number in groups was unspecified). There were a total of 11 exposures of 6 h/d (3 exposures during first week, 5 second week, and 3 during third week). Gross necropsies were performed on all rats. Body weights and food consumption were measured weekly. The terminal body weights were determined on the animals at the terminal sacrifice. No mortality occurred and no treatment related toxic effects were observed in any of the test group animals. There were no statistically significant differences in group body weights or food consumption. No treatment-related effects were observed at gross necropsy. A free-standing NOAEL of 150 ppm was identified from this study.

3.3.5.4 Summary of Derivation of Acute ReV and acute ESL

3.3.5.4.1 POD and Critical Effect

The free-standing NOAEL of 100 ppm for general and reproductive or developmental toxicity (RCC Ltd 2005, as cited in OECD 2006) was used as the POD to derive the acute ReV and acute ESL for CPTMS. The critical effect for this free-standing NOAEL POD is the absence of general and developmental/reproductive toxicity.
3.3.5.4.2 Dosimetric Adjustments

For a free-standing NOAEL, no duration adjustment is made due to lack of information on dose-response (TCEQ 2012). Therefore the POD_{adj} is equal to the POD of 100 ppm.

The POD_{adj} was then adjusted to the POD_{hec} using an animal-to-human dosimetric adjustment. 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.

- If CTPMS was considered a Category 3 vapor, the POD_{adj} was adjusted to a POD_{hec} using the following equation:

  \[ \text{POD}_{\text{HEC}} = \text{POD}_{\text{ADJ}} \times \left( \frac{(Hb/g)_A}{(Hb/g)_H} \right) \]

  Since the measured blood/air partition coefficients in the rat ((Hb/g)_A) and human ((Hb/g)_H) for CTPMS are not available, a default value of one is used as the DAF (i.e., (Hb/g)_A / (Hb/g)_H) (TCEQ 2012). The resulting subacute POD_{HEC} is equal to the POD_{ADJ} of 100 ppm.

- If the critical effect for CTPMS had occurred in the respiratory tract, then the most conservative RGDR for the respiratory tract would be used: the RGDR_{ET} region, which is equal to one (TCEQ 2014b). Therefore, the POD_{HEC} would be identical to the POD_{HEC} derived for systemic effects. The resulting subacute POD_{HEC} is equal to the POD_{ADJ} of 100 ppm.

3.3.5.4.3 Adjustment of POD_{HEC}

The POD_{HEC} was then used to derive the acute ReV and ESL by applying the following UFs, with total UFs = 90:

- a UF_H of 10 for intraspecies variability,

- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,

- a UF_D of 3 was used, although only one animal species was studied. A larger UF_D was not used because two well-conducted subacute inhalation studies were reported. One study was a one-generation, multi-day reproductive/developmental study that reported a free-standing NOAEL of 100 ppm. The second study was a two-week study that identified a free-standing NOAEL of 150 ppm. Confidence in the database is considered medium to high.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

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Acute ReV = \( \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_D)} \)
= 100 ppm / (10 x 3 x 3)
= 1.111 ppm
= 1,100 ppb (rounded to two significant figures)

The acute ESL of 330 ppb (2,700 µg/m\(^3\)) for CPTMS was set based on the acute ReV of 1,100 ppb or 8,900 µg/m\(^3\) multiplied by a HQ of 0.3. Refer to Table 7 for summary information below.

### 3.3.6 Summary of the Acute Evaluations

Table 7 summarizes the derivation of acute toxicity factors, respectively, for TMS, MTMS, VTMS, CPTMS, and TetMS.
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methytrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Table 8 Acute ReV and acute ESL for Tri- and Tetramethoxysilanes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TMS</th>
<th>TetMS</th>
<th>MTMS</th>
<th>VTMS</th>
<th>CPTMS</th>
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</thead>
<tbody>
<tr>
<td>Study</td>
<td>MPI Research 1998</td>
<td>- - -</td>
<td>ECHA 2007</td>
<td>ECHA 2011</td>
<td>RCC Ltd 2005</td>
</tr>
<tr>
<td>Half-life</td>
<td>&lt; 0.3 min</td>
<td>Rapid</td>
<td>2.2 h</td>
<td>&lt; 2.4 h</td>
<td>53.3 min</td>
</tr>
<tr>
<td>4-h LC₅₀</td>
<td>60 ppm</td>
<td>63 ppm</td>
<td>&gt; 8,700 ppm</td>
<td>2,773 ppm</td>
<td>Not available</td>
</tr>
<tr>
<td>GLP</td>
<td>Yes</td>
<td>- - -</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Animals</td>
<td>SD rats, 5/sex/group</td>
<td>- - -</td>
<td>SD rats, 5/sex/group</td>
<td>25 CD(R) timed-pregnant rats/group</td>
<td>SD male/female rats</td>
</tr>
<tr>
<td>Exposure</td>
<td>72, 158, 181, 206, and 243 ppm</td>
<td>- - -</td>
<td>0, 400, 800, 4,000 and 8,000 ppm</td>
<td>0, 25, 100, and 300 ppm</td>
<td>0, 5, 25 and 100 ppm</td>
</tr>
<tr>
<td>Duration</td>
<td>30 min</td>
<td>- - -</td>
<td>6 h/d, 5 d/week for 14 d</td>
<td>6 h/d on GD 6-15</td>
<td>Males 6 h/d for 28 d; females multiple days a</td>
</tr>
<tr>
<td>Critical effects</td>
<td>Respiratory effects</td>
<td>- - -</td>
<td>Minimal urinary bladder epithelial hyperplasia</td>
<td>Maternal toxicity (decreased body weight gain)</td>
<td>Absence of general, maternal, reproductive and developmental toxicity</td>
</tr>
<tr>
<td>POD</td>
<td>72 ppm (NOAEL)</td>
<td>- - -</td>
<td>400 ppm (NOAEL)</td>
<td>25 ppm (NOAEL)</td>
<td>100 ppm (free-standing NOAEL)</td>
</tr>
<tr>
<td>POD <em>ADJ</em></td>
<td>44.64 ppm</td>
<td>- - -</td>
<td>727 ppm</td>
<td>45 ppm</td>
<td>100 ppm</td>
</tr>
<tr>
<td>POD <em>HEC</em></td>
<td>44.64 ppm</td>
<td>- - -</td>
<td>727 ppm</td>
<td>45 ppm</td>
<td>100 ppm</td>
</tr>
<tr>
<td>Total UFs</td>
<td>180 UF₇₁ 10; UF₆₃; UF₆ 6</td>
<td>- - -</td>
<td>180 UF₇₁ 10; UF₆₃; UF₆ 6</td>
<td>90 UF₇₁ 10; UF₆₃; UF₆ 3</td>
<td>90 UF₇₁ 10; UF₆₃; UF₆ 3</td>
</tr>
<tr>
<td>ReV</td>
<td>250 ppb (1,200 µg/m³)</td>
<td>- - -</td>
<td>4,000 ppb (22,000 µg/m³)</td>
<td>500 ppb (3,000 µg/m³)</td>
<td>1100 ppb (8,900 µg/m³)</td>
</tr>
<tr>
<td>acute ESL</td>
<td>75 ppb (360 µg/m³)</td>
<td>360 µg/m³ b</td>
<td>1,200 ppb (6,700 µg/m³)</td>
<td>150 ppb (910 µg/m³)</td>
<td>330 ppb (2,700 µg/m³)</td>
</tr>
</tbody>
</table>

