Weight of Evidence (WOE) Approach for Chemicals with Limited Toxicity Data (LTD)

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Beyond Science and Decisions Workshop Case Study

Problem Formulation

- The TCEQ is required to derive effects screening levels (ESLs) for all chemicals permitted in the state
- We have formal guidelines detailing the approach to derivation of toxicity factors, including ESLs for chemicals with limited toxicity data
- The TCEQ guidelines discuss potential methods
- These methods are broad and do not offer a detailed description of how different lines of evidence for chemicals with limited toxicity data is weighted

Effects Screening Levels (ESLs)

- Chemical-specific air concentrations set to protect human health and welfare

  - ❖ Short-term ESLs are based on data concerning acute health effects [1-hr intermittent], odor/nuisance potential, and vegetative effects

  - ❖ Long-term ESLs [annual] are based on data concerning chronic non-carcinogenic and/or carcinogenic health effects and vegetative effects

WOE Methods

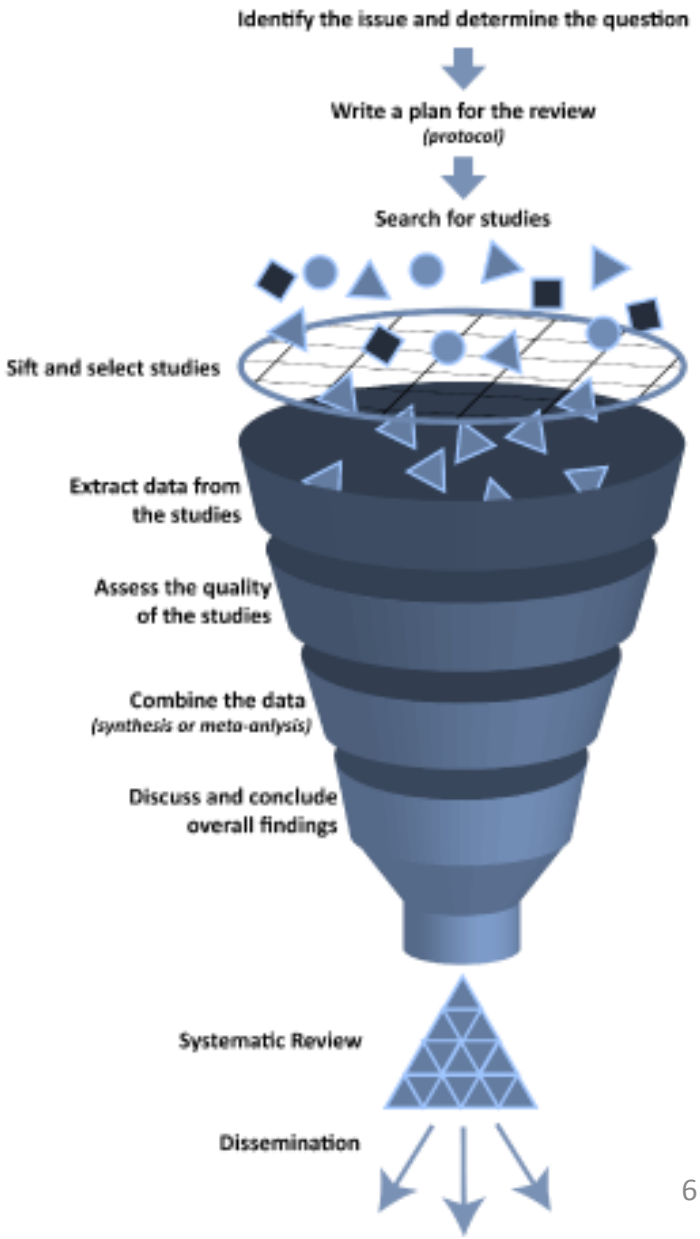
- Systematic narrative review
- Criteria-based causal inference
- Statistical technique (e.g., meta-analysis)
- Hierarchy of data types
- Mixed approach (epi and tox)

Narrative Review

- Statement of Purpose
- Literature search methods
- Inclusion and exclusion criteria for reviewed studies
- Methods for summarizing evidence
- Methods for interpreting evidence
- Criteria for conclusion
- Recommendation
- Goal: to describe state of the science

Hill Criteria for Causation

- Consistency
- Strength
- Dose-response
- Temporality
- Experimentation
- Specificity
- Biological plausibility
- Coherence
- Analogy



Potential Problems with ESLs for LTD Chemical

- Lack of transparency
  - Need to describe how data was chosen
  - Need to describe how data was interpreted
- Variance in definitions and or applications of data
  - Harmonization of terminology and approaches
- Different weighting systems
  - Harmonize approaches or generate a framework that clearly describes data selection and hierarchy
- Role of scientific or professional judgment
  - Varies from scientist to scientist but needs to be communicated

