A Weight of Evidence Approach for Chemicals with Limited Data: Methods for Deriving Effects Screening Levels (ESLs) for Silanes

(Workshop VIII)

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A Weight of Evidence Approach for Chemicals with Limited Toxicity Data: Methods for Deriving Effects Screening Levels (ESLs) for Silanes

(Workshop VIII)

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1.0 Problem Formulation

The Texas Commission on Environmental Quality (TCEQ) employs several interactive programs to ensure concentrations of air toxics do not exceed levels of potential health concern (Capobianco et al. 2013). The air permitting program conducts comprehensive review of permit applications or amendments to ensure that modeled impacts would not pose a concern to human health or welfare. Modeled chemical concentrations are compared to screening values called effects screening levels (ESLs). These values are derived by the Toxicology Division at the TCEQ. However, the amount of data available to derive these ESLs is highly variable. Of the approximate 5300 screening values, the vast majority represent chemicals with limited toxicity data (LTD chemicals), creating a need for a systematic, scientifically-defensible approach to derive values for chemicals with limited data. The purpose of this case study is as follows:

- Discuss the meaning of weight of evidence (WOE) approach in the context of LTD chemicals
- Describe the various methods the TCEQ utilizes to generate ESLs for LTD chemicals
- Using silanes as an example, describe how these methods may be applied to derive toxicity factors
- Discuss how the body of evidence is evaluated and prioritized
- Describe how chemical analogues are selected when data from a more data-rich chemical must be used as substitute for a LTD chemical
- Illustrate how analogue selection itself can be used in a conservative manner to result in health and welfare protective values
- Generate a framework that can be used as guidance to derive toxicity factors for LTD chemicals

The term WOE is commonly used in risk assessment. Ironically, the term itself has broad, often multi-faceted meanings that frequently result in confusion. The general concept behind a WOE approach is to conduct a systematic review of available scientific evidence, then, based on defensible reasoning, use that body of evidence or some part of it to come to a conclusion. In simple terms, WOE approaches are interpretive methodologies. Some of the weaknesses of many

WOE approaches include: no description of how data was collected, lack of transparency, underreporting, omission of studies or data without clear reason, and no description of how the body of available evidence was surveyed and used to generate a conclusion. Furthermore, weighting evidence includes a good deal of scientific or value judgments, which themselves are inherently variable (Rhomberg, 2013; Weed, 2005). Based on the aforementioned factors, it is easy to see how members of the public or scientific community would find methods used to generate toxicity factors for LTD chemicals arcane at best and at worst simply pulled out of thin air.

The concept of deriving toxicity factors for LTD chemicals is hardly new. However, the methods themselves are broad and variable among regulatory agencies and organizations. Likewise, there are limited discussions regarding how data should be evaluated as a whole and how surrogates should be chosen in the event data is so sparse that data from another chemical must be used to fill apparent data gaps. The TCEQ has described several approaches for deriving ESLs for LTD chemicals, including the N-to-L ratio, relative potency/ toxicity, read-across, surrogate, category (TOC), route-to-route extrapolation, and quantitative structure activity ((Q)SAR) approaches (Grant et al., 2007; TCEQ 2012). The approach selected for deriving an ESL for a LTD chemical is dependent on the available data, the resultant conclusions regarding those data as well as the time and resource constraints inherent to a given project.

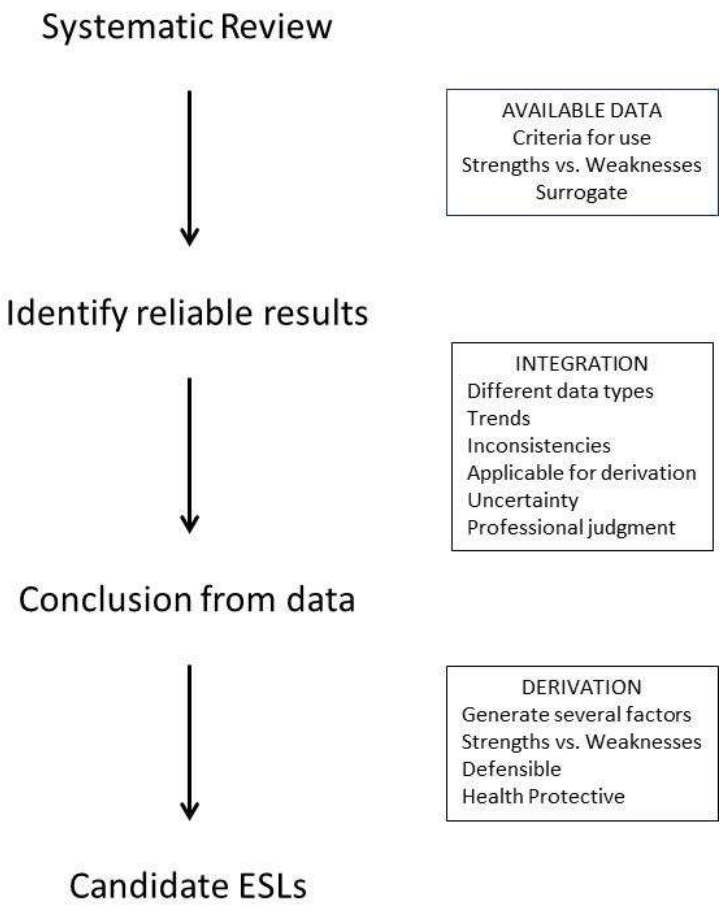
An end-product of this case study will be a framework that describes various methods to derive ESLs for LTD chemicals and some of the WOE considerations that arise when considering chemical substitutions and interpolation. This framework and methods described in this case study are useful in addressing the problem of generating ESLs for LTD chemicals. The outcome will be a system that enables users to communicate the data collected, how data was evaluated, identification of data gaps, possible ways of filling those data gaps, and mechanisms for generating an ESL in the absence of an information-rich database.

2.0 Case Study Summary

The purpose of this case study is to develop a framework to guide the genesis of ESLs for LTD chemicals. These methods are a form of hazard identification, dose-response evaluation, and mode of action (MOA) analysis. However, they are also an expansion of those ideas in a context that more heavily relies on filling data gaps with surrogates or broad information describing entire categories of chemicals.

At the heart of WOE approaches, is the review of available data, selection of possible hypotheses for the given observations, comparison of hypotheses, and selection of a hypothesis that is thought to best explain the data as a whole (Figure 1) (Rhomberg, 2013, Rhomberg et al., 2013). Chemicals that are candidates for ESL derivation at the TCEQ as the subject of an air permit review are structurally diverse. A request may be presented to the agency with nothing more than a CAS number and structure or be the subject of a large body of scientific investigation. Nonetheless, agency staff must derive a toxicity factor for these chemicals.

FIGRUE 1



Typically, data-rich chemicals will have a toxicity factor derived by conventional methods such as adjusting an appropriate point of departure (POD) with uncertainty factors (UFs) to reflect data limitations and to derive a value that is below levels where health effects would be expected to occur. However, one does not often have acute and chronic human or animal data for a chemical of concern. Our guidelines for derivation of toxicity factors primarily describe methods for deriving toxicity factors for chemicals with sufficient data. If the basic data requirements are not met to develop a reference value (ReV), then a generic screening value is derived instead. The approaches described in our guidelines include using a chemical surrogate, read-across tables, N-to-L ratio approach, route-to-route extrapolation, and relative toxicity or potency approaches. Each method has strengths and weaknesses that must be evaluated in light of the body of available data (TCEQ, 2012).

In this case study, we present a framework that weighs the strengths and weaknesses to the various approaches available to derive ESLs for LTD chemicals. The framework is flexible, making it applicable to a broad array of chemicals. The framework enables users to consider the advantages and disadvantages to each approach and develop an ESL based on the available data.

It also considers various options available to fill data gaps in a manner that takes into account, basic chemical structure, physical/chemical properties, MOA, and dose-response to provide a means of generating a screening value for any chemical.

This case study document contains the following items:

- A copy of excerpts from the TCEQ guidance document that describes methods for deriving ESLs for LTD chemicals (in a separate methods file)

- A framework for derivation of ESLs for LTD chemicals (Appendix A)

- Examples of that framework being applied to a family of LTD chemicals. In this case, we used members of the silanes family of chemicals for examples. Silanes are often used in industrial settings for the purposes of adhesion, crosslinking, coatings, sealants, fillers and water scavengers. They rapidly hydrolyze and this reactivity is often irritating to mucosal, ocular, or dermal surfaces upon exposure. Silanes can be grouped based on their basic chemical groups, which are used in this case study to illustrate derivation of ESLs using the aforementioned framework (Appendix B and C).

    1. Chlorosilanes are a chemical group with limited data. Available data indicate that these chemicals are irritants due to hydrolysis yielding Cl^- and silanols. Silanols are of lower toxicity than hydrogen chloride (HCl), thus toxicity in large part is driven by the HCl hydrolysis product. Beyond lethality studies, there are no studies to develop acute or chronic toxicity factors. This case study offers insight into the use of the N-to-L ratio and HCl as a surrogate for derivation of acute or chronic ESLs (see Appendix B).

    2. Methoxysilanes are groups of limited data silanes. They hydrolyze to methanol and associated silanols. Available data indicate that the short-term toxicity of this group of chemicals is driven by respiratory irritation induced by methanol. Thus, data from this alcohol will be used as surrogates along with lethality data to arrive at potential short-term toxicity factors. Chronic animal studies were available and indicate that these chemicals are bladder and kidney toxicants. Comparisons to long-term methanol toxicity were made as another means of ESL generation (Appendix C and D).

The broad purpose of this case study is to obtain guidance and comments from the panel on the framework presented for derivation of ESLs for LTD chemicals. In addition, comments regarding WOE considerations and strengths and weaknesses of various approaches would be of value rather than commentary regarding chemical-specific procedures used to calculate 1-hour (hr) or chronic ESLs for silanes in this case study.

References

1. Capobianco, T, Hildebrand SM, Honeycutt M, Lee JS, McCant D, Grant RL. 2013. Impact of Three Interactive Texas State Regulatory Programs to Decrease Ambient Air Toxic Levels. *J Air Waste Manag Assoc*.63:507-520.

2. Grant RL, Kadlubar BJ, Erraguntala NK, Honeycutt M. 2007. Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. *Regul Toxicol Pharmacol*, 47:261-273.