a Females throughout the 14-d pre-pairing, pairing and gestation period until the individual day 19 post coitum

b The acute ESL of 360 µg/m³ for TetMS was surrogated from the acute ESL of 360 µg/m³ for TMS.
3.4 Welfare-Based Chronic ESLs

3.4.1 Odor Perception
Methoxysilanes generally have sweet fruity odors that become less apparent as the molecular weight increases (NRC 2012). No data were reported regarding odor threshold values for methoxysilanes.

3.4.2 Vegetation Effects
No studies were located to derive an $^{\text{acute}}$ESL$^{\text{veg}}$ for methoxysilanes.

3.5. Short-Term ESLs for Air Permits
The short-term ESLs used for air permit evaluations are as follows:

- TMS $^{\text{acute}}$ESL = 360 µg/m$^3$ (75 ppb)
- TetMS $^{\text{acute}}$ESL = 360 µg/m$^3$ (surrogated to the $^{\text{acute}}$ESL of 360 µg/m$^3$ for TMS)
- MTMS $^{\text{acute}}$ESL = 6,700 µg/m$^3$ (1,200 ppb)
- VTMS $^{\text{acute}}$ESL = 910 µg/m$^3$ (150 ppb)
- CPTMS $^{\text{acute}}$ESL = 2,700 µg/m$^3$ (330 ppb)

3.6 Acute Inhalation Observed Adverse Effect Levels (IOAELs)
The acute inhalation observed adverse effect levels for the methoxysilanes with adequate data are as follows:

- TMS $^{\text{acute}}$IOAEL = 790 mg/m$^3$ (158 ppm)
- TetMS $^{\text{acute}}$IOAEL = inadequate data
- MTMS $^{\text{acute}}$IOAEL = 4400 mg/m$^3$ (800 ppm)
- VTMS $^{\text{acute}}$IOAEL = 610 mg/m$^3$ (100 ppm)
- CPTMS $^{\text{acute}}$IOAEL = inadequate data (free-standing NOAEL = 100 ppm)

The acute inhalation observed adverse effect levels are the LOAEL$^\text{HEC}$ determined from animal studies. No duration adjustments were made although animal-to-human dosimetric adjustments were performed. 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. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The acute
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methytrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

Chapter 4 Chronic Evaluation

4.1 Physical/Chemical Properties
See Section 3.1.

4.2 MOA Analysis and Dose Metric
As described in Section 3.2, tri- and tetramethoxysilanes typically cause respiratory irritation and nephrotoxicity. The MOA for nephrotoxicity is unclear, but both the respiratory toxicity (i.e., lesions) and nephrotoxicity (i.e., calculi and renal dilation) observed in animals are assumed to be relevant to human health.

The type of toxicity caused by methoxysilanes is dependent on their underlying chemistry. This is due to the fact that methoxysilanes vary in their intrinsic stability. Carbon bonding has a significant effect on the hydrolysis rate of the silicon bond (X-Si), slowing the process. Electron withdrawing groups, such as oxygen or halogens, accelerate hydrolysis rates. This phenomenon is visible in the rates reported herein. TMS and TetMS have rapid hydrolysis rates (i.e., seconds to minutes). MTMS, VTMS, CPTMS have slower hydrolysis rates (i.e., hours) (Arkles et al., 1992; Kallos et al., 1991).

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. As previously discussed, the hydrolysis process produces methanol and various silanol species. Silanols are highly reactive intermediates, which subsequently react with surrounding chemicals (i.e., possibly biomolecules) or condense to form siloxanes (Arkles et al., 1992; Brinker, 1988). Thus, it is possible that methoxysilanes that hydrolyze rapidly form these reactive intermediates in the respiratory tract. Furthermore, the rate of siloxane formation and the size of the subsequent condensates are dependent on the number of electron withdrawing groups present on the methoxysilane (Brinker, 1988). These data would indicate that tetramethoxysilanes and trimethoxysilanes would be capable of forming larger polymeric condensates, which could also contribute to inflammation and cellular damage in the respiratory tract that is observed in rodents exposed to TetMS (Kolesar et al., 1989). Specific details regarding the MOA for these respiratory effects are unknown.

Methoxysilanes that hydrolyze more slowly (i.e., in hours) are inhaled as the parent compound, including MTMS, VTMS, and CPTMS. The toxicokinetics and toxicodynamics of methoxysilanes are not known. However, given the longer hydrolysis half-life, silanol formation, further metabolism or condensation would occur during distribution and excretion (Brinker,
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

1988). These substances are thought to be excreted in the kidney, which is probable given that this is a site of chemical-induced tissue damage (Nakashima, 1998).

In the kidney, urine is formed by filtration and concentrated in the nephron via the corticomedullary gradient. The role of this gradient is to aid in the reabsorption of water and excretion of wastes (Zalyapin et al., 2008). However, due to changes in pH and osmolarity, some chemicals may precipitate or condense in the kidney causing nephritis and deposition of calculi in the bladder and subsequent cystitis. In cases where a chemical is capable of forming precipitates, or in the case of methoxysilanes condensates, in urine larger occlusions may develop at higher chemical concentrations, resulting in renal dilation.