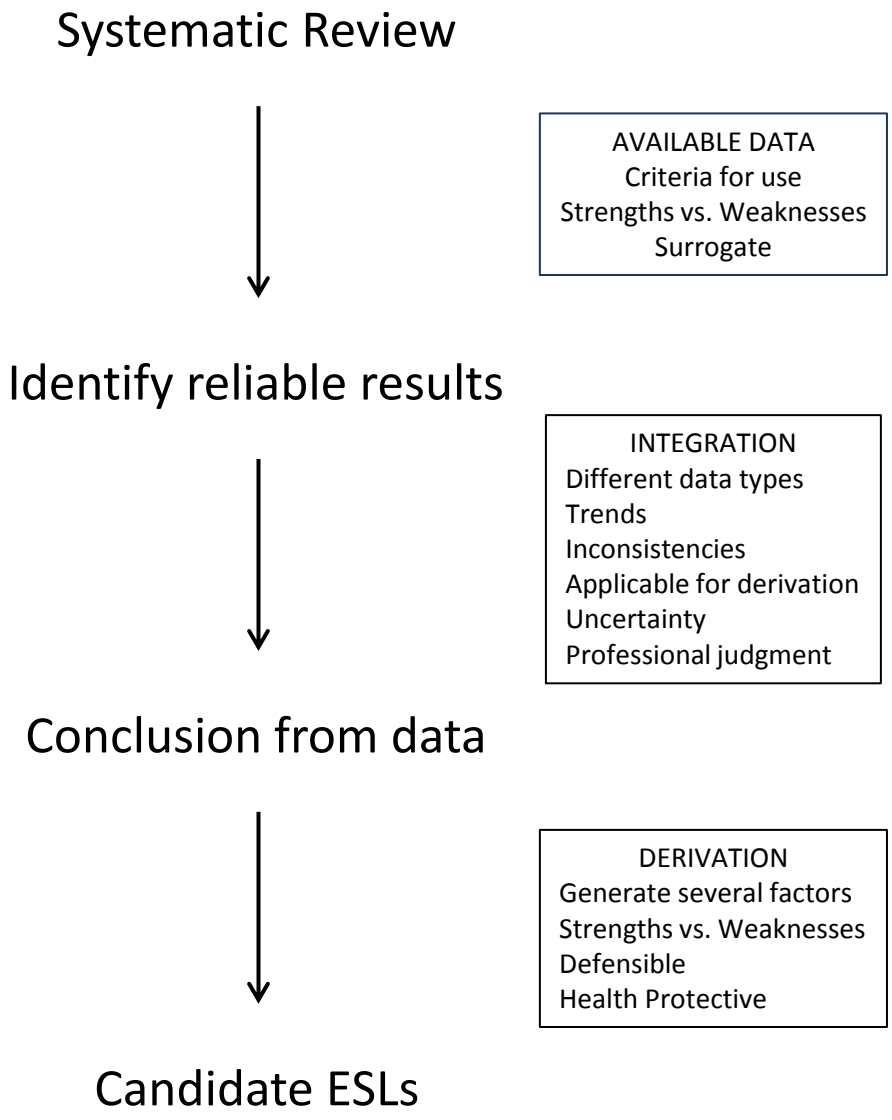
The Not so Simple Solution…

- Formalized methods reduce subjectivity and variance
- Increase transparency
- Expert judgment will increase as available data decreases
- Communication and clarity are critical

Goals of this Case Study

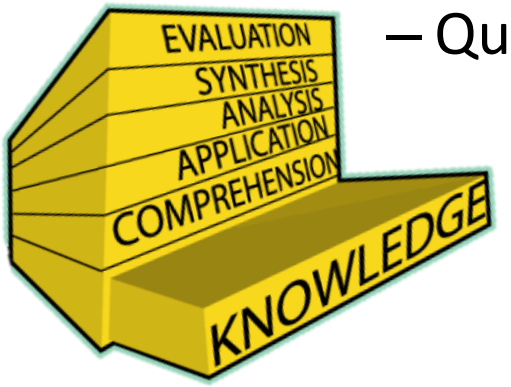
- To describe the *meaning* of Weight of Evidence (WOE) and *methods* used to evaluate available information and derive ESLs for LTD chemicals
- The generate a scientifically-defensible WOE framework approach that can be used by risk assessors evaluating LTD chemicals

Synthesis of Evidence



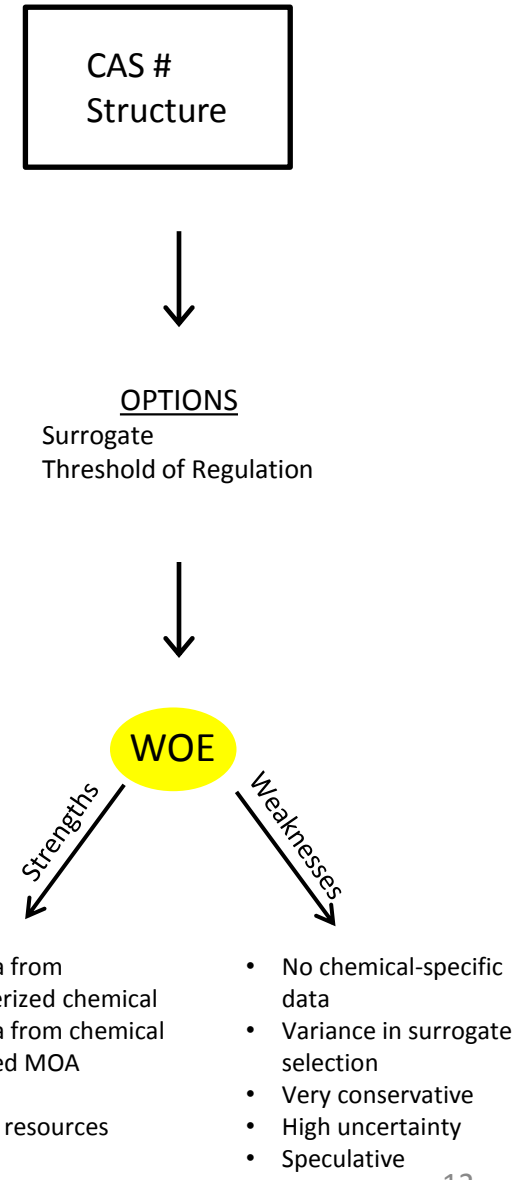
Current Methods for LTD Chemicals

- The TCEQ Guidelines for derivation of Toxicity Factors recommends several methods
  - Route-to-route Extrapolation
  - Relative Toxicity/Relative Potency Approach
  - NOAEL-to-LC_{50} Ratio (Grant et al., 2007)
  - NOAEL or LOAEL adjusted with a safety factor
  - Threshold of Regulation
  - Read-across tables
  - Quantitative Structure-Activity Relationship