3. Rhomberg LR. 2013. Hypothesis-based weight of evidence: an approach to assessing causation and its application to regulatory toxicology. Working paper prepared for: Methods for research synthesis: A cross-disciplinary workshop, Harvard Center for Risk Analysis.

4. Rhomberg LR, Goodman JE, Bailey LA, Prueitt RL, Beck NB, Bevan C, Honeycutt M, Kaminski NE, Paoli G, Pottenger LH, Scherer, Wise KC, Becker RA. 2013. A survey of frameworks for best practices in weight-of-evidence analyses. *Crit Rev Toxicol* 43:753-784.

5. Weed DL. 2005. Weight of evidence: a review of concepts and methods. *Risk Anal* 25:1545-1557.

6. Texas Commission on Environmental Quality. TCEQ 2012. TCEQ Guidelines to Develop Toxicity Factors, RG-442 Final. Texas Commission on Environmental Quality, available at http://m.tceq.texas.gov/toxicology/esl/guidelines/about.html

APPENDIX A: Framework for Derivation of Toxicity Factors for Chemicals with Limited Data

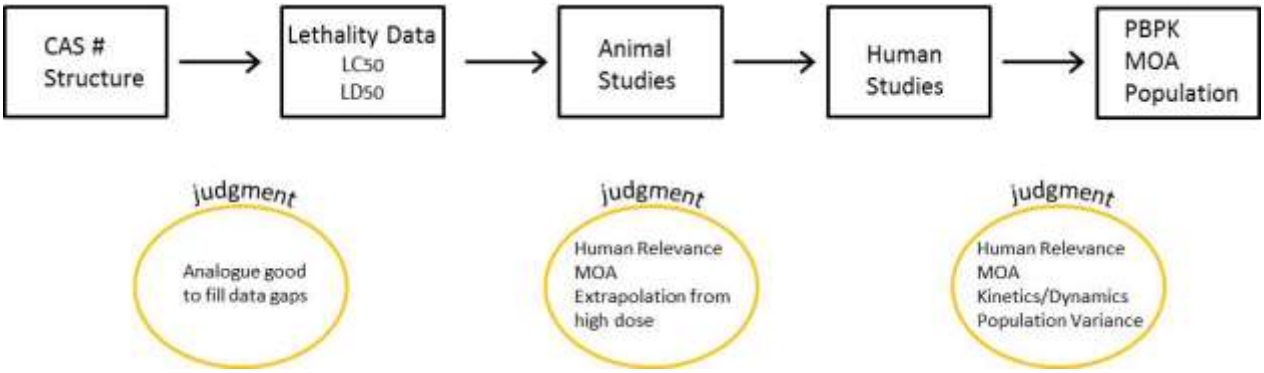
Introduction

The previous sections of this case study summary discussed the general methods for derivation of inhalation ESLs for LTD chemicals. In this section, we show a framework for deriving ESLs for LTD chemicals. This framework illustrates the various approaches available to the user based upon the data available for a given chemical of concern. It is important to note that more often than not, a risk assessor is tasked with filling data gaps via interpolation or use of some data surrogate. Thus, best practices must be considered to most effectively apply available resource. Likewise, communication regarding the basis of a derived value is critical. Key items to document include:

- Analogue selection
- Basis of conservatism
- Limitations of available data
- Weighting of available data
- Time and resource constraints

It may be that several approaches are considered concomitantly, with professional judgment being used to select the final value. With increasing amounts of data, the areas where professional judgments are applied change and become increasingly complex. Figure 1 illustrates the general data that are available for ESL derivation, with increasing database information.

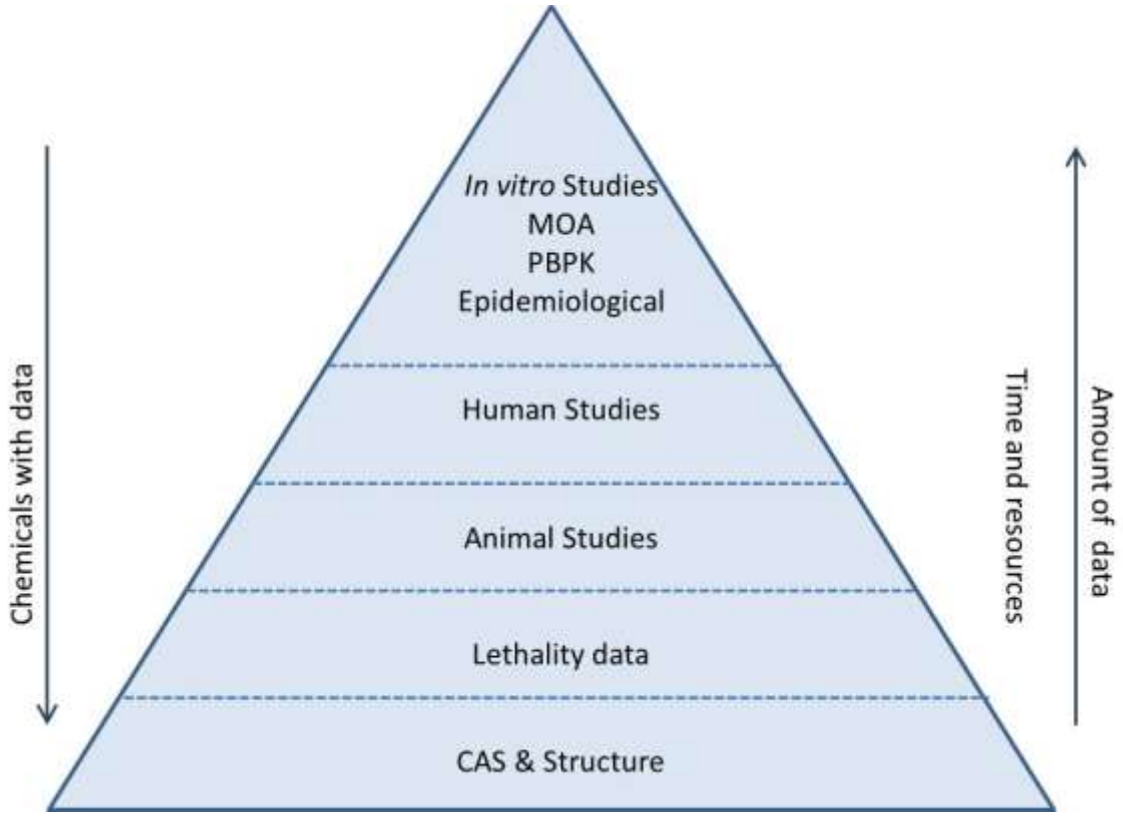
FIGURE 1



The continuum of available data from essentially no data to data rich demonstrates an increasing demand for resources and time (Figure 2). It is rare for extensive MOA data or PBPK modeling to be available. In fact, the majority of chemicals for which the TCEQ develops ESLs are characterized by little more than a CAS number and structure. Occasionally, acute animal studies

are available. Thus, many of our ESLs for air permitting are derived based on methods used for LTD chemicals.

FIGURE 2



There are many factors that must be considered when deriving a screening level based solely on chemical structure. When selecting a surrogate as the basis of an ESL for a chemical of concern, the applicability and adequacy of the surrogate must be taken into consideration. Structural and physicochemical properties should be similar if a surrogate is chosen on the assumption that shared properties cause analogous toxicities. Table 1 highlights some chemical characteristics that should be considered for surrogate selection.

TABLE 1

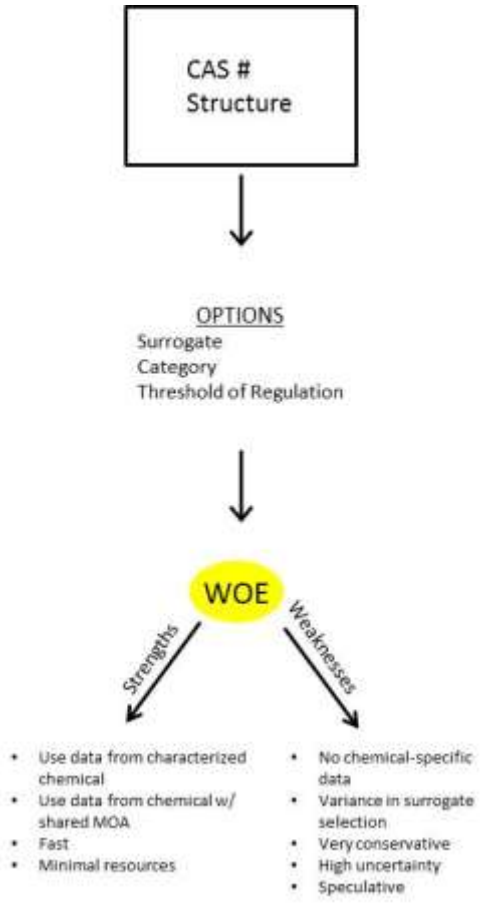
Considerations for Surrogate Selection			
Physicochemical Properties	**Structural**	**Biological**	**Chemical Family**
Physical state Hydrolytically unstable Reactive Molecular weight Size Log Kow	Functional groups Electronic features Sterics Individual bond energies	MOA-predictions Irritants POE effects Systemic effects Genotoxicity Direct adduction of biological molecules	Generally shared structures Shared physical/chemical properties Known to be particulate

A risk assessor has greater confidence that a candidate surrogate will adequately serve as a substitute when that surrogate shares many chemical and structural characteristics with the chemical of concern. Often, structures may give an assessor a sense of how a chemical of concern will act on a biological system. For example, highly reactive chemicals are likely to be irritants with greatest impacts occurring at the portal of entry (POE). Conversely, high molecular weight chemicals may not be bioavailable via inhalation. These considerations may also allow a risk assessor to select a surrogate that is particularly conservative to insure that the subsequent ESL is health protective. For example, the TCEQ will often base ESLs for various metals on the form of the metal known to be most toxic (e.g., the ESL for inorganic arsenic is also the ESL for other forms of arsenic) as a means of accounting for the uncertainty created by lack of data.