Rodents (i.e., rats and mice) may act be a particularly sensitive animal model for calculi formation due to the presence of high levels of protein and salts in their urine relative to human urine. Urine composed of higher protein and salt may favor the formation of calculi via condensation or precipitation. Furthermore, rodents’ horizontal stature may make them able to retain calculi for longer periods of time, enhancing the magnitude and duration of resultant cystitis and bladder hyperplasia (Ashizawa and Shimo, 2013). Given that calculi formation, renal dilation, and cystitis are considered relevant to human health, these animal studies were used as the basis for derivation of the chronic methoxysilanes values (Dellarco and Baetcke, 2005; Meek et al., 2003; USEPA, 1988).

Since available inhalation studies for methoxysilanes are based on animals exposed to the parent chemicals, exposure concentration of the parent chemicals will be used as the default dose metric.

4.3 Health-Based Toxicity Factors

No chronic toxicity studies on tri- and tetramethoxysilane were available. Chemical-specific subchronic toxicity data in animals are available for MTMS, VTMS, and CPTMS and were used to develop chronic toxicity factors. For TMS, a 90-d subchronic study was available, but only reported a free-standing NOAEL (OECD 2007), so this study was not used (see Section 4.3.1 below). The only available study for TetMS was a 4-week subacute study and was used to develop chronic toxicity factors. There was a 4-week subacute study also available for TMS (Breckenridge et al. 1980), however, the results of this study indicated that the time- and dose-response for TMS is steep (see Section 3.3.1.3.2).

4.3.1 TMS

4.3.1.1 Bushy Run Research Center (1995)

Bushy Run Research Center (1995, as cited in ECHA 2015a, OECD 2007 and 2008) reports that exposure of rats to TMS vapor at concentrations of 0.02, 0.1 or 0.5 ppm 6 h/d for 90 d, followed by a 4-week recovery period, produced no exposure-related effects in the biologic parameters monitored during this study. The free-standing NOAEL in this 90-d inhalation study with rats
was determined to be 0.5 ppm. The dose groups administered in this study were low (i.e., 0.02, 0.1 or 0.5 ppm), OCED (2007) indicate that the free-standing NOAEL was at least 0.5 ppm. Therefore, the free-standing NOAEL of 0.5 ppm was not informative and did not provide information on the dose-response relationship above the NOAEL. Therefore, it was not used to derive chronic toxicity factor.

4.3.1.2 Breckenridge et al. (1980)

The 4-week subacute inhalation study was described in the acute evaluation, but the information is reproduced below.

In a GLP 4-week study conducted by the Dow Chemical, ten SD rats/sex/exposure level were exposed 7 h/d, 5 d/week, for 4 weeks to TMS at concentrations of 0, 0.5, 5, or 10 ppm (Breckenridge et al. 1980, as cited in OECD 2008, NRC 2012). In rats exposed to 10 ppm, 20/20 had bronchitis and bronchiolitis upon histopathological examination compared to 0/20 in the 0.5 ppm group and controls. During weeks 2 and 3 of treatment, 60% of the high-concentration animals died and 40% of the mid-concentration animals died by the end of the fourth week. No mortalities occurred in the control or low-dose groups. Exposure in the high dose group was terminated at day 21 and the survivors were immediately sacrificed due to the high mortality levels. High- and mid-dose animals exhibited lung congestion, generalized weakness, and a statistically significant decrease in body weight and food consumption while the low-dose group was comparable to controls and showed no clinical signs. Histopathologic examination was performed on the 0, 0.5, and 10 ppm groups only. All 20 rats in the 10-ppm group had bronchitis and bronchiolitis, whereas none of the rats in the 0.5 ppm and control groups exhibited these effects. Hematology results showed a concentration-dependent increase in the RBC, hematocrit and hemoglobin values in the 5 and 10 ppm groups and a concentration-dependent decrease in the white blood cells in most of the treated animals. Based on the body weight, organ weight, clinical pathology, histopathologic observations, and deaths, OECD (2007, 2008) indicate that the NOAEL and LOAEL from this study appeared to be 0.5 and 5 ppm, respectively.

The 28-d NOAEL of 0.5 ppm was considered conservative. As described in Section 3.3.1.3.2, the results of this study indicated that the time- and dose-response for TMS is steep. In addition, the level of 0.5 ppm was also a free-standing NOAEL identified from the 90-d Bushy Run Research Center (1995) study. OCED (2007) indicates that the 90-d free-standing NOAEL would be at least 0.5 ppm (Section 4.3.1.1 above).

The 4-h LC50 (60 ppm) for TMS is similar to the 4-h LC50 (63 ppm) for TetMS indicating the relative potency of these methoxysilanes would be equipotent. Likewise, the 28-d NOAEL (10 ppm) for TetMS (Section 4.3.2.1 below) is much higher than the 90-d NOAEL (0.5 ppm) for TMS. As described in Section 4.3.1.1, the 90-d free-standing NOAEL of 0.5 ppm was not used to derive chronic toxicity factors for TMS. 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 (see Section 4.3.2 below).

4.3.2 TetMS

4.3.2.1 Key Animal Study (Kolesar et al. 1989)

The 28-d subacute/subchronic inhalation study conducted by Kolesar et al. (1989) was chosen as the key study for the chronic evaluation. This study was described in the acute evaluation, but the information is reproduced below.

In a subacute/subchronic inhalation study, Kolesar et al. (1989) exposed ten SD rats/sex/group to TetMS at 0, 1, 5, or 10 ppm (Phase 1) and 0, 15, 30, or 45 ppm (Phase 2) 6 h/d, 5 d/week for 28 d. The results showed that a statistically significant difference was observed in food consumption, body weight, and hematologic and clinical parameters in those exposed to 30 ppm. No microscopic lesions were found in the respiratory tract of rats or ocular epithelium at 1, 5, or 10 ppm. However, at ≥ 15 ppm, respiratory tract and corneal lesions were observed. At 15 ppm, there were nasal changes in 2/20 rats indicative of minimal acute inflammation and minimal acute keratitis with no epithelial desquamation in 4/20 rats. At 30 ppm, moderate to severe upper respiratory tract, bronchiolar, and inflammatory lesions were observed. Signs of toxicity were dose-dependent. A NOAEL 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.