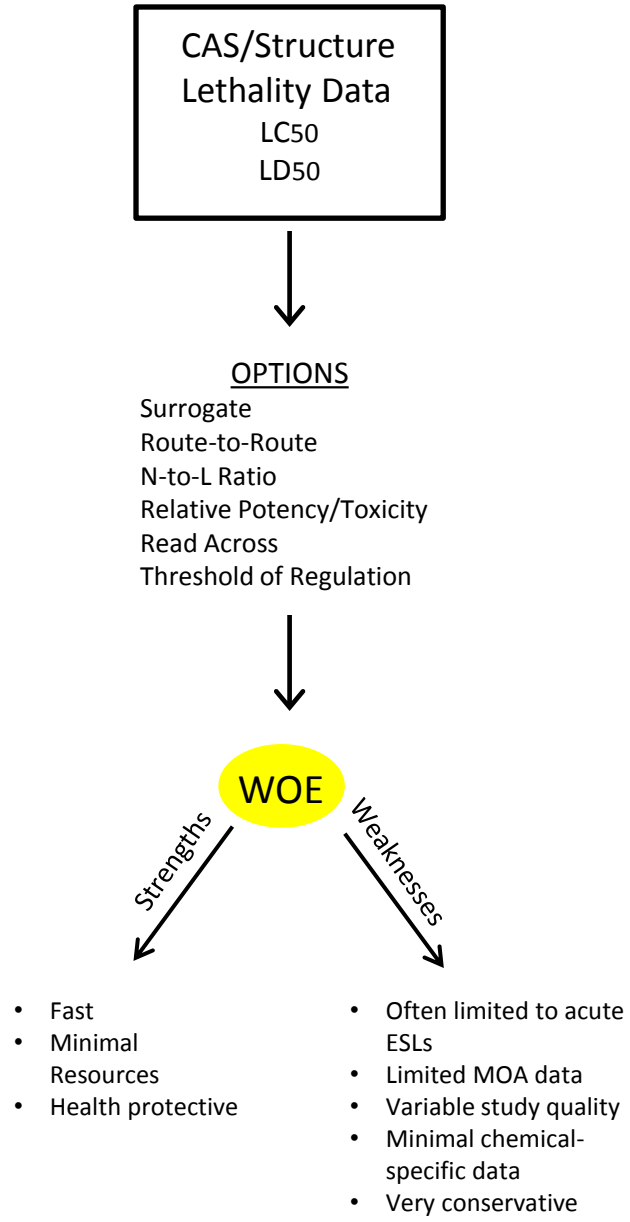


A Framework Approach

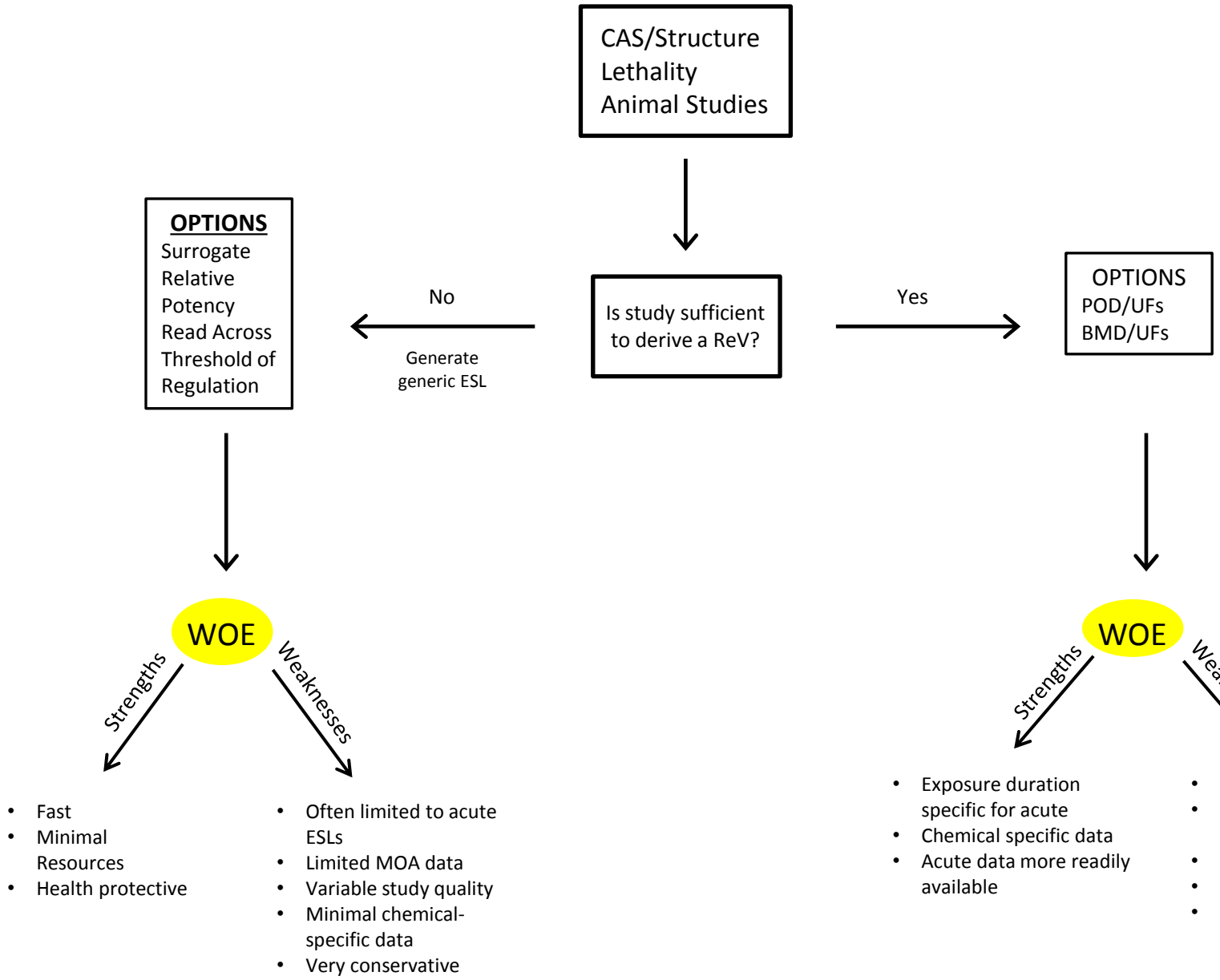
- Consider available data
- Identify possible approaches
- More than one option?
- Strengths
- Uncertainties or weaknesses
- WOE Analysis