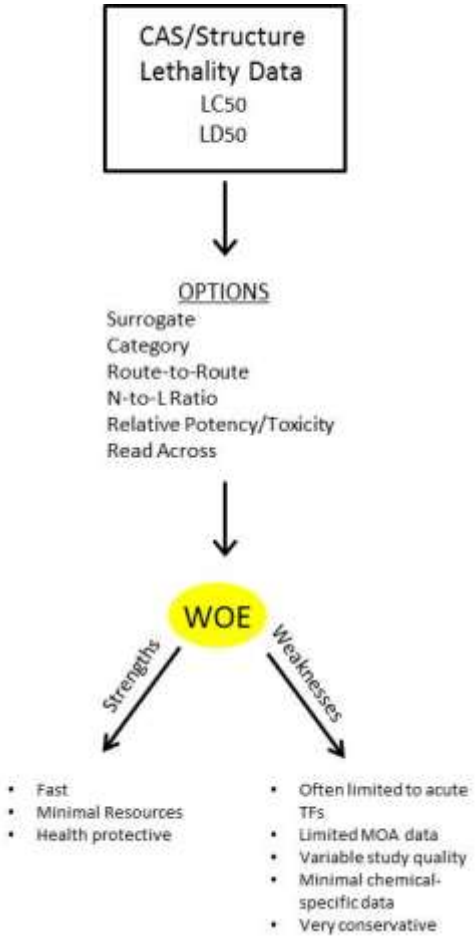
Chemicals of concern with more data available for consideration will open more options as means of deriving a health-protective ESL. Each approach has both strengths and weaknesses that are determined by the breadth of the available data and resources available to the risk assessor. Weaknesses are often defined by limitations inherent in different model systems or methodologies used in the study itself. The less data there is for a chemical of concern, the more health protective assumptions are made to derive the screening values. These are summarized in Figure 3 A, B, C and D.

FIGURE 3

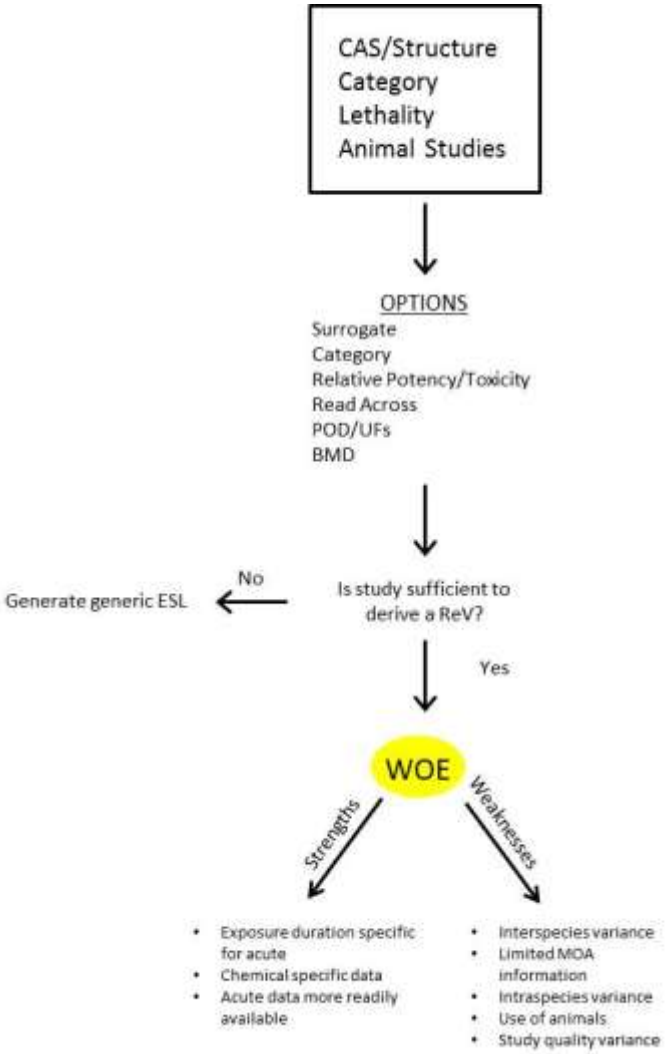
A



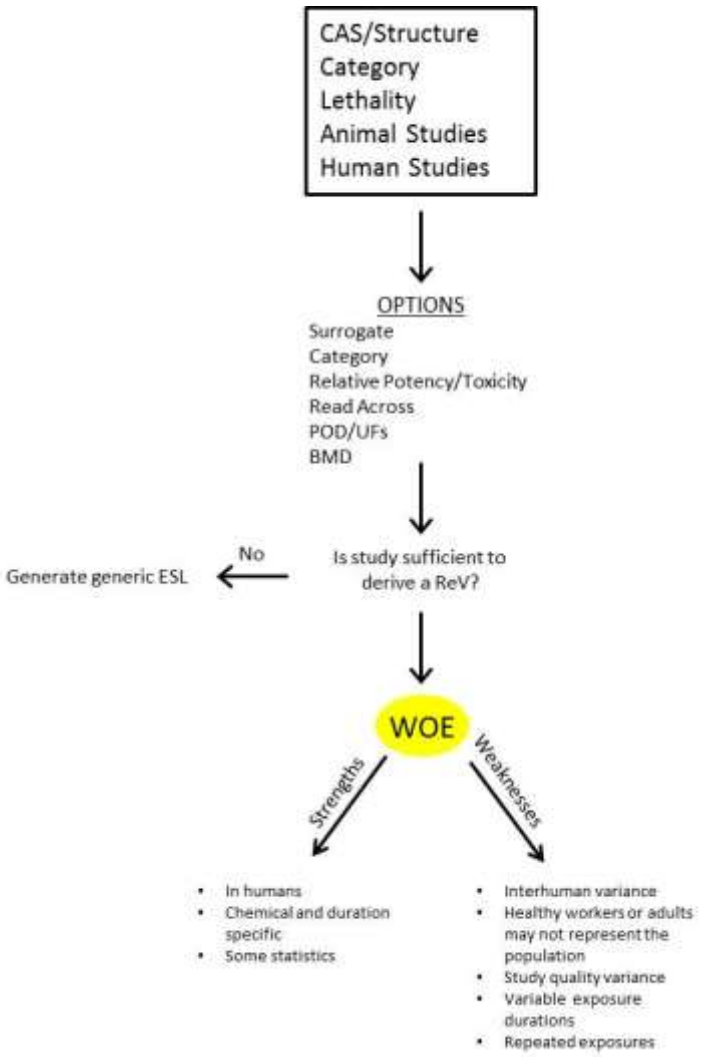
B



C


CAS/Structure
Category
Lethality
Animal Studies
OPTIONS
Surrogate
Category
Relative Potency/Toxicity
Read Across
POD/UFs
BMD
Is study sufficient to derive a ReV?
No
Generate generic ESL
Yes
WOE
Strengths
Weaknesses
Exposure duration specific for acute
Chemical specific data
Acute data more readily available
Interspecies variance
Limited MOA information
Intraspecies variance
Use of animals
Study quality variance

D



The value of different approaches and the extent to which the merits of a given approach outweigh those of another are at the discretion of the risk assessor and/or policy makers. This case study will illustrate the application of this WOE framework via the derivation of ESLs for various silanes. Within each example, strengths and weaknesses of various approaches will be discussed, as well as what the authors considered to be the basis of conservatism in the different approaches.

APPENDIX B: Examples of ESL Derivation for Chlorosilanes

Example: Development of ESLs for Chlorosilanes

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Abstract

Chlorosilanes are used in industrial settings to produce silicone products. Few studies have investigated the toxicity of these chemicals. These silanes rapidly hydrolyze releasing hydrogen chloride (HCl) and silanols. Based on this chemistry, the primary toxicity caused by this chemical class would be due to the hydrolysis product HCl, which is a potent irritant. Upon evaluation, a surrogate approach using HCl as the basis of chlorosilanes ESLs is defensible and conservative. The toxicity of chlorosilanes is directly proportional to the number of chlorine groups on the silane. Thus, monochlorosilanes are assigned acute and chronic generic ESLs that are equal to that of HCl (130 ppb and 5.4 ppb). Di-, tri-, and tetra chlorosilanes have a large number of molar equivalents of HCl. These compounds were assigned ESLs based on adjusting the HCl ESL proportional to the number of chlorine equivalents on the silane, making the acute ESLs 65ppb, 43 ppb, and 32 ppb, respectively. Long-term ESLs were also assigned on the basis of HCl (5.4 ppb (mono), 2.7 ppb (di), 1.8 ppb (tri), and 1.4 ppb (tetra)).

Introduction

The Texas Commission on Environmental Quality (TCEQ) has historically developed effects screening levels (ESLs) to be used in air permits programs. Often ESLs must be derived for LTD chemicals in order to evaluate proposed emissions. These ESLs need to be derived in a timely manner often with limited data resources. The TCEQ has developed several approaches to derive generic ESLs for LTD chemicals, including the N-to-L ratio, route-to-route extrapolation, surrogates, and relative toxicity/potency approaches (see TCEQ guidance document RG422). These approaches are flexible and health protective and can be used systematically based on the data available for a chemical of concern (see WOE framework above).

In this example, generic ESLs are derived for a group of chlorosilanes. Chlorosilanes are primarily used in industrial settings as intermediates in the synthesis of silicone products. Thus, it is unlikely that the general public will be exposed to them from sources other than industrial emissions. Chlorosilanes hydrolyze rapidly (i.e., half-life of < 17 seconds) to form HCl and silanols. Silanols subsequently condense to higher molecular weight siloxanes, which will have reduced bioavailability and lower toxicity.

Chlorosilanes are a group of LTD chemicals. No formal human inhalation studies have been conducted evaluating the toxicity or irritancy of these chemicals. One report details the effects of a silicon tetrachloride spill at a chemical plant (Kizer et al., 1984). The study reports that silicon tetrachloride was released from a damaged pipeline, generating a cloud of chemical that spread through an area populated with workers and other area businesses. While no concentrations of this chemical were reported or modeled, a number of people exposed to vapors were sent to nearby hospitals with complaints of eye and airway irritation. Exposure durations were reported as less than 20 minutes and symptoms consistent with irritation resolved within a 24-hr period. Follow-up pulmonary function tests indicated that changes in respiratory function had been mild and reversible.

Acute lethality studies indicate that chlorosilanes toxicity is proportional to the number of chlorine moieties on the silane molecule (Jean et al., 2006; AEGL, 2009). Based on the fact that chlorosilanes rapidly hydrolyze in water and that toxicity is proportional to the number of chlorine anions (Cl^-) (Table 1), toxicity for this group of chemicals is likely based on the Cl^- released during hydrolysis (AEGL,

2009). There are no additional acute inhalation studies in animal models available for chlorosilanes. There are also no other studies available investigating the toxicity of these chlorosilanes.