4.3.2.2 Summary of Derivation of Chronic ReV and chronic ESL

4.3.2.2.1 POD and Critical Effect

The subacute/subchronic NOAEL of 10 ppm identified from the Kolesar et al. (1989) study was used as the POD to derive the chronic ReV and chronic ESL for TetMS. The critical effects at the LOAEL of 15 ppm are upper respiratory tract lesions (nasal region) and keratitis of the ocular epithelium.

4.3.2.2.2 Duration and Dosimetric Adjustments

The POD of 10 ppm was adjusted from a discontinuous exposure (6 h/d for 5 d/week) to continuous exposure concentration.

\[
\text{POD}_{\text{ADJ}} = \text{POD} \times \left(\frac{D}{24 \text{ h}}\right) \times \left(\frac{F}{7 \text{ d}}\right)
\]

where:

\[
D = \text{Exposure duration, hours per day}
\]

\[
F = \text{Exposure frequency, days per week}
\]

\[
\text{POD}_{\text{ADJ}} = 10 \text{ ppm} \times \left(\frac{6}{24}\right) \times \left(\frac{5}{7}\right) = 1.786 \text{ ppm}
\]
Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)

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TetMS was considered a Category 1 vapor (respiratory effects, a portal-of-entry (POE) effect). However, it is not clear if respiratory effects occurred in the extrathoracic (ET) region, the tracheobronchial region, or the pulmonary region. The POD_{ADJ} was conservatively adjusted to the POD_{HEC} using a default RGDR_{ET} value of one (TCEQ 2014b), which is the most conservative RGDR for these three regions. The resulting POD_{HEC} is 1.786 ppm.

4.3.2.2.3 Adjustment of POD_{HEC}

The POD_{HEC} was used to derive the chronic ReV and ESL by applying the following UFs, with total UFs = 270:

- a UF_{H} of 10 for intraspecies variability,
- a UF_{A} of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- a UF_{Sub} of 3 was deemed appropriate. A larger UF_{Sub} was not used because TetMS is expected to rapidly hydrolyze (i.e., have a short half-life of minutes) and has a log K_{ow} of -0.67, which indicates it will not bioaccumulate. The critical effect at the LOAEL are minimal respiratory tract and keratitis of the ocular epithelium, a POE effect, so although the POD is from a subacute/subchronic study, chronic effects would not be expected to differ significantly from the subacute/subchronic effects.
- a UF_{D} of 3 was used because only one animal species was studied and only one subacute/subchronic study was available. A larger UF_{D} was not used because TetMS is similar to TMS, as discussed in Section 3.3.5. For TMS, there were data on several species (Dow Corning Corp.1981), which indicate species variability is low. The TCEQ agrees with NRC (2012) who assumed species variability would also be low for TetMS. There were no reproductive/developmental studies available for TetMS, but oral and inhalation studies conducted for other methoxysilanes, chlorosilanes, or acetoxysilanes do not indicate the silane group is a reproductive/developmental toxicant. MeOH is not considered a reproductive/developmental toxicant (TCEQ 2014). Confidence in the database is considered medium.

\[
\text{Chronic ReV} = \frac{\text{POD}_{\text{HEC}}}{\left(\text{UF}_{\text{H}} \times \text{UF}_{\text{A}} \times \text{UF}_{\text{Sub}} \times \text{UF}_{\text{D}}\right)} = \frac{1.786 \text{ ppm}}{(10 \times 3 \times 3 \times 3)} = 0.00661 \text{ ppm} = 7 \text{ ppb (rounded to two significant figures)}
\]

The chronic ESL of 2.1 ppb (13 µg/m\(^3\)) for TetMS was set based on the chronic ReV of 7 ppb or 44 µg/m\(^3\) multiplied by a HQ of 0.3. Refer to Table 8 for summary information.
4.3.3 MTMS

4.3.3.1 Key Animal Study (ECHA 2007)

A subchronic inhalation toxicity study in rats was conducted following OECD TG 413 (OECD 2009a) where Crl: CD (SD) rats were exposed (whole body) (10 rats/sex/concentration) to MTMS at concentrations of 0.14, 0.56, 2.2, and 8.9 mg/L, for 6 h/d, 5 d/week for 13 weeks. The corresponding concentrations in mg/m³ were 140, 560, 2,200, and 8,900 mg/m³ and the 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 d, followed by a 28-d recovery period without exposure to MTMS.

- The following effects were observed in the 8,900 mg/m³ groups: one male died during the study; increased incidence of abdominal and urogenital soiling; calculi in the urinary bladder were found at necropsy in 4 males and 1 female; a statistically significant increase of 12 % relative weights in female kidney; a statistically significant increase of 25 and 27 % absolute and relative weights, respectively, in female adrenal glands; 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; kidney dilation was observed in male rats; and histopathological findings were observed in the urinary bladder (epithelial hyperplasia) in males and females, and in the kidney (hyperplasia of the pelvic epithelium and granulomatous inflammation) of male animals.

- The following effects were observed in the 2,200 mg/m³ groups: one male died during the study; increased incidence of abdominal and urogenital soiling; a statistically significant increase of 18% absolute weights in female adrenal glands; calculi in the urinary bladder were found at necropsy in 2 males and females; histopathological findings (epithelial hyperplasia) were observed in the urinary bladder in males and females.

- Prostatic inflammation seen in all groups with a slight increase in severity at the 8,900 mg/m³ level.

A NOAEL of 560 mg/m³ (100 ppm) and a LOAEL of 2,200 mg/m³/day (400 ppm) were identified, based on the increased incidence of grossly observed urinary bladder calculi along with the kidney dilation. The NOAEL of 100 ppm was used as a subchronic POD to derive chronic toxicity factors following the TCEQ (2012) Guidelines.