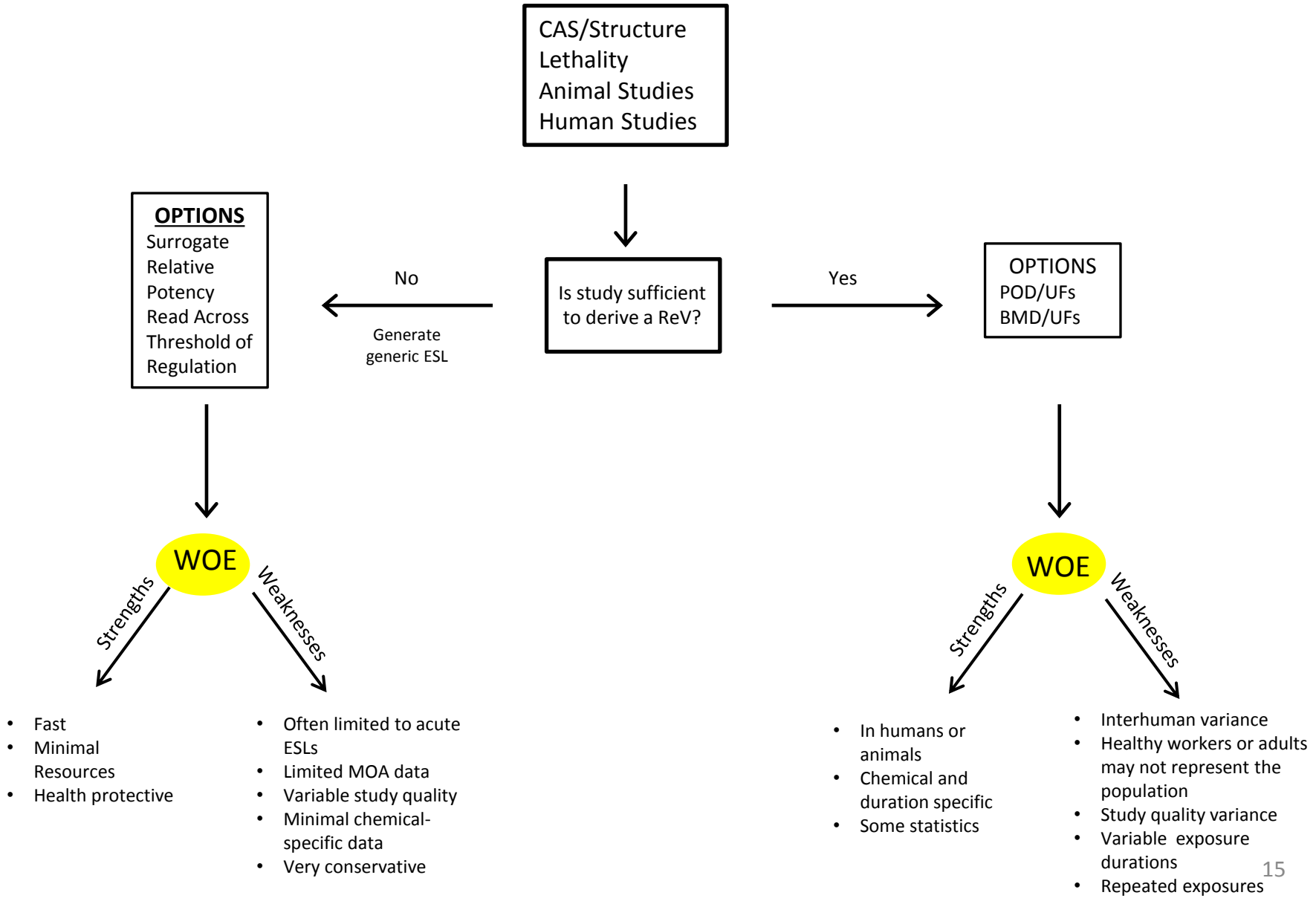
A Framework Approach



A Framework Approach



A Framework Approach



Approach	Strengths	Uncertainties	Alternatives
Surrogate	Fast, minimal resources Data-rich chemicals can be surrogates Can apply to both acute and chronic ESLs Can apply to many candidate LTD silanes	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 silane groups	Use of other silanes with chemical specific toxicity data as alternative surrogate N-to-L Ratio Relative Potency/Toxicity
N-to-L Ratio	Fast, minimal resources, health protective Can directly derive ESLs for LTD chemicals when only lethality data are available No need to compare to other chemicals Conservative	Must have data and study quality may vary, be unreliable, or inconsistent No human data Interspecies variance Limited MOA information Can only apply to acute ESL May be too conservative	Relative Potency/Toxicity A default acute ESL of 2 µg/m^3 may be used for an acute ESL (called Threshold of Regulation) Category TOC for acute ESLs
Relative Potency/Toxicity	Chemical specific data comparison Index chemical(s) have reliable toxicity factors for comparison Can be used for acute and chronic ESLs	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 for acute ESLs A default acute ESL of 2 µg/m^3 may be used for an acute ESL Category TOC acute ESLs
Route-to-Route	Fast, minimal resources Apply only when no inhalation lethality data are available Can be used for acute and chronic ESLs	Limited to oral lethality data Can only apply to acute ESL Oral MOA may be irrelevant to inhalation MOA High uncertainty May not be applicable (i.e., POE effects)	A default acute ESL of 2 µg/m^3 may be used Category TOC for acute ESLs
Chemical-Specific Data	Chemical-specific Can be used for acute and chronic ESLs	Study quality No human data Interspecies variance Limited MOA information	Surrogate N-to-L Ratio Category TOC for acute ESLs