TABLE 1

Compound	Measured LC_{50} (ppm) (95% conf. limits)	Predicted LC_{50} (ppm)	Predicted Ratio of LC_{50} values	Measured Ratio of LC_{50} values
Hydrogen Chloride	3627 ppm			
Tetrachlorosilane	1312 (1006-1529)	3627 ÷ 4 = 907	4 : 1	2.8 : 1
Propyl trichlorosilane	1352 (1254-1455)	3627 ÷ 3 = 1209	3 : 1	2.7 : 1
Vinyl trichlorosilane	1611 (1505-1724)	3627 ÷ 3 = 1209	3 : 1	2.3 : 1
Methyl trichlorosilane	1365 (1174-2104)	3627 ÷ 3 = 1209	3 : 1	2.7 : 1
Ethyl trichlorosilane	1257 (1175-1320)	3627 ÷ 3 = 1209	3 : 1	2.9 : 1
Methylvinyl dichlorosilane	2021 (1806-2257)	3627 ÷ 2 = 1814	2 : 1	1.8 : 1
Dimethyl dichlorosilane	2092 (1492-2240)	3627 ÷ 2 = 1814	2 : 1	1.7 : 1
Methyl dichlorosilane	1785 (1671-1963)	3627 ÷ 2 = 1814	2 : 1	2: 1
Trimethyl chlorosilane	4257 (4039-4488)	3627 ÷ 1 = 3627	1 : 1	0.9 : 1
Dimethyl chlorosilane	4478 (4281-6327)	3627 ÷ 1 = 3627	1 : 1	0.8 : 1

Table 1 was taken from AEGL, 2009 (data from Jean et al., 2006). This table reports the observed 1-hr LC_{50} values for HCl and mono-, di-, tri-, and tetrachlorosilanes. It also demonstrates that HCl can be used to estimate the LC_{50} values for chlorosilanes based on the molecular equivalents of chlorine present in the molecule. As the two columns to the right demonstrate, the predicted LC_{50}s, estimated based dividing the HCl LC_{50} by the number of chlorines present in the chlorosilane of interest are very similar to those measured in animals lethality studies. Values reported in the right most column are the ratio of the reported value to that of the predicted value, demonstrating that HCl can be used to conservatively estimate chlorosilane toxicity.

Weight of Evidence Evaluation

Possible Approaches

The available database for chlorosilanes is limited to some inhalation lethality studies and chemical knowledge (i.e., physical chemical properties and products of hydrolysis). With this amount of data, the calculation of an ESL could be based upon the N-to-L ratio, a surrogate, or a relative potency approach.

1. Surrogate Approach

Given the highly reactive nature of chlorosilanes, their toxicity will be largely driven by POE effects and that chlorosilanes hydrolyze to produce Cl^- and a silanol, HCL could serve as a reasonable surrogate for this group of chemicals based on MOA information. Since the chlorosilanes have a higher toxicity than that of the hydrolysis product silanols, and a lower toxicity than HCl, it is likely that Cl^- released during hydrolysis is the primary contributor to the toxicity of these chemicals (OECD, 2010; USEPA, 2009). Likewise, HCl appears to be slightly more toxic than monochlorosilanes, particularly those with alkyl substitution. Thus, HCl is an acceptable and conservative surrogate for chlorosilanes. Another advantage to using HCl as the basis for chlorosilanes is that the TCEQ has already published ESLs for HCl in a Development Support Document (DSD) that outlines how acute and chronic values were derived (TCEQ, 2014). This DSD is consistent with our guidelines and has been through a public review and comment period.

As mentioned above, the toxicity of chlorosilanes is proportional to the number of chlorine moieties on the silane (Table 1). Thus, ESLs for di-, tri-, and tetra chlorinated silanes were also based on the HCl surrogate, but were derived by the number of molar equivalents of Cl^- that come from the chlorinated silane of concern.

The acute ESL for HCl was derived from a study evaluating the effects of inhaled HCl on exercising asthmatics with the critical effects being upper and lower respiratory symptoms consistent with irritation and reduced lung function (Stevens et al., 1992). The POD of 1.8 ppm was identified as a free-standing NOAEL and was adjusted by an interspecies uncertainty factor of 3. After duration adjustment and uncertainty factor application, the final acute ESL for HCl was 190 µg/m^3 (130 ppb).

The HCl ESL serves as the basis for mono-chlorosilanes. To adjust for the molar equivalents of chlorine found in the di-, tri-, and tetrachlorosilanes, the HCl ESL is divided by 2, 3, and 4, respectively. Table 2 summarizes the ESLs for polychlorosilanes.

TABLE 2

Chlorinated Silanes	Acute ESLs	Chronic ESLs
HCl	190 µg/m³ (130 ppb)	7.9 µg/m³ (5.4 ppb)
Monochlorinated	190 µg/m³ (130 ppb)	7.9 µg/m³ (5.4 ppb)
Dichlorinated	95 µg/m³ (65 ppb)	4 µg/m³ (2.7 ppb)
Trichlorinated	63 µg/m³ (43 ppb)	2.6 µg/m³ (1.8 ppb)
Tetrachlorinated	48 µg/m³ (33 ppb)	2 µg/m³ (1.4 ppb)

There are no chronic human studies investigating the effects of HCl in humans that are suitable for ESL derivation. Animal studies are available and the observed adverse effect induced by chronic inhalation is applicable to human health. Sellakumar and colleagues (1985) exposed Sprague-Dawley rats to HCl for 6hr/day, 5days/week over the duration of the animals' life. A LOAEL of 10 ppm was identified based upon increased incidence of hyperplasia in the nasal mucosa, larynx, and trachea of HCl exposed rodents. Duration and dosimetric adjustments were made on the LOAEL to calculate an adjusted POD (POD_{ADJ}), which was subsequently reduced by a factor 100 to account for uncertainties (TCEQ, 2014). Using this approach, the long-term ESL for monochlorosilanes is 7.9 µg/m^3 (5.4 ppb). For di-, tri-, and tetrachlorosilanes, the long-term ESLs would be adjusted to account for the increased molecular equivalents of Cl, making the ESLs 4 µg/m^3 (2.7 ppb), 2.6 µg/m^3 (1.8 ppb), and 2 µg/m^3 (1.4 ppb), respectively (Table 2).

2. N-to-L Ratio Approach

The alternative approach for chlorosilanes is limited to the available lethality data for this group of chemicals. Lethality data can be adjusted by the N-to-L ratio (i.e., multiply the 4-hr LC_{50} by 8.3 x10 $^{-5}$) to calculate an acute ESL (Grant et al., 2007). Upon collection of LC_{50} values for a number of chlorosilanes, one observation is that the LC_{50} values vary from study to study. It is likely that with chemically labile substances, the experimental set up and analytical techniques used to determine the LC_{50} are critical for the generation of reliable data. While some LC_{50}s come from cited scientific literature, others were available on Material Safety Data Sheets (MSDS) where the source of the value

was undocumented. Data from documented sources with details regarding methods and experimental set up are preferred for the basis of ESL generation. Data from undocumented sources may be unreliable and certainly increase uncertainty. Jean et al. (2006) determined LC_{50}s for mono-, di-, tri-, and tetra-chlorosilanes. The intent of this study was to produce a LC_{50} prediction model for chlorosilanes. Given that data were collected in a common experimental set up (i.e., same exposure chamber, animal model, and laboratory) for several chlorosilanes, this study is an acceptable source of data for comparison of relative toxicity among polychlorosilanes and for N-to-L ratio calculations. The study reported the LC_{50} values for mono-, di, and trichlorosilanes. There is one value for tetrachlorosilane. The average of the LC_{50} measurements is calculated when more than one member was reported (e.g., average the four LC_{50}s reported for trichlorosilanes) to arrive at a single LC_{50} value for each group of polychlorosilanes. To derive an ESL using the N-to-L ratio approach, the mean 1-hr LC_{50} identified by Jean and colleagues (2006) needs to undergo duration adjustment using Haber's Rule to a 4 hr LC_{50} before the N-to-L ratio can be applied (Grant et al., 2007). It is assumed that lethality is both duration and concentration dependent, so duration adjustment was calculated where n=1 (ten Berge et al., 1986).

TABLE 3

Chemical	1-hr LC50 (ppm)	4-hr LC50 (ppm)	N-to-L (ppm)	ESL (ppb)
HCl	3627	907	0.075	75
Monochlorinated	4368	1092	0.091	91
Dichlorinated	1966	491	0.041	41
Trichlorinated	1396	349	0.029	29
Tetrachlorinated	1312	328	0.027	27

As can be seen in Table 3, the acute values would be slightly lower than those calculated from the surrogate approach with HCl. However, acute exposure to chlorosilanes is likely to have a MOA similar to that of HCl, i.e., direct reactivity causing respiratory irritation and cellular damage. Thus, while the N-to-L ratio yielded conservative results, the WOE suggests that the MOA for toxicity from short-term exposure is likely to be analogous to HCl. However, had HCl data not been available, it is reasonable to believe that the N-to-L ratio would have produced health protective screening values.

3. Relative Potency Approach

A final alternative approach to consider for acute and chronic ESL derivation is to conduct a relative potency approach. This approach estimates the toxicity of an LTD chemical in relation to that of an index chemical with better characterized toxicity. Figure 1 depicts the calculation used to arrive at the relative potency ratio.

FIGURE 1

$$\text{Relative Potency} = \frac{\text{Relevant Endpoint}_{\text{LTD Chemical}}}{\text{Relevant Endpoint}_{\text{Index Chemical}}}$$

In this case, the index chemical is HCl. The relative potency is calculated by taking the ratio of LC_{50} LTD/LC_{50} index and multiplying it by the reference chemical ESL (Table 4). Like the acute MOA, chronic chlorosilanes exposure is anticipated to have a similar effect to that of chronic HCl exposure. It is important to consider MOA in this case because it varies from chemical to chemical and with the duration of exposure. The MOA for cholorosilanes is similar to that of HCl, making the use of HCl as a surrogate defensible. Since the HCl ESL as a surrogate for the chronic chlorosilanes ESL, adjusted for molecular equivalents of Cl- is defensible.