In comparison to the 14-d subacute range finding study (ECHA 2007) (Section 3.3.2), a NOAEL of 400 ppm and minimal LOAEL of 800 ppm for minimal urinary bladder epithelial hyperplasia in one female rat were identified. The difference between the minimal LOAEL of 800 ppm from the 14-d study was only two times greater than the LOAEL of 400 ppm from the 13-week study.
4.3.3.2 Summary of Derivation of Chronic ReV and chronic ESL

4.3.3.2.1 POD and Critical Effect
The subchronic NOAEL of 100 ppm identified from the key study was used as the subchronic POD to derive the chronic ReV and chronic ESL for MTMS. The critical effect is increased incidence of grossly observed urinary bladder calculi along with the kidney dilation.

4.3.3.2.2 Dosimetric Adjustments
The subchronic POD of 100 ppm was then adjusted from discontinuous exposure (6 h/d for 5 d/week) to continuous exposure concentration.

\[
\text{POD}_{\text{adj}} = \text{POD} \times \left(\frac{D}{24 \text{ h}}\right) \times \left(\frac{F}{7 \text{ d}}\right)
\]

\[
\text{POD}_{\text{adj}} = 100 \text{ ppm} \times \left(\frac{6}{24}\right) \times \left(\frac{5}{7}\right) = 17.86 \text{ ppm}
\]

The POD_{adj} of 17.86 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). MTMS is considered a Category 3 vapor (systemic effects), so the POD_{adj} was adjusted to POD_{HEC} using a default value of one as the DAF (i.e., \(\frac{(Hb/g)_A}{(Hb/g)_H}\)). The resulting subchronic POD_{HEC} from the POD_{adj} of 17.86 ppm is 17.86 ppm.

4.3.3.2.3 Adjustment of POD_{HEC}
The POD_{HEC} was then used to derive the chronic ReV and ESL by applying the following UFs, with total UFs = 270:

- a UF_{H} of 10 for intraspecies variability,
- a UF_{A} of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- a UF_{Sub} of 3 was considered appropriate to account for the use of a subchronic study. MTMS has a log K_{ow} of -0.67, which indicates the potential for bioaccumulation is low. In addition, the difference between the minimal LOAEL of 800 ppm from the 14-d study (ECHA 2007) was only two times greater than the LOAEL of 400 ppm from the 90-day study (ECHA 2007). Therefore, chronic effects would not be expected to be significantly lower than subchronic effects,
- a UF_{D} of 3 was used because only one animal species was studied. A higher UF_{D} was not used because there is information indicating the rat is a sensitive species for the critical effect (grossly observed urinary bladder calculi along with the kidney dilation) as discussed in Section 4.2. There was one reproductive/developmental oral study available for MTMS (ECHA 2007) and oral and inhalation studies conducted for other
methoxysilanes, chlorosilanes or acetoxy silanes. These studies do not indicate the silane groups are reproductive/developmental toxicants. MeOH is not considered a reproductive/developmental toxicant (TCEQ 2014a). For this methoxysilane, confidence in the database is considered medium to low because only one animal species was used in inhalation bioassays. However, additional information is available for the entire class of methoxysilanes.

\[
\text{Chronic ReV} = \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_{\text{Sub}} \times \text{UF}_D)}
\]
\[
= \frac{17.86 \text{ ppm}}{(10 \times 3 \times 3 \times 3)}
\]
\[
= 0.06615 \text{ ppm}
\]
\[
= 66 \text{ ppb (rounded to two significant figures)}
\]

The chronic ESL of 20 ppb (110 µg/m³) for MTMS was set based on the chronic ReV of 66 ppb (370 µg/m³) multiplied by a HQ of 0.3. Refer to Table 8 for summary information.

4.3.4 VTMS

4.3.4.1 Key Animal Study (OECD 2009b, ECHA 2011)

In a repeated dose inhalation toxicity study, 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 chronic study since it is longer than 3 months (TCEQ 2012). Ten rats per sex per group were sacrificed following the 14-week exposure regimen; the remaining rats were sacrificed after a 4-week recovery period. An additional ten male rats assigned to both the control and high concentration groups were designated for perfusion fixation of the kidneys for examination by electron microscopy. The following results were cited directly from ECHA (2011):

"There were no findings in the 10 ppm exposed group. Positive findings in the assessments for toxicity were present in the rats of the 400 and 100 ppm groups. These abnormalities were minimal to mild in severity and usually infrequent in occurrence. For most of the abnormalities, a return to normality was observed following the 4-week post-exposure period, indicating recovery. There were no mortalities throughout the study. Clinical signs in the 400 ppm group included urogenital area wetness and alopecia. There were no treatment-related eye lesions. Male and female rats of the 400 ppm group had decreases (11 to 16% below control values) in body weights. Occasional decreases in body weights of the female rats of the 100 ppm group were also observed. Food consumption was not altered. Water consumption was increased in the male rats of the 400 ppm group at study weeks 1, 5, 8, and 14 and for females during the first week. Urinalysis results indicated that male rats of the 400 ppm group had lower osmolality, lower electrolyte concentrations, and a decrease in
estimated creatinine clearance. Female rats of the 400 ppm group had similar changes, but at week 14 only. A decrease in urine osmolality with a concomitant increase in urine volume was observed in male rats of the 100 ppm group at week 1. There were no biologically significant changes in hematology or serum chemistries in rats exposed to A-171. At necropsy, there were no exposure-related lesions, and changes in organ weights in rats of the 400 ppm group were considered to result from body weight depression. Noteworthy microscopic lesions in rats of the 400 ppm group were observed in two tissues, the urinary bladder, and the kidney. Minimal cystitis in the bladder submucosa was observed at 14 weeks, and submucosal mastocytosis was observed at 18 weeks. Renal lesions in a few of the 400 ppm-exposed rats included papillary necrosis, interstitial edema, and/or papillary hyperplasia of the transitional epithelium. Electron microscopic examination of the kidneys supported the light microscopic findings.”

ECHA (2011) concluded that rats repeatedly exposed to 400 ppm VTMS for 14 weeks had minimal to mild alterations in body weight, water consumption, urinalysis, organ weights, and bladder and kidney histopathology. A concentration of 100 ppm was a minimum-effect concentration for decreased urine osmolality and sodium, potassium and chloride concentrations in males and slight decrease in body weight and body weight gain in females. The levels of 10 and 100 ppm were considered a NOAEL and LOAEL by OECD (2009b) for urinary bladder and kidney systemic effects by OECD (OCED 2009b, ECHA 2011). The TCEQ, however, considers the minimal effects (decreased urine osmolality and sodium, potassium and chloride concentrations) observed in the 100 ppm-exposed rats as “non-adverse” and thus 100 ppm was considered the lowest observed effect level (LOEL). The level of 100 and 400 ppm will be considered a NOAEL and LOAEL, respectively, for urinary bladder and kidney systemic effects. Thus, the chronic NOAEL of 100 ppm was used as the POD to derive a chronic toxicity factor.