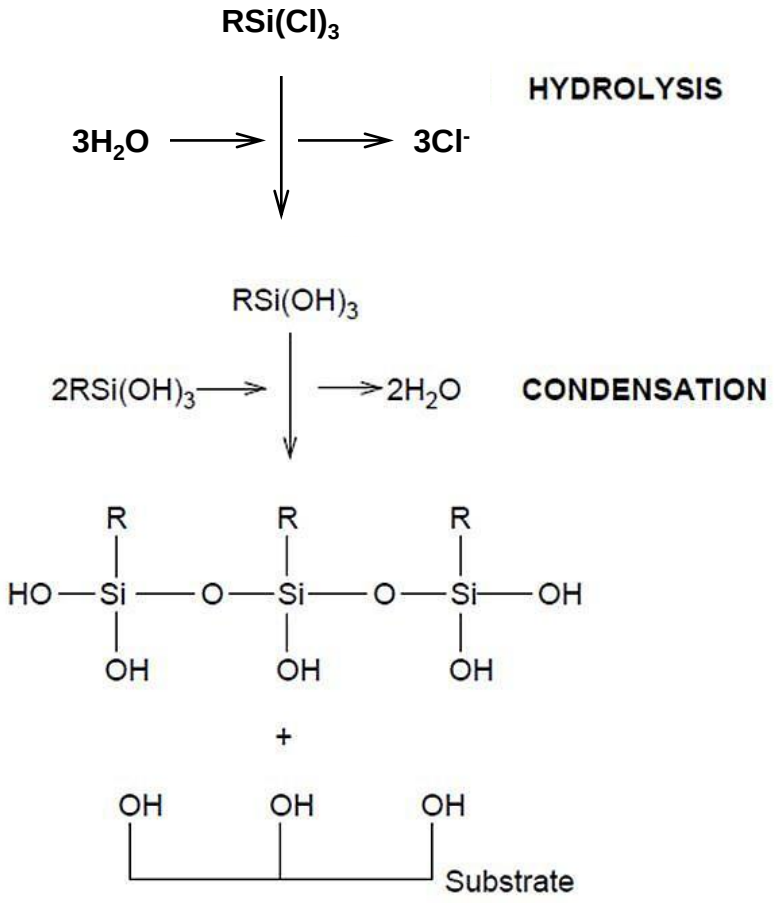
Summary: A Framework Approach

- The presented framework is applicable to many different scenarios depending on available data
- Identify possible approaches
- Data quality can be considered
- When there is more than one option, several approaches may be investigated
- Strengths
- Uncertainties or weaknesses
- WOE Analysis

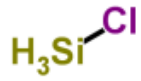
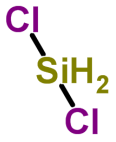
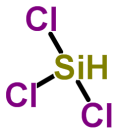
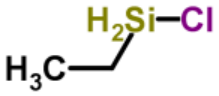
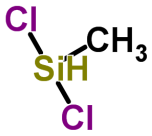
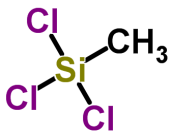
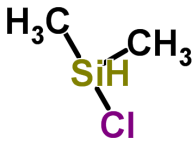
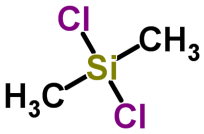
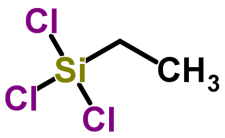
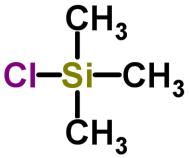
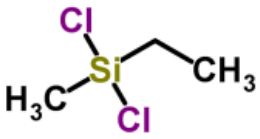
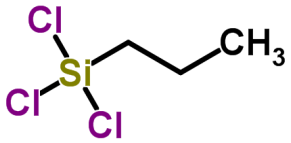
Silanes

- Silanes are widely used in industrial applications.
  - Adhesion promoter
  - Sealant and coating
  - Crosslinking agent
  - Water scavengers
  - Coupling agent
  - Fillers

Chlorosilanes Chemistry



Chlorosilanes

Mono-Cl	Di-Cl	Tri-Cl	Tetra-Cl
			
			
			
			

Chlorosilanes Data

Data	Mono-Cl	Di-Cl	Tri-Cl	Tetra-Cl
Human	--	--	--	Data from spill at chemical plant- eye and respiratory irritation (no info about concentration)
Animal Lethal	- GLP - Good quality study	- GLP - Good quality- single study - Toxicity > 1 chloro	- GLP - Quality study - Toxicity > 1 and 2 chloro	- GLP - Quality study - Toxicity > 1, 2, and 3 chloro
Animal Non-Lethal	--	--	--	--
Analogue or Category	- Rapid hydrolysis yields Cl - HCl is a good analogue - HCl is data-rich and has a DSD	- Rapid hydrolysis to Cl - Two molar equivalents of HCl	- Rapid hydrolysis to Cl - Three molar equivalents of HCl	- Rapid hydrolysis to Cl - Four molar equivalents of HCl

Chlorosilanes Lethality Data

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

Surrogate Approach: HCl

Considerations for Surrogate Selection			
Physicochemical Properties	**Structural**	**Biological**	**Chemical Family**
Physical state Hydrolytically unstable Reactive Molecular weight Size Log K_{ow}	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

- Chlorosilanes hydrolyze
- They are irritants based on limited human data
- They share:
  1. Structural: hydrolysis produces Cl-
  2. MOA is similar to HCl
  3. Chemical properties are similar

Surrogate Approach: HCl

Chlorinated Silanes	Acute ESLs	Chronic ESLs
HCl	130 ppb	5.4 ppb
Monochlorinated	130 ppb	5.4 ppb
Dichlorinated	65 ppb	2.7 ppb
Trichlorinated	43 ppb	1.8 ppb
Tetrachlorinated	33 ppb	1.4 ppb

N-to-L Ratio Approach

Chemical	1-hr LC50 (ppm)	4-hr LC50 (ppm)	Acute ESL (ppb)
HCl	3627	907	75
Monochlorinated	4368	1092	91
Dichlorinated	1966	491	41
Trichlorinated	1396	349	29
Tetrachlorinated	1312	328	27