TABLE 4

Chemical	LC50 ratio	Acute ESL (ppb)	Chronic ESL (ppb)
HCl	1	130	5.4
Monochlorinated	1.2	160	6.5
Dichlorinated	0.54	70	2.9
Trichlorinated	0.38	49	2.0
Tetrachlorinated	0.36	46	1.9

The relative potency approach interestingly yields ESL values that are also very similar to those produced by the N-to-L ratio and surrogate approaches. In this case, the similarity is likely the result of using a robust lethality study where LC_{50} values were conducted in the same laboratory and model system, making relative potency ratios more predictive and representative of the toxicity of the chlorosilanes that were tested, which was in part the goal of the study authors (Jean et al., 2006). It also illustrates the importance of study quality when conducting a WOE analysis to determine which LTD approaches to consider for ESL derivation. For chlorosilanes, a single, high quality lethality study along with chemical/physical properties provided adequate information to produce reasonable and scientifically defensible ESLs.

4. Selected Values

The surrogate approach was selected as the basis for all chlorosilanes. The use of HCl as a surrogate is scientifically-defensible because HCl is a data-rich, conservative substitute for chlorosilanes. Table 5 displays the chlorosilanes ESLs.

TABLE 5

Chlorinated Silanes	Acute ESLs	Chronic ESLs
Monochlorinated	190 µg/m³ (130 ppb)	7.9 µg/m³ (5.4 ppb)
Dichlorinated	95 µg/m³ (65 ppb)	4 µg/m³ (2.7 ppb)
Trichlorinated	63 µg/m³ (43 ppb)	2.6 µg/m³ (1.8 ppb)
Tetrachlorinated	48 µg/m³ (33 ppb)	2 µg/m³ (1.4 ppb)

It is important to note that while the surrogate approach was selected for chlorosilanes, the N-to-L ratio or the relative potency approaches would have also provided adequate values due to the quality and consistency observed in the lethality data, which was the basis of both. In this case, a surrogate was the favored approach because the MOA for acute and chronic toxicity for chlorosilanes is likely analogous to that of HCl, making the existing ESLs, which have be subjected to review and public comment the highest quality ESL available for chlorosilanes regulation.

Conclusions

- The surrogate approach was chosen for derivation of a generic ESL for monochlorosilanes.
- The ESL values derived using the N-to-L ratio and relative potency approaches were similar to those calculated as HCl-based surrogate values.
- The toxicity among polychlorosilanes was found to be directly proportional to the number of chlorine atoms on the silane of concern. Thus, a relative toxicity approach (i.e., account for Cl^- molar equivalents) was used for derivation of an ESL for di-, tri-, and tetra-chlorinated silanes.
- The proposed 1-hr, health-protective generic ESLs for chlorosilanes are:
    - Mono: 190 µg/m^3 (130 ppb)
    - Di: 95 µg/m^3 (65 ppb)
    - Tri: 63 µg/m^3 (43 ppb)
    - Tetra: 48 µg/m^3 (33 ppb)
- The long-term generic ESL for monochlorosilanes, 7.9 µg/m^3 (5.4 ppb), was based on HCl as a surrogate.
- The long-term generic ESL for HCl was adjusted by factors of 2, 3, and 4 as a relative potency approach for polychlorosilanes.
    - Mono: 7.9 µg/m^3 (5.4 ppb)
    - Di: 4 µg/m^3 (2.7 ppb)
    - Tri: 2.6 µg/m^3 (1.8 ppb)
    - Tetra: 2 µg/m^3 (1.4 ppb)
- Based on chemical and biological data, HCl is an appropriate surrogate for the chlorosilanes generic ESLs. The surrogate HCl is adequately representative of chlorosilanes based on MOA and a WOE approach. The resultant generic ESLs are anticipated to be conservative and subsequently health protective.

References

1. Acute Exposure Guidelines Levels (AEGLs) for selected chlorosilanes. NAC/Proposed 1: April 2009.

2. Grant RL, Kadlubar BJ, Erraguntla NK, Honeycutt M. 2007. Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. *Regul Toxicol Pharmacol*, 47:261-273.

3. Jean PA, Gallavan RH, Kolesar GB, Siddiqui WH, Oxley JA, Meeks RG. 2006. Chlorosilane acute inhalation toxicity and development of an LC50 prediction model. *Inhal Toxicol* 18:515-522.

4. Kizer KW, Garb LG, Hine CH. 1984. Health effects of silicon tetrachloride- report of an urban accident. *J Occup Med* 26:33-36.

5. Organisation for Economic Co-operation and Development (OECD). 2010. Screening Information Data Set (SIDS) Initial Assessment Profile: Alkyl chlorosilanes Category. Available from: http://webnet.oecd.org/hpv/UI/handler.axd?id=c6629ed7-47de-4e03-8180-cf9cca16be28

6. Sellakumar AR, Snyde CA, Solomon JJ, Albert RE. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. *Toxicol Appl Pharmacol* 81:401-406.

7. Stevens B, Koenig JQ, Rebolledo V, Hanley QS, Covert DS. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. *J Occup Med* 34:923-929.

8. ten Berge WF, Zwart A, Appelman LM. 1986. Concentration time mortality response relationship of irritant and systemically acting vapours and gases. *J Hazard Mater* 13:301-309.

9. Texas Commission on Environmental Quality (TCEQ). 2014. Development support document hydrogen chloride, CAS registry numbers: 7647-01-0.Texas Commission on Environmental Quality, Toxicology Division, Office of the Executive Director, available at: http://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/mar2014/hydrogen_chloride_7647-01-0_revised.pdf

10. Texas Commission on Environmental Quality (TCEQ). 2012. Guidelines to develop toxicity factors. RG-442.

APPENDIX C: Examples of ESL Derivation for Methoxysilanes

Example: Derivation of ESLs for Methoxysilanes

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Abstract

Methoxysilanes are used for coatings, adhesion promoters, crosslinkers, and water scavengers. These chemicals hydrolyze to release methanol and the associated silanols. For this group of chemicals, some chemical-specific data is available for tri- and tetramethoxysilanes. WOE analysis is used to determine which approach appears to be most appropriate and health protective. Acute studies investigating mono- and dimethoxysilane toxicity in animals are limited to lethality data or studies investigating toxicity via oral exposure. Due to hydrolytic instability, inhalation data are more appropriate. Thus, acute ESLs for mono- and dimethoxysilanes need to be derived via an approach for LTD chemicals. Chemical specific data are available for tri- and tetramethoxysilanes. Using available data, ESLs for mono-, di-, tri, and tetramethoxysilanes are derived using a combination of surrogates and chemical-specific data.

Introduction

Methoxysilanes undergo rapid (i.e., seconds to minutes) hydrolysis in the presence of water (Kallos et al., 1991) (Figure 1). The hydrolysis products, methanol and silanols, are expected based on the chemical structure of methoxysilanes at a ratio of the number of methoxy groups to the number of silanols (Witucki 1993). For example, dimethoxydimethylsilane (DMDMS) hydrolyzes quickly (i.e., half-life of < 0.6 hours) to form 2 moles methanol and 1 mole dimethylsilanediol (OECD, 2010). Depending on the pH and concentration of the substance, the resultant silanols may condense to form oligomers.

FIGURE 1

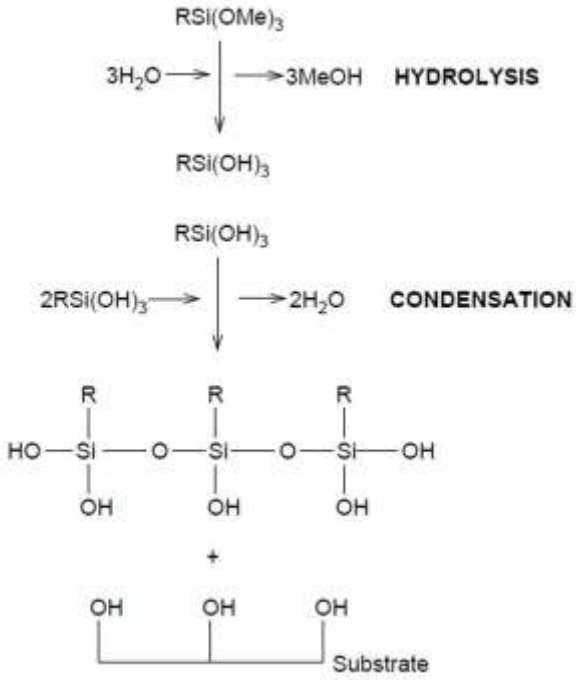

Figure 1 was adapted from a Silane Coupling Agent Guide produced by United Chemical Technologies.

Available data indicate that trimethoxysilane and tetramethoxysilane are of higher toxicity than can be attributed to exclusively to the molecular equivalents of methanol. The reason for this observed toxicity is unknown, but may be due to the fact that some silicon reaction product is systemically bioavailable from these chemicals. Since chemical-specific data are available, they were used to develop ESLs. Given the complexity of the methoxysilanes database, this example demonstrates the importance of WOE analysis for the selection of methodology utilized to develop ESLs for LTD chemicals.

Weight of Evidence Evaluation

Possible Approaches

The available database for methoxysilanes is limited to subchronic animal studies for a few members of this chemical group, lethality studies, and chemical knowledge. The majority of animal data were collected for subchronic exposure durations, limiting applicability to chronic ESLs. Therefore, the calculation of acute and chronic ESLs for these chemicals could be based upon POD/UFs, N-to-L ratio, relative potency, or surrogate approach. Importantly, due to the fact that data is available for only some members of this group, interpolation or an LTD approach of some type will be necessary.

1. Surrogate Approach

When considering the basic chemistry of these compounds, it is reasonable to hypothesize that acute toxicity could be caused by the methanol formed by the hydrolysis reaction, and thus could be similar to that seen following inhalation of methanol. Another important consideration is the hydrolysis half-life. If the hydrolysis half-life is longer than a few seconds to minutes, it is possible that both parent compound and hydrolysis products will be inhaled. Given the aforementioned hydrolytic instability, route-to-route extrapolation is not a favored approach due to acute toxicity being driven to an extent by portal-of-entry effects. Thus, the surrogate approach appears to be a scientifically-defensible choice.