No significant effects on reproductive organs were observed in this study. In the 400 ppm group, the absolute testes weight was statistically significantly decreased compared to control mean values, however when expressed as a percentage of body weight, the testes weights were statistically equivalent. There was no effect on absolute testes weight in the 400 ppm recovery group animals. There were no histopathological lesions or noted effects reported for any of the reproductive organs (testes, epididymides, prostate (and associated sex glands), uterus, vagina, cervix, ovaries, fallopian tubes, or mammary tissue) examined at all three VTMS exposure groups.
4.3.4.2 Summary of Derivation of Chronic ReV and chronic ESL

4.3.4.2.1 POD and Critical Effect

The NOAEL of 100 ppm for urinary bladder and kidney systemic effects was used as the POD to derive chronic toxicity factor for VTMS. The critical effects are slight decrease in body weight and body weight gain and minimal urinary bladder and kidney systemic effects.

4.3.4.2.2 Dosimetric Adjustments

The chronic POD of 100 ppm was adjusted from a discontinuous exposure (6 h/d for 5 d/week) to a continuous exposure concentration.

\[
POD_{ADJ} = POD \times \left( \frac{D}{24 \text{ h}} \right) \times \left( \frac{F}{7 \text{ d}} \right)
\]

\[
POD_{ADJ} = 100 \text{ ppm} \times \left( \frac{6}{24} \right) \times \left( \frac{5}{7} \right) = 17.857 \text{ ppm}
\]

The corresponding POD_{ADJ} of 17.857 ppm was then adjusted to POD_{HEC}. VTMS was considered a Category 3 vapor (systemic effects), so the POD_{ADJ} was adjusted to POD_{HEC} using a default value of one as the DAF (i.e., \((H b/g)_A/(H b/g)_H\)). The resulting chronic POD_{HEC} from the POD_{ADJ} of 17.857 ppm is 17.857 ppm.

4.3.4.2.3 Adjustment of POD_{HEC}

The POD_{HEC} was then used to derive the chronic ReV and ESL by applying the following UFs, with total UFs = 180:

- a UF_H of 10 for intraspecies variability,
- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- 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,
- a UF_D of 3 was used because only one animal species was studied. A higher UF_D was not used because inhalation and gavage subacute studies were available (ECHA 2011) and the critical effect was identified in a repeat-dose subacute study. Reproductive/developmental studies were also conducted for both inhalation and gavage. Confidence in the database is considered medium.

\[
\text{Chronic ReV} = \frac{POD_{HEC}}{(UF_H \times UF_A \times UF_{Sub} \times UF_D)}
\]

\[
= \frac{17.857 \text{ ppm}}{(10 \times 3 \times 2 \times 3)}
\]

\[
= 0.09920 \text{ ppm}
\]

\[
= 99 \text{ ppb} \text{ (rounded to two significant figures)}
\]
The chronic ESL of 30 ppb (180 µg/m$^3$) for VTMS was set based on the chronic ReV of 99 ppb (600 µg/m$^3$) multiplied by a HQ of 0.3. Refer to Table 8 for summary information.

4.3.5 CPTMS

4.3.5.1 Key Animal Study (Dow Corning Corporation 1993)

In a subchronic inhalation study by Dow Corning Corporation (1993, as cited in OECD 2006, ECHA 2015c), groups of male and female rats were exposed to target concentrations of 0, 0.5, 5, 100, and 200 ppm of CPTMS vapors for 6 h/d, 5 d/week for 90 d (13 weeks). The actual overall mean exposure concentration for the test groups was 0.5, 5, 99, and 189 ppm. The results showed that no statistically significant differences in mean body weights or food consumption between the test and control groups. There were no statistically significant differences in male or female organ weights among the groups. There were no exposure-related microscopic changes in any of the organs or tissues of the respiratory tract examined. Histopathology changes (increased incidence of hyperplasia) in the urinary bladder/kidneys were observed in both male and female rats exposed to 100 ppm. The results of this study demonstrate test article-related histopathologic changes in the urinary bladder and kidneys of animals exposed to 100 ppm (814 mg/m$^3$).

Although the effect on the histopathological changes in the urinary bladder and kidney was not observed in all repeated inhalation exposure studies, OECD (2006) conservatively considered the level of 5 ppm a NOAEL for this effect. OECD (2006) concludes that biological variation is plausible and is often seen among different tests; and between testing laboratories. Thus, the 90-d study should be considered as carrying the most weight as it is the study with the longest duration and provides the most conservative NOAEL. The NOAEL of 5 ppm was used as POD to derive chronic toxicity factors. It should be noted that since there is a large gap between 5 and 100 ppm dose groups, the NOAEL could have been higher.

4.3.5.2 Supporting Animal Study (Dow Corning Corporation 1992)

Groups of male and female rats (10/sex/group) were exposed by inhalation to CPTMS at target concentrations of 0, 10, 50, 100, and 200 ppm 6 h/d, 5 d/week for 28 d (a subacute/subchronic study). The measured mean exposure concentrations of the test material for the various test groups were 0, 10, 50, 98, and 192 ppm (Dow Corning Corporation 1992, as cited in OECD 2006). No mortality or apparent treatment-related clinical signs were observed in any of the test groups. No statistically significant differences were noted in either mean body weights or food consumption. No treatment-related effects were seen in the clinical pathology parameters. There were no microscopic changes in any of the respiratory tract organs or other tissues examined in all exposure groups. Statistically significant increases were noted in the absolute and relative weights of adrenal glands of male rats from the 50, 100 and 200 ppm exposure groups and females at 100 and 200 ppm. Statistically significant increases were also observed in liver and kidney weights of males at 200 ppm. The organ weight changes were supported by the findings of microscopic lesions in these organs. Histopathological changes were detected in the adrenal glands, kidneys, liver, and urinary bladder in some rats from one or more exposure groups at
concentrations as low as 10 ppm. Histopathologic changes included adrenal cortical hypertrophy in males at 100 ppm and in both sexes at 200 ppm; hyaline droplet nephropathy in males at 50, 100, and 200 ppm; hepatocellular hypertrophy in males at 200 ppm and hyperplasia of urinary bladder epithelium in females at 10 ppm and both sexes at 50, 100 and 200 ppm. Statistically significant increases in micronucleated cells were observed in female rats of the 200 ppm group. The NOAEL was not established in this study. However, the level of 10 and 50 ppm for hyperplasia of urinary bladder epithelium in females and males, respectively, were considered LOAELs. The LOAEL of 10 ppm for females in this 28-d study support the NOAEL of 5 ppm determined in the 90-d study.