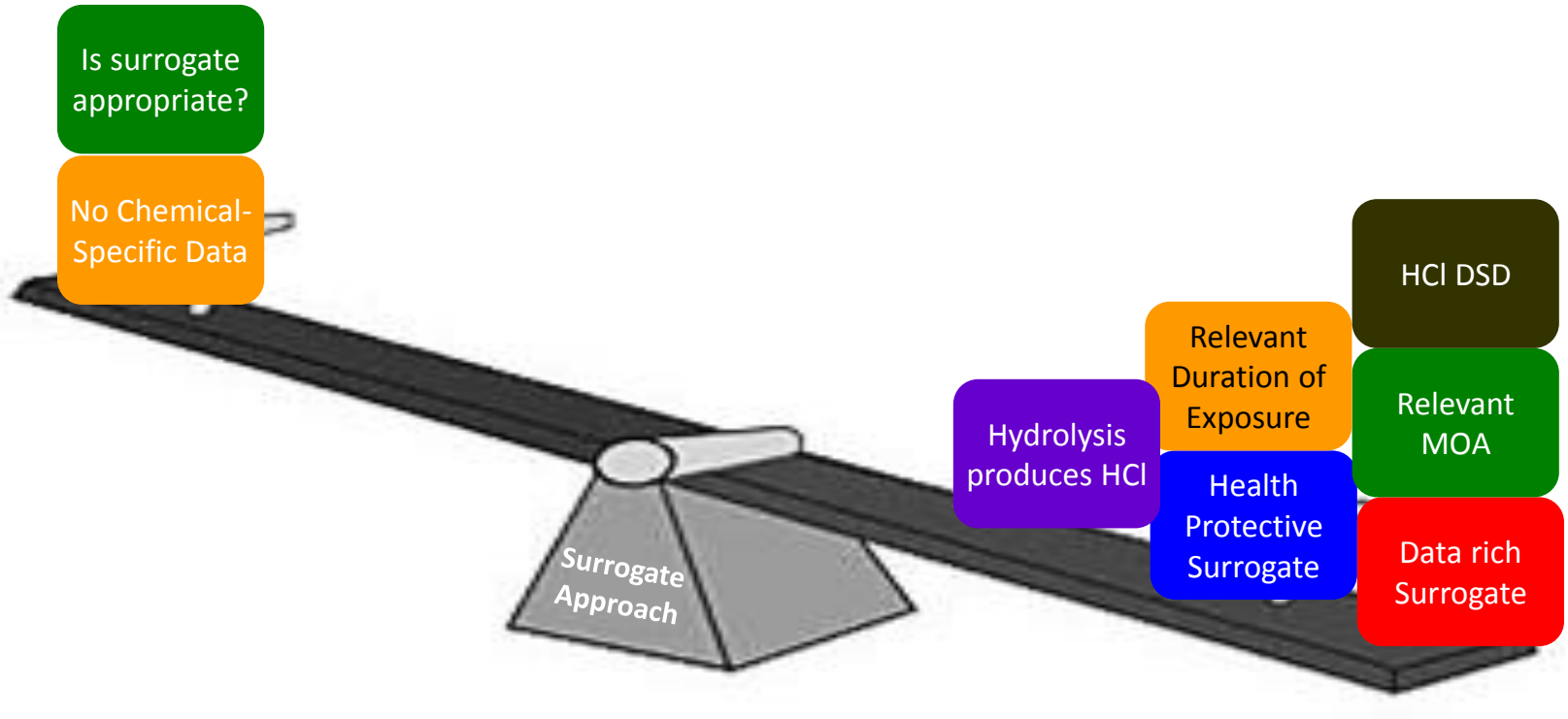
- N-to-L Ratio Approach previously discussed in
  1. Grant et al., 2007
  2. Previous case study
- Duration adjustment of LC50 to 4-hr using Haber's Rule
- Multiply by 8.3×10^{-5}
- Conservative – value lower than HCl ESL

Relative Potency Approach

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

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

WOE Analysis: Surrogate Approach

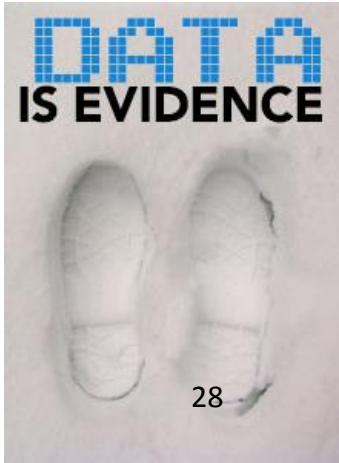


Uncertainties

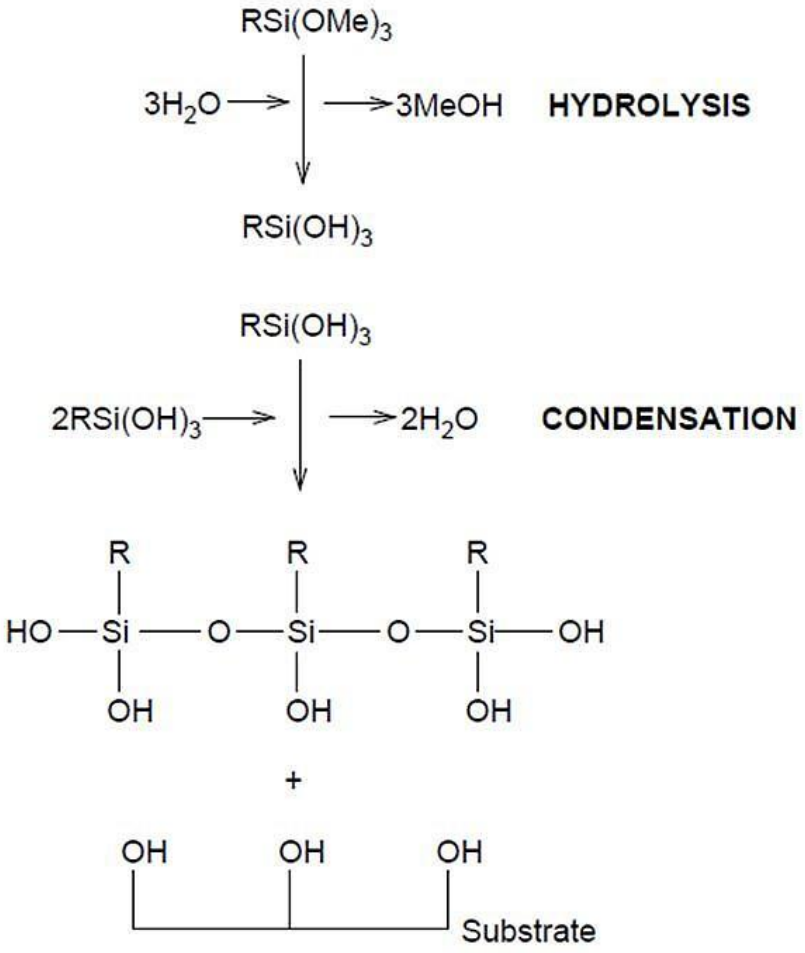
Strengths

Summary & Conclusions

- Three separate approaches resulted in very similar ESLs
- MOA of HCl is similar to that of chlorosilanes
- Surrogate approach for ESLs
  - Conservative
  - MOA appropriate (key studies for acute and chronic exposure)
  - ESLs have been reviewed and subjected to public comment