The half-life of the methoxysilanes is longer than that of the chlorosilanes. The half-lives of trimethoxysilane and tetramethoxysilane are less than 1 minute in saline or 10% rat serum. In water, hydrolysis appears to be more dependent on chemical structure with half-lives ranging from minutes to seconds (tetramethoxysilane > methyltrimethoxysilane > trimethoxysilane) (Kallos et al., 1991). Silanols are considered less toxic than the methoxysilanes. However, the toxicity of silanols is poorly characterized. Likewise, the amount of silanols produced and their extent of condensation varies with ambient conditions, making derivation of ESLs challenging. The bioavailability of condensation products would be less than that of methanol, which has an abundant toxicity database. Thus, methanol is a reasonable surrogate for methoxysilanes.

Methanol is a respiratory irritant (Mann et al., 2002; Kawai et al., 1991). In 2014, the TCEQ published a DSD for methanol, which was subjected to external peer review and public comments (for details: http://www.tceq.state.tx.us/assets/public/implementation/tox/dsd/proposed/may13/methanol.pdf). Briefly, the acute methanol ESL was derived from an exposure study conducted in human subjects. The effects were described by the study authors as mild subclinical nasal inflammation as detected by increases in biomarkers of inflammation following a 203.5 ppm exposure for 4 hr (Mann et al., 2002). This value was used as a free-standing NOAEL since the increases in biomarkers associated with inflammation were not accompanied by subjective symptoms consistent with nasal irritation. The NOAEL was used as a point of departure (POD), which was not subjected to duration adjustment since respiratory irritation is considered to be driven by concentration only. Uncertainty factors were used to

adjust the POD to account for interhuman variability (10) and database uncertainty (2) due to the fact that the key study was considered to be of medium quality. The resultant reference value (13000 µg/m^3) was then converted to an ESL using a hazard quotient(HQ) of 0.3 to account for cumulative aggregate exposure, making the methanol ESL equal to 3900 µg/m^3 (3000 ppb) (TCEQ, 2014).

The chronic methanol ESL was derived from a study evaluating the effects of methanol exposure in an occupational setting (Kawai et al., 1991). Chronic methanol exposure induced nasal irritation in workers. A LOAEL of 459 ppm was identified as a POD and adjusted from intermittent daily occupation exposure to continuous exposure considered relevant to the general population (POD_{ADJ} = 163.93), which is consistent with TCEQ guidance (TCEQ, 2012, TCEQ, 2014). Uncertainty factors were applied to the POD_{ADJ} to account for the use of a LOAEL rather than a NOAEL as POD (UF_L= 3) and interhuman variance (UF_H= 10). The resultant chronic ESL (HQ = 0.3) is 2100 µg/m^3 (1600 ppb) (TCEQ, 2014).

Importantly, the database for methanol is considered medium to high quality. The data available for developing acute screening values for methoxysilanes is limited. Thus, filling data gaps using a data-rich chemical characterized by a high-quality study conducted in human subjects could be defensible, considering that methanol is a hydrolysis product of methoxysilanes. Table1 displays both acute and chronic methanol ESLs ranging from one molar equivalent to four molar equivalents. Insufficient data are available for the development of chronic ESLs for mono- and dimethoxysilanes. Thus, the chronic ESLs for these chemicals are based on extrapolation from methanol as a surrogate.

TABLE 1

Chemical	Acute ESL	Chronic ESL
Methanol	3900 µg/m^3 (3000 ppb)	2100 µg/m^3 (1600 ppb)
2 Molar Equivalents Methanol	1950 µg/m^3 (1500 ppb)	1050 µg/m^3 (800 ppb)
3 Molar Equivalents Methanol	1300 µg/m^3 (1000 ppb)	700 µg/m^3 (530 ppb)
4 Molar Equivalents Methanol	975 µg/m^3 (750 ppb)	525 µg/m^3 (400ppb)

In contrast, data are available for derivation of acute and chronic ESLs for tri-, and tetramethoxysilanes. A detailed description of chronic ESL calculations for tetramethoxysilane is available in Appendix D with a brief discussion in the following section.

2. Chemical-Specific Data Approach

Available data indicate that tri- and tetramethoxysilanes act as respiratory irritants and nephrotoxicants. The MOA for nephrotoxicity is unclear, but both the respiratory toxicity (i.e., lesions) and nephrotoxicity (i.e., calculi and renal dilation) are relevant to human health. As observable in Table 2, the database for methoxysilanes is of limited quality and/or quantity. The WOE indicates that the MOA of toxicities observed from long-term exposure are similar to that of methanol (i.e., respiratory irritation and lesions) with the exception of the observed nephrotoxicity, the dose-response relationship of which is not well-characterized. Methanol-induced nephrotoxicity is not generally associated with inhalation exposure and instead is generally associated with metabolic acidosis induced by large oral exposures (Verhelst et al., 2004). This evidence indicates that toxicities induced by chronic exposure to the tri- and

tetramethoxysilanes may be governed by MOA(s) that differ from methanol, making chemical-specific data preferable to the use of a surrogate.

Since data indicate that trimethoxy- and tetramethoxysilanes are of greater toxicity than what would be predicted using methanol as a surrogate (Table 2), chemical-specific data are preferred or substitution with a surrogate that could be assumed to be conservative. A NOAEL of 100 ppm, identified in a 90-day inhalation study in rats, was used as a subchronic POD to derive chronic toxicity factors for methyltrimethoxysilane (MTMS). A NOAEL of 10 ppm from a 28-day inhalation study in rats was used as either the subacute or subchronic POD to derive both acute and chronic toxicity factors for tetramethoxysilane (TetMS) (for details see Appendix D). The 90-day NOAEL for trimethoxysilane (TMS) (0.5 ppm) is much lower than the subchronic NOAEL (10 ppm) for tetramethoxysilane. The 90-day NOAEL of 0.5 ppm is also lower than a 9-day NOAEL (0.2 ppm) for TMS. Therefore, the 90-day NOAEL (0.5 ppm) was not appropriate for the derivation of toxicity factors for TMS. The 4-hr LC_{50} (60 ppm) for TMS, however, is almost the same as the 4-hr LC_{50} (63 ppm) for tetramethoxysilane. Thus, the long- and short-term ESLs for tetramethoxysilane are used as surrogate for TMS.

TABLE 2

Chemical	Study	POD (ppm)	Acute ESL	Chronic ESL	Notes
Monomethoxysilane	N/A	N/A	N/A	N/A	No studies available
Dimethoxysilane	N/A	N/A	N/A	N/A	No studies available
Methyltrimethoxysilane (MTMS)	90-day rat	100	N/A	330 µg/m³ (60 ppb)	90-day study not appropriate for acute ESL calculation
Trimethoxysilane (TMS)	90-day rat	0.5	N/A	**Not Used**	Study results inconsistent and possibly unreliable ESL not derived from this study
Tetramethoxysilane (TetMS)	28-day rat	10	360 µg/m³ (60 ppb)	36 µg/m³ (6 ppb)	Study could be used for both chronic and acute ESL derivation

3. N-to-L Ratio Approach

Since some lethality data is available, the N-to-L ratio approach is a reasonable means of calculating an acute ESL. Table 3 depicts the available lethality data, which unfortunately were not available in a single study as the data were for the chlorosilanes, and corresponding N-to-L ratios. The N-to-L ratio is calculated by adjusting all observed LC_{50}s to a 4-hr value using Haber's rule as modified by ten Berge. The 4-hr value is multiplied by the N-to-L ratio (8.3×10^{-5}) to generate the final ESL value (Grant et al., 2007).

TABLE 3

Chemical	Reported LC50 (ppm)	4-hr LC50 (ppm)	N-to-L (ppm)	Acute ESL (ppb)
Methanol (MeOH)	145000 (1 hr)	64000	5.3	5300
Dimethoxydimethylsilane (DMDMS)	ND	> 4300	0.36	360
Trimethoxymethylsilane (MTMS)	> 7640 (6 hr)	> 8700	0.72	720
Trimethoxysilane (TMS)	154 (1 hr)	60	0.005	5
Tetramethoxysilane (TetMS)	ND	63	0.0052	5.2

A weakness of the N-to-L ratio approach is that it can only be used to calculate acute ESLs. Furthermore, lethality data originating from different studies may vary. However, the cause of the variance (e.g., experimental conditions, GLP or non-GLP study, animal model, etc.) is often not identifiable. Such variance affects confidence in the database. If estimated lethality values are considered unreliable due to some level of uncertainty, the N-to-L ratio approach is considered a less desirable approach. Variance in lethality data can also affect the relative potency approach because significant variance among studies may result in lethality being unreliable for determining relative potency among chemicals of concern. In this case, it is unlikely that the variance in observed toxicity is simply limited to some form of variance due to the magnitude of variance between methoxysilanes. Available data indicate that toxicity of methoxysilanes, relative to methanol (MeOH), is as follows:

Based on the available lethality data, the ESL for dimethoxysilanes would be 360 ppb, using the N-to-L ratio, which is less than the value derived using methanol as a surrogate (800 ppb). No data for monomethoxysilanes lethality was found. Lethality data for trimethoxysilanes was variable (i.e., 60 ppm for TMS vs. > 8700 ppm for MTMS). However, it is likely that the 60 ppm value for TMS is more reliable due to its use in an AEGL document, which selects the highest quality studies (e.g., GLP) as the basis for AEGL values. Likewise, the additional methyl group on the MTMS may impact toxicity. While the reported lethality data are variable, to a certain extent, they indicate that certain members of the methoxysilanes family are significantly more toxic than methanol, suggesting that for these chemicals the use of methanol as a surrogate is not conservative or appropriate. This data would indicate that while DMDMS and MTMS could be 7-15 times more toxic than methanol, which would not be predicted from a molar equivalent of methanol standpoint. Unfortunately, since the LC50s for DMDMS and MTMS are reported as being greater than a tested exposure concentration, the exact LC50 is unknown and could be significantly higher than the reported value. From a WOE perspective, a relative toxicity approach is more defensible for these chemical than a surrogate approach using methanol due to the possibility that these methoxysilanes (i.e., DMDMS and MTMS) are more toxic than methanol. It is possible that at lower exposures, governed by different MOA, the potency of methoxysilanes would be different. However, there is no available data to address this uncertainty.

4. Relative Potency Approach

Data available to conduct a relative potency approach is limited to lethality data for acute ESL generation. The acute generic ESLs for LTD methoxysilanes were estimated by adjusting the index chemical (methanol) 4-hr LC_{50} value by the relative potency factor derived by the following equation (TCEQ, 2012):

$$\text{Relative Potency} = \frac{\text{Relevant Endpoint (4hr LC50)}_{\text{LTD methoxysilane}}}{\text{Relevant Endpoint (4hr LC50)}_{\text{Index Chemical (methanol)}}}$$

$$\text{Generic ESL}_{\text{LTD Chemical}} = \text{ESL}_{\text{Index Chemical}} \times \text{Relative Potency}$$

Table 4 summarizes generic ESLs derived by the relative potency approach by calculation relative to the methanol ESL.