4.3.5.3 Summary of Derivation of Chronic ReV and chronic ESL

4.3.5.3.1 POD and Critical Effect
The 90-d NOAEL of 5 ppm for systemic effects was used as the POD to derive a chronic toxicity factor for CTPMO. The critical effects are histopathologic changes in the urinary bladder/kidneys.

4.3.5.3.2 Dosimetric Adjustments
The subchronic POD of 5 ppm was adjusted from a discontinuous exposure (6 h/d for 5d/week) to a continuous exposure concentration.

\[
\text{POD}_{\text{ADJ}} = \text{POD} \times \left( \frac{D}{24 \text{ h}} \right) \times \left( \frac{F}{7 \text{ d}} \right)
\]

\[
\text{POD}_{\text{ADJ}} = 5 \text{ ppm} \times \left( \frac{6}{24} \right) \times \left( \frac{5}{7} \right) = 0.8929 \text{ ppm}
\]

The corresponding POD_{ADJ} of 0.8929 ppm was then adjusted to POD_{HEC}. CTPMO was considered a Category 3 vapor (systemic effects), so the POD_{ADJ} was adjusted to a POD_{HEC} using a default value of one as the DAF. The resulting subchronic POD_{HEC} is equal to the POD_{ADJ} of 0.8929 ppm

4.3.5.3.3 Adjustment of POD_{HEC}
The POD_{HEC} was then used to derive acute ReV and ESL by applying the following UFs, with total UFs = 180:

- a UF_{H} of 10 for intraspecies variability,
- a UF_{A} of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans, but not toxicodynamic differences,
- a UF_{Sub} of 2 instead of 10 was used to account for the use of a subchronic 90-day study because CPTMS has a low log K_{ow} of -1.13, which indicates that bioaccumulation will
not occur. The supporting study of 28-days demonstrates the difference between the
minimal LOAEL of 10 ppm (Dow Corning 1992) is only two times higher than the
NOAEL of 5 ppm in the 90-d study (the subchronic NOAEL of 5 ppm might be higher
given that the subchronic LOEL of 100 ppm only caused minimal systemic effects) (Dow
Corning 1993). Therefore, chronic effects would not be expected to differ significantly
from subchronic effects,

- a UF_D of 3 was used, although only one animal species was studied. However, multiple
  inhalation studies were reported (RCC LTD 2005; Dow Corning 1993; Dow Corning
  1992). A reproductive/developmental study was also conducted (RCC LTD 2005). A
  larger UF_D was not used because the subchronic NOAEL of 5 ppm might be higher given
  that the subchronic LOEL of 100 ppm only caused minimal systemic effects. Confidence
  in the database is considered medium to high.

\[
\text{Chronic ReV} = \frac{\text{POD}_{\text{HEC}}}{(\text{UF}_H \times \text{UF}_A \times \text{UF}_{\text{Sub}} \times \text{UF}_D)} \\
= \frac{0.8929 \text{ ppm}}{(10 \times 3 \times 2 \times 3)} \\
= 0.005 \text{ ppm} \\
= 5 \text{ ppb (rounded to two significant figures)}
\]

The chronic ESL of 1.5 ppb (12 µg/m^3) for CPTMS was set based on the chronic ReV of 5 ppb
(40 µg/m^3) multiplied by a HQ of 0.3. Since the derived chronic ReV was based on a low-end
NOAEL, the chronic ESL for CPTMS is considered conservative. Refer to Table 8 for summary
information.