Methoxy Silanes



- Hydrolyze at different rates
- Produces methanol and associated silanols

Available Data

Data	Mono-methoxy	Di-methoxy	Tri-methoxy	Tetra-methoxy
Human	--	--	--	--
Animal Lethal	--	- Rodent 4-h LC50 - Not exact number observed	- Rodent - MTMS - TMS	- Rodent - TetMS
Animal Non-Lethal	--	- Oral - No inhalation	- 90-day study inhalation	- 28-day study inhalation
Analogue or Category	- Rapid hydrolysis yields MeOH - MeOH is a good analogue - MeOH is data-rich and has a DSD	- Rapid hydrolysis to MeOH - Two molar equivalents of MeOH	- Rapid hydrolysis to MeOH - Three molar equivalents of MeOH	- Rapid hydrolysis to MeOH - Four molar equivalents of MeOH

Surrogate Approach

Chemical	Acute ESL	Chronic ESL
Methanol	3000 ppb	1600 ppb
2 Molar Equivalents Methanol	1500 ppb	800 ppb
3 Molar Equivalents Methanol	1000 ppb	530 ppb
4 Molar Equivalents Methanol	750 ppb	400 ppb

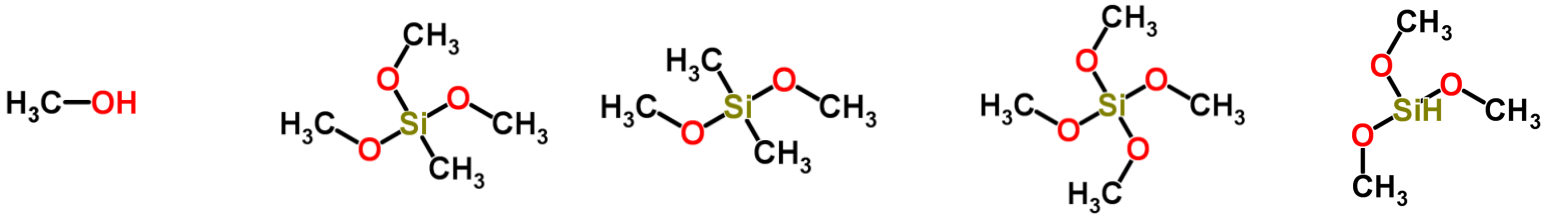
- Methoxysilanes hydrolyze to produce methanol and silanols
- They are irritants based on limited animal data, which is similar to methanol
- Methanol has an ESL that has been derived and subjected to review and public comment

N-to-L Ratio Approach

Chemical	4-hr LC50 (ppm)	Acute ESL (ppb)
Methanol (MeOH)	64000	5300
Dimethoxydimethylsilane (DMDMS)	> 4300	360
Trimethoxymethylsilane (MTMS)	> 8700	720
Trimethoxysilane (TMS)	60	5
Tetramethoxysilane (TetMS)	63	5.2

- Methoxysilanes appear to be more toxic than methanol
- The toxicity alone does not appear to be strictly related to molecular equivalents of methanol present
- Silanols are generally thought to be less toxic
- MOA is unclear
  1. Lung lesions
  2. Nephrotoxicity (calculi and dilation)

Toxicity of Methoxysilanes



MeOH << MTMS < DMDMS <<<< TetMS ≤ TMS

- Methanol is less toxic than the methoxysilanes and likely a poor surrogate
- Animal studies are available for derivation of chemical-specific values for MTMS, TetMS, and TMS
- It is possible to surrogate methoxysilanes with no chemical-specific data to methoxysilanes with some data

Chemical-Specific Data

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/m^3 (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/m^3 (60 ppb)	36 µg/m^3 (6 ppb)	Study could be used for both chronic and acute ESL derivation