TABLE 4

Chemical	4-hr LC50 (ppm)	Relative Potency Ratio	Acute ESL (ppb)	Chronic ESL (ppb)
Methanol (MeOH)	64000	1	3000	1600
Dimethoxydimethylsilane (DMDMS)	> 4300	0.067	200	100
Methyltrimethoxysilane (MTMS)	> 8700	0.14	420	220
Trimethoxysilane (TMS)	60	0.0009	2.7	1.4
Tetramethoxysilane (TetMS)	63	0.001	3	1.6

Based on the fact that TMS and TetMS have LC_{50} values that are essentially the same (i.e., relative potency of 0.95 TMS to 1 TetMS), it is reasonable to use TetMS as a surrogate for TMS given that TetMS ESLs are based upon chemical-specific data.

5. Selected Values

The WOE analysis indicates that a number of methods would be recommended for derivation of ESLs for methoxysilanes. Based on our knowledge of potency among methoxysilanes and available MOA data, a combination of approaches was used, including the surrogate approach, relative potency/toxicity approach, and chemical-specific data. Given that ESLs derived from chemical-specific studies (MTMS and TetMS) are lower than those derived using methanol as a surrogate, methanol was not selected as surrogate for methoxysilanes. Instead, methanol was used as an index chemical for relative potency comparison. Since no acute or chronic data was available for monomethoxysilanes, DMDMS was used as a surrogate for this group of chemicals. The use of DMDMS is defensible because toxicity appears to increase with methoxylation. Thus, DMDMS would likely be a conservative surrogate compared to methanol.

Chemical-specific ESLs were directly used for MTMS and TetMS, respectively. Furthermore, the lethality data for trimethoxysilanes was variable (i.e., 60 ppm for TMS vs. > 8700 ppm for MTMS), the derived ESLs for MTMS was not selected as a surrogate for other trimethoxysilanes as the WOE indicated that TMS was of greater toxicity than MTMS. Since the 4-hr LC_{50} (60 ppm) for TMS is closer to that (63 ppm) for TetMS, both the short- and long-term ESLs derived for TetMS were conservatively selected for TMS. Table 5 summarizes ESLs derived for methoxysilanes, which represent a combination of the surrogate approach, relative potency approach and POD/UFs calculations from chemical-specific studies. In all cases, the priority was derivation of a health-protective value that prevented a number of adverse health effects.

TABLE 5

Chemical	Acute ESL (ppb)	Basis	Chronic ESL (ppb)	Basis
Methanol (MeOH)	3000	MeOH DSD	1600	MeOH DSD
Monomethoxysilane (MMS)	200	Surrogate (DMDMS)	100	Surrogate (DMDMS)
Dimethoxydimethylsilane (DMDMS)	200	Relative Potency (MeOH)	100	Relative Potency (MeOH)
Methyltrimethoxysilane (MTMS)	420	Relative Potency (MeOH)	60	Chemical-Specific
Trimethoxysilane (TMS)	60	Surrogate (TetMS)	6	Surrogate (TetMS)
Tetramethoxysilane (TetMS)	60	Chemical-Specific	6	Chemical--Specific

Conclusions

- The WOE analysis resulted in the use of a combination of approaches for methoxysilanes. Strengths and uncertainties associated with given approaches are displayed in Table 6.

TABLE 6

Approach	Strengths	Uncertainties	Alternatives
Surrogate	Fast, minimal resources Use data-rich chemical (e.g., MeOH) Applicable to acute and chronic ESLs	Can not apply to all candidate LTD silanes Other hydrolysis products (silanols) not considered Limited chemical specific data No human data May not be protective for certain methoxysilanes	Select another Surrogate N-to-L Ratio* Relative Potency/Toxicity Category TOC*
N-to-L Ratio	Fast, minimal resources Conservative Applicable when data are limited to lethality No need to compare to other chemicals	Study quality may be unreliable or inconsistent No human data Interspecies variance Limited MOA information Can only derive acute ESLs	Surrogate Relative Potency/Toxicity Category TOC*
Relative Potency/Toxicity	Chemical-specific data comparison Index chemical has reliable toxicity factors for comparison Can be used for acute and chronic	Variance in index chemical(s) selection Study quality variance Interspecies variance No human data Limited MOA information Limited chronic toxicity data Time consuming	Surrogate N-to-L Ratio* Category TOC*
Chemical-Specific Data	Chemical-specific	Study quality No human data Interspecies variance Limited MOA information	Surrogate N-to-L Ratio* Category TOC*

*Acute evaluation only

- The surrogate approach (as DMDMS) was chosen for derivation of generic acute and chronic ESLs for monomethoxysilanes.

- Chemical-specific acute and chronic ESLs were derived for tetramethoxysilane (TetMS).

- Chemical-specific data were used to derive a chronic ESL for methyltrimethoxysilane (MTMS).
- TetMS ESLs were used as surrogate for trimethoxysilane (TMS) on the basis of relative potency.
- The surrogate approach using methanol was applied for monomethoxysilane due to lack of data for this chemical.
- The relative potency approach was used for dimethoxydimethylsilane (DMDS) and methyltrimethoxysilane (MTMS) with methanol serving as an index chemical.
- Acute toxicity for methoxysilanes is similar to that of methanol (i.e., respiratory irritation and cellular damage). The WOE indicates similar MOAs for these chemicals, which supports the use the relative potency approach (i.e., relative to methanol) for monomethoxysilanes, dimethoxysilanes (i.e., DMDMS), and MTMS.
- The proposed 1-hr, health-protective generic ESLs for methoxysilanes are (refer to Table 5 in Appendix C):
    - Mono: 200 ppb, as surrogate to DMDMS
    - Di: 200 ppb, as DMDS relative potency to MeOH
    - Tri (excluding MTMS): 360 µg/m^3 (60 ppb), as TetMS
    - Potency relative to methanol was used for MTMS: 420 ppb
    - Tetra: 360 µg/m^3 (60 ppb), as TetMS
- The long-term generic ESL for methoxysilanes are based on methanol adjusted by factors of 2, 3, or from chemical-specific data (refer to Table 2 in Appendix C).
    - Mono: 100 ppb, as surrogate to DMDMS
    - Di: 100 ppb, as relative potency to MeOH
    - Tri (excluding MTMS): 36 µg/m^3 (6 ppb), as TetMS
    - The derived chronic ESL for MTMS is 360 µg/m^3 (60 ppb)
    - Tetra: 36 µg/m^3 (6 ppb), as TetMS

References

1. Grant RL, Kadlubar BJ, Erraguntla NK, Honeycutt M. 2007. Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. *Regul Toxicol Pharmacol*, 47:261-273.

2. Kallos GJ, Tou JC, Malczewski RM, Boley WF. 1991. Stability studies of alkoxysilanes in aqueous media. *Am Ind Hyg Assoc J*, 52: 259-62.

3. Kawai T, Yasugi T, Mizunuma K, Horiguchi S, Hirase Y, Uchida Y, Ikeda M. 1991. Methanol in urine as a biological indicator of occupational exposure to methanol vapor. *Int Arch Occup Environ Health*, 63:311-8.

4. Mann WJ, Muttray A, Schaefer D, Klimek L, Faas M, Konietzko J. 2002. Exposure to 200 ppm of methanol increases the concentrations of interleukin-1beta and interleukin-8 in nasal secretions of healthy volunteers. *Ann Otol Rhinol Laryngol* 111:633-8.

5. Organisation for Economic Co-operation and Development (OECD). 2010. Screening Information Data Set (SIDS) Initial Assessment Profile: Dimethoxydimethylsilane. Available from: http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?id=06b66bbe-8dfd-4346-8379-3d07ed5202d1

6. Texas Commission on Environmental Quality (TCEQ). 2014. Development support document methanol, CAS registry numbers: 67-56-1. Texas Commission on Environmental Quality, Toxicology Division, Office of the Executive Director, available at: http://www.tceq.state.tx.us/assets/public/implementation/tox/dsd/proposed/may13/methanol.pdf

7. Texas Commission on Environmental Quality (TCEQ). 2012. Guidelines to develop toxicity factors. RG-442. Available at: http://www.tceq.texas.gov/publications/rg/rg-442.html

8. Verhelst D, Moulin P, Haufroid V, Wittebole X, Jadoul M, Hantson P. 2004. Acute renal injury following methanol poisoning: analysis of a case series. *Int J Toxicol* 23:267-73.

9. Witucki GL. 1993. A Silane Primer: Chemistry and Applications of Alkoxy Silanes. *J. of Coatings Technology*, 65:57-60.

APPENDIX D: Chronic ESL Derivation for Methoxysilanes

Methyltrimethoxysilane (MTMS)

No acute inhalation toxicity studies were reported.

A subchronic inhalation toxicity study in rats was reported (OECD 2009), MTMS was exposed (whole body) to 10 rats/sex/concentration at ca. 0.14, 0.56, 2.2 and 8.9 mg/L, for 6 hr/day, 5 days/week for 90 days. A NOAEL of 0.56 mg/L (100 ppm) and a LOAEL of 2.2 mg/L/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. The subchronic POD of was then adjusted from discontinuous exposure (6 hr/day for 5days/week) to continuous exposure concentration. The POD_{ADJ} of 17.8 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). MTMS was considered Category 3 vapor (systemic effects), so the POD_{ADJ} was adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}) using the following equation:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

Since the measured blood/air partition coefficients in the rat ($(H_{b/g})_A$) and human ($(H_{b/g})_H$) for MTMS are not available, a default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A/(H_{b/g})_H$) (TCEQ 2012). The resulting subchronic POD_{HEC} from the POD_{ADJ} of 17.8 ppm is 17.8 ppm. The POD_{HEC} was then used to derive chronic ReV and ESL by applying the following UFs:

- 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 1 was considered appropriate to account for the use of a subchronic study due to MTMS has a short hydrolysis half-life of 2.2 h and a log K_{ow} of -0.67. Therefore, chronic effects would not be expected to differ significantly from subchronic effects;
- a UF_D of 3 was used because only one animal species was studied. Confidence in the database is considered medium to low because only one animal species was used in inhalation bioassays. The total UF = 90.