**4.3.6 Summary of the Chronic Evaluations**

Table 8 below summarizes the derivation of chronic toxicity factors for TMS, MTMS, VTMS,
CPTMS, and TetMS.
Table 9 Chronic ReV and chronic ESL-thresholds for the Tri- and Tetramethoxysilanes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TMS</th>
<th>TetMS</th>
<th>MTMS</th>
<th>VTMS</th>
<th>CPTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Study</td>
<td>---</td>
<td>Kolesar et al. 1989</td>
<td>ECHA 2007</td>
<td>ECHA 2011</td>
<td>Dow Corning 1993</td>
</tr>
<tr>
<td>Half-life</td>
<td>&lt; 0.3 min</td>
<td>Rapid</td>
<td>2.2 h</td>
<td>&lt; 2.4 h</td>
<td>53.3 min</td>
</tr>
<tr>
<td>4-h LC₅₀</td>
<td>60 ppm</td>
<td>63 ppm</td>
<td>&gt; 8,700 ppm</td>
<td>2,773 ppm</td>
<td>Not available</td>
</tr>
<tr>
<td>GLP</td>
<td>---</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Animals</td>
<td>---</td>
<td>SD rats, 10/sex/group</td>
<td>SD rats, 10/sex/group</td>
<td>20 Fischer 344 rats/sex/group</td>
<td>SD male/female rats</td>
</tr>
<tr>
<td>Exposure concentration</td>
<td>---</td>
<td>0, 1, 5, or 10 and 0, 15, 30, or 45 ppm</td>
<td>0, 25, 100, 400, and 1600 ppm</td>
<td>0, 10, 100, and 400 ppm</td>
<td>0, 0.5, 5, 100, and 200 ppm</td>
</tr>
<tr>
<td>Duration</td>
<td>---</td>
<td>6 h/d, 5 d/week for 28 d</td>
<td>6 h/d, 5 d/week for 90 d</td>
<td>6 h/d, 5 d/week for 14 weeks</td>
<td>6 h/d, 5 d/week for 13 weeks</td>
</tr>
<tr>
<td>Critical effects</td>
<td>---</td>
<td>Upper respiratory tract, bronchiolar, and inflammatory lesions</td>
<td>Increased incidence of urinary bladder calculi along with kidney dilation</td>
<td>Urinary bladder and kidney effects</td>
<td>Histopathologic changes in the urinary bladder/kidneys</td>
</tr>
<tr>
<td>POD</td>
<td>---</td>
<td>10 ppm (NOAEL)</td>
<td>100 ppm (NOAEL)</td>
<td>100 ppm (NOAEL)</td>
<td>5 ppm (NOAEL/NOEL)</td>
</tr>
<tr>
<td>POD_ADJ</td>
<td>---</td>
<td>1.786 ppm</td>
<td>17.86 ppm</td>
<td>17.86 ppm</td>
<td>0.8929 ppm</td>
</tr>
<tr>
<td>POD_HEC</td>
<td>---</td>
<td>1.786 ppm</td>
<td>17.86 ppm</td>
<td>17.86 ppm</td>
<td>0.8929 ppm</td>
</tr>
<tr>
<td>Total UFs</td>
<td>---</td>
<td>270 UF₇ H 10; UF₇ A 3; UF₇ Sub 3; UF₇ D 3</td>
<td>270 UF₇ H 10; UF₇ A 3; UF₇ Sub 3; UF₇ D 3</td>
<td>180 UF₇ H 10; UF₇ A 3; UF₇ Sub 2; UF₇ D 3</td>
<td>180 UF₇ H 10; UF₇ A 3; UF₇ Sub 2; UF₇ D 3</td>
</tr>
<tr>
<td>ReV</td>
<td>---</td>
<td>7 ppb (44 µg/m³)</td>
<td>66 ppb (370 µg/m³)</td>
<td>99 ppb (600 µg/m³)</td>
<td>5 ppb (40 µg/m³)</td>
</tr>
<tr>
<td>ESL</td>
<td>13 µg/m³*</td>
<td>2.1 ppb (13 µg/m³)</td>
<td>20 ppb (110 µg/m³)</td>
<td>30 ppb (180 µg/m³)</td>
<td>1.5 ppb (12 µg/m³)</td>
</tr>
</tbody>
</table>

* The chronic ESL of 13 µg/m³ for TMS was surrogated from the chronic ESL of 13 µg/m³ for TetMS

4.4 Welfare-Based Chronic ESLs

No data were found regarding long-term vegetation effects.
4.5 Carcinogenic Potential

OECD reports that TMS, MTMS, and VTMS were not mutagenic in vitro in bacteria reverse mutation assays and available information suggests that these substances are not likely to be genotoxic (refer to OECD 2007, 2008, 2009a, 2009b). No in vivo data exists that indicate that tri- or tetramethoxysilanes (i.e., TMS, MTMS, VTMS, CPTMS and TetMS) are of carcinogenic potential (OECD 2006, 2007, 2008, 2009a, 2009b). No data are available on the genotoxicity of TetMS in laboratory animals (NRC 2012). CPTMO was not considered to be an inducer of micronuclei in vivo, but is mutagenic in vitro (positive in bacterial mutation assays and in the presence of metabolic activation, and in an in vitro mouse lymphoma mutagenesis assay) (OECD 2006).

4.6. Long-Term ESLs for Air Permits

The long-term ESLs used for air permit evaluations are as follows:

- TMS\textsuperscript{chronic ESL} = 13 µg/m\textsuperscript{3} (surrogated to the \textsuperscript{chronic ESL} of 13 µg/m\textsuperscript{3} for TetMS)
- TetMS\textsuperscript{chronic ESL-threshold(nc)} = 13 µg/m\textsuperscript{3} (2.1 ppb)
- MTMS\textsuperscript{chronic ESL-threshold(nc)} = 110 µg/m\textsuperscript{3} (20 ppb)
- VTMS\textsuperscript{chronic ESL-threshold(nc)} = 180 µg/m\textsuperscript{3} (30 ppb)
- CPTMS\textsuperscript{chronic ESL-threshold(nc)} = 12 µg/m\textsuperscript{3} (1.5 ppb)

4.7 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)

The chronic inhalation observed adverse effect levels for the methoxysilanes with adequate data are as follows:

- TMS\textsuperscript{chronic IOAEL} = inadequate data
- TetMS\textsuperscript{chronic IOAEL} = 93 mg/m\textsuperscript{3} (15 ppm)
- MTMS\textsuperscript{chronic IOAEL} = 2200 mg/m\textsuperscript{3} (400 ppm)
- VTMS\textsuperscript{chronic IOAEL} = 2400 mg/m\textsuperscript{3} (400 ppm)
- CPTMS\textsuperscript{chronic IOAEL} = 810 mg/m\textsuperscript{3} (100 ppm)

The chronic inhalation observed adverse effect levels are the LOAEL\textsubscript{HEC} determined from animal studies. No duration adjustments were made, although animal-to-human dosimetric adjustments were performed. 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. Importantly, effects are not a certainty due to
potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

Chapter 5 References

5.1 References Cited in the DSD


Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methytrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)


Dow Corning Corp. 1990a (as cited in OECD 2006). A two-week range-finding vapor inhalation toxicity study with chloropropyltrimethoxysilane in the rat. Report number 1990-I0000-35076


European Chemicals Agency (ECHA). 2015b. Chemical Information for TetMS. [http://apps.echa.europa.eu/registered/data/dossiers/DISS-d7f5f034-9d29-0c95-e044-00144f67d031/AGGR-98e203f1-60a0-4808-9bc7-2ec442de9a3e_DISS-d7f5f034-9d29-0c95-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-d7f5f034-9d29-0c95-e044-00144f67d031/AGGR-98e203f1-60a0-4808-9bc7-2ec442de9a3e_DISS-d7f5f034-9d29-0c95-e044-00144f67d031.html)


Trimethoxysilane (TMS); Tetramethoxysilane (TetMS); Methyltrimethoxysilane (MTMS); Vinyltrimethoxysilane (VTMS); 3-Chloropropyltrimethoxysilane (CPTMS)


5.2 References Reviewed but Not Cited in the DSD