Chronic ReV = $POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D)$
= 17.8 ppm / (10 x 3 x 1 x 3)
= 0.198 ppm
= 200 ppb or 1,100 µg/m^3

The chronic ESL of 60 ppb (330 µg/m^3) was set based on the chronic ReV multiplied by a HQ of 0.3.

Trimethoxysilane (TMS)

TMS (or methyl silicate) undergoes rapid hydrolysis in water; the half-life at pH 7 and 2°C is < 0.3 minutes. Hydrolysis of TMS expected to produce 3 moles of methanol and 1 mole of silanetriol (OECD, 2007). The data on TMS were limited. No reproductive or developmental toxicity studies have been conducted with TMS. A GLP LC_{50} study was conducted by Union Carbide (Nachreiner and Dodd 1988, as cited in AEGL 2007).

Several inhalation repeated-dose studies of various durations have been conducted in rats and other mammals with TMS (OECD 2007). Union Carbide (1991, as cited in AEGL 2007) conducted an inhalation study exposing Fisher 344 rats to 0, 0.2, 1, or 5 ppm TMS vapor for 6 hr/day for 9 days over an 11-day 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 for laryngitis, weight loss, increased lung weight, and bronchopneumonia were identified. In a GLP 4-week rat study, 10 SD rats/sex/exposure level were exposed 7 hr/day, 5 days/week, for 4 weeks to TMS at concentrations of 0, 0.5, 5, or 10 ppm (Breckenridge et al. 1980, as cited in AEGL 2007). In animals 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. No signs of systemic toxicity were observed and histopathological changes were seen only in the respiratory tract (the site of contact).

OECD (2007) reports that exposure of rats to TMS vapor at much lower concentrations of 0.02, 0.1, or 0.5 ppm for 90 days, followed by a 4-week recovery period produced no exposure-related effects in the biologic parameters monitored during this study. The NOAEL in this 90-day inhalation study with rats was determined to be at least 0.5 ppm.

The subacute NOAEL of 0.2 and 0.5 ppm identified respectively from the Union Carbide (1991) and Breckenridge et al. (1980) studies were at or lower than a NOAEL of 0.5 ppm from a 90-d subchronic study (see below) and thus, were not used to derive acute toxicity factors. The NOAEL of 0.5 ppm identified from the 90-day subchronic study was a free-standing NOAEL. As indicated in the OCED report, the NOAEL was at least 0.5 ppm. Given that the 4-hr LC_{50} (60 ppm) for TMS is almost the same as the 4-hr LC_{50} (63 ppm) for tetramethoxysilane, and that the subchronic NOAEL (10 ppm) for tetramethoxysilane is much higher than the 90-day NOAEL (0.5 ppm) for TMS, the 90-day NOAEL of 0.5 ppm was not used to derive toxicity factors for TMS. For these reasons, the short- and long-term ESLs for tetramethoxysilane are used as surrogate for TMS. Table 1 (below) summarizes the lethality, subacute and subchronic inhalation toxicity data for TMS.

TABLE 1

4-hr LC_{50}	**9-day NOAEL**	**9-day LOAEL**	**4-week NOAEL**	**90-day NOAEL**
60 ppm	**0.2 ppm**	**1 ppm**	**0.5 ppm**	**0.5 ppm (free-standing)**

Tetramethoxysilane (TetMS)

Like TMS, tetramethoxysilane is expected to undergo rapid hydrolysis in water to produce 4 moles of methanol and 1 mole of silanetriol. In a subchronic inhalation study, Kolesar et al. (1989, as cited in AEGL 2007 and ACGIH 2007) exposed ten SD rats/sex/group to tetramethoxysilane concentration of 0,

1, 5, or 10 ppm (Phase 1) and 0, 15, 30 or 45 ppm (Phase 2) 6 hr/day, 5 days/week for 28 days. 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. The males exposed to 15 ppm had only a decrease in total protein. No microscopic lesions were found in the respiratory tract of rats at 1, 5 or 10 ppm. However, at ≥ 15 ppm, respiratory tract and corneal lesions were observed. Signs of toxicity (upper respiratory tract, bronchiolar, and inflammatory lesions) were dose-dependent and began at 15 ppm. A NOAEL of 10 ppm and a LOAEL of 15 ppm were identified from this subchronic study. The NOAEL of 10 ppm was used as either the subacute or subchronic POD to derive both acute and chronic toxicity factors.

Derivation of Acute Toxicity Factors

The subacute POD of 10 ppm was then adjusted from 6-hr exposure to 1-hr exposure concentration using Haber's rule as modified by ten Berge with a default value of "n"=3 (TCEQ 2012). The POD_{ADJ} of 18.2 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). Tetramethoxysilane was considered Category 1 vapor (respiratory lesions, a POE effect), so the POD_{ADJ} was adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}) using a default value of one as RGDR for the extrathoracic region (i.e., $RGDR_{ET} = (V_E/SA_{ET})_A / (V_E/SA_{ET})_H$).

The resulting subacute POD_{HEC} from the POD_{ADJ} of 18.2 ppm is 18.2 ppm. The POD_{HEC} was then used to derive acute ReV and ESL by applying the following UFs:

- 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. Confidence in the database is considered medium to low because only one animal species was used in inhalation bioassays. The total UF = 90

Acute ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 18.2 ppm / (10 x 3 x 3)
= 0.202 ppm
= 200 ppb or 1,200 µg/m^3

The acute ESL of 60 ppb (360 µg/m^3) was set based on the acute ReV multiplied by a HQ of 0.3.

Derivation of Chronic Toxicity Factors

The subchronic POD of 10 ppm was then adjusted from discontinuous exposure (6 h/d for 5d/week) to continuous exposure concentration. The corresponding POD_{ADJ} of 1.79 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). Tetramethoxysilane was

considered Category 1 vapor (respiratory lesions, a POE effect), so the POD_{ADJ} was adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}) using a default value of one as RGDR for the extrathoracic region (i.e., $RGDR_{ET} = (V_E/SA_{ET})_A / (V_E/SA_{ET})_H$).

The resulting subchronic POD_{HEC} from the POD_{ADJ} of 1.79 ppm is 1.79 ppm. The POD_{HEC} was then used to derive acute ReV and ESL by applying the following UFs:

- 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 1 instead of 10 was used account for the use of a subchronic study because tetramethoxysilane is expected to rapid hydrolyzed and the critical effect is respiratory tract lesions (POE effect) and a log K_{ow} of -0.67. Therefore, chronic effects would not be expected to differ significantly from subchronic effects;
- a UF_D of 3 was used because only one animal species was studied. Confidence in the database is considered medium to low because only one animal species was used in inhalation bioassays. The total UF = 90

Chronic ReV = $POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D)$
= 1.79 ppm / (10 x 3 x 1 x 3)
= 0.02 ppm
= 20 ppb or 120 µg/m^3

The chronic ESL of 6 ppb (36 µg/m^3) was set based on the chronic ReV multiplied by a HQ of 0.3.

Dimethoxydimethylsilane (DMDMS)

DMDMS undergoes rapid hydrolysis in water (i.e., half-life of < 0.6 hours at pH 7 and 25°C) to form 2 moles methanol and 1 mole dimethylsilanediol (OECD, 2010). The 4-hr inhalation LC_{50} for DMDMS in rats is > 4300 ppm (NTIS, OTS0539962).The oral (gavage) LD_{50} in male and female rats of DMDMS was 4235 mg/kg conducted in accordance with OECD TG 401. Central nervous system effects were the predominant clinical sign of toxicity. In a combined repeated-dose/reproductive/developmental toxicity screening test, DMDMS was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250 and 1000 mg/kg bw/day for 28-29 days. A NOAEL of 250 mg/kg/d and a LOAEL of 1,000 mg/kg/d for systemic toxicity were identified from this study (OECD, 2010). No additional studies investigating the toxicity this chemical were found. Due to lack of inhalation data for this chemical, a surrogate approach will be used for ESL generation.

References

1. Acute Exposure Guidelines Levels (AEGLs) for trimethoxysilane (CAS No. 2487-90-3) and tetramethoxysilane (CAS No. 681-84-5). NAC/Proposed 1: November 2007.

2. ACGIH 2007. (American Conference of Governmental Industrial Hygienists, Inc.). TLVs and BEIs. Threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH: Cincinnati.

3. Breckenridge C, Lulham G, Bier C, Berry G, Qureshi S, Procter B. 1980. An evaluation of the potential toxicity of inhaled trimethoxysilane in the albino rat. Bio-Research Laboratories, Project No. 9331, p. 1-168.

4. Kolesar GB, Siddiqui WH, Geil RG, Malczewski RM, Hobbs EJ. 1989. Subchronic inhalation toxicity of tetramethoxysilane in rats. *Fundamental Applied Toxicology* 13:285-95.

5. Nachreiner DJ and Dodd DE. 1988. Trimethoxysilane: acute vapor inhalation toxicity study in rats. Project Report No. 50-147. Union Carbide- Bushy Run Research Center. P. 1-38.

6. Organisation for Economic Co-operation and Development (OECD). 2010. Screening Information Data Set (SIDS) Initial Assessment Profile: Dimethoxydimethylsilane. Available from: http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?id=06b66bbe-8dfd-4346-8379-3d07ed5202d1

7. Organisation for Economic Co-operation and Development (OECD). 2009. Screening Information Data Set (SIDS) Initial Assessment Profile: Methyltrimethoxysilane. Available from: http://webnet.oecd.org/HPV/ui/SIDS_Details.aspx?id=a8cb7340-f105-4b1d-a1f6-61e4a34c2929

8. Organisation for Economic Co-operation and Development (OECD). 2007. Screening Information Data Set (SIDS) Initial Assessment Profile: Trimethoxysilane. Available from: http://webnet.oecd.org/HPV/ui/SIDS_Details.aspx?id=a0056bc2-89f5-4304-b1db-6df1334dc9ac

9. Texas Commission on Environmental Quality (TCEQ). 2012. Guidelines to develop toxicity factors. RG-442. Available at: http://www.tceq.texas.gov/publications/rg/rg-442.html

10. Union Carbide. 1991. Letter from Union Carbide Chem. and Plast. C to USEPA containing preliminary lab findings from immune system toxicology study with attachments. EPA Document No. 89-910000201. Microfiche No. OTS0204852-4.