Relative Potency Approach

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

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

MeOH ESL x Relative Potency = ESL

Methoxysilanes ESLs

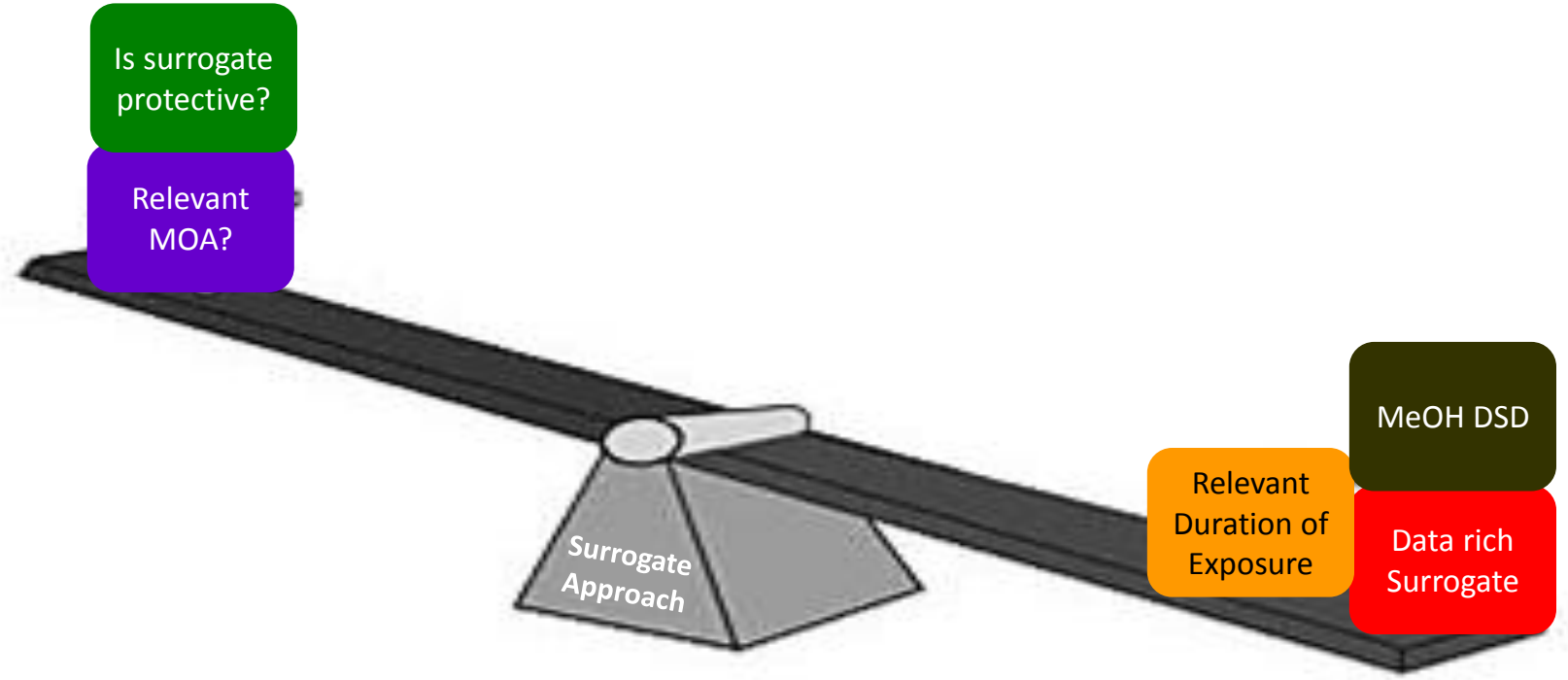
Chemical	Acute ESL (ppb)	Basis	Chronic ESL (ppb)	Basis
Methanol (MeOH)	3000	MeOH DSD	1600	MeOH DSD
Monomethoxysilane (MMS)	200	Surrogate (DMDMS)	100	Surrogate (DMDMS)
Dimethoxydimethylsilane (DMDMS)	200	Relative Potency (MeOH)	100	Relative Potency (MeOH)
Methyltrimethoxysilane (MTMS)	420	Relative Potency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

Data Priorities

- Interpretations of limited data should be considered in the context of the entire body of data
- When a ReV cannot be derived, generic approaches should be considered
- Generic approaches vary in their utility and applicability
- Sometimes a suitable surrogate cannot be identified
- Index chemicals do not necessarily need to be more or less toxic- just more data rich

Padian, 2013

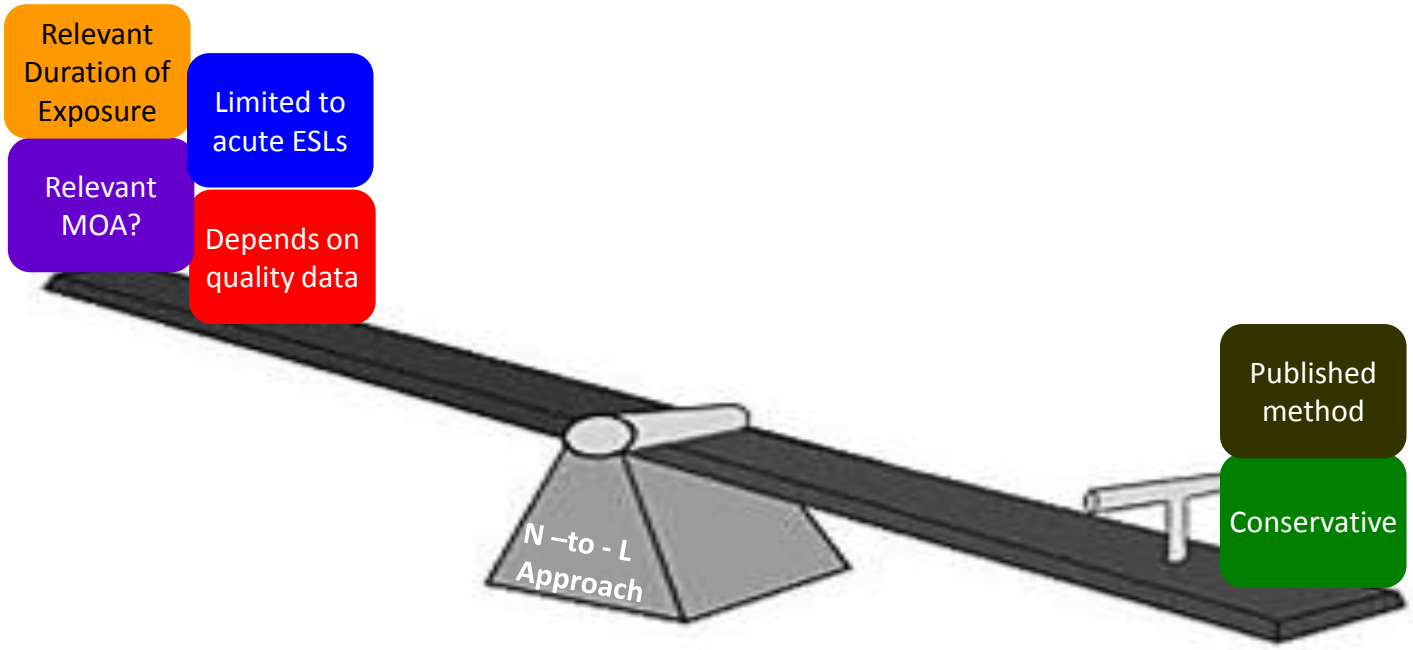
WOE Analysis: Surrogate Approach



Uncertainties

Strengths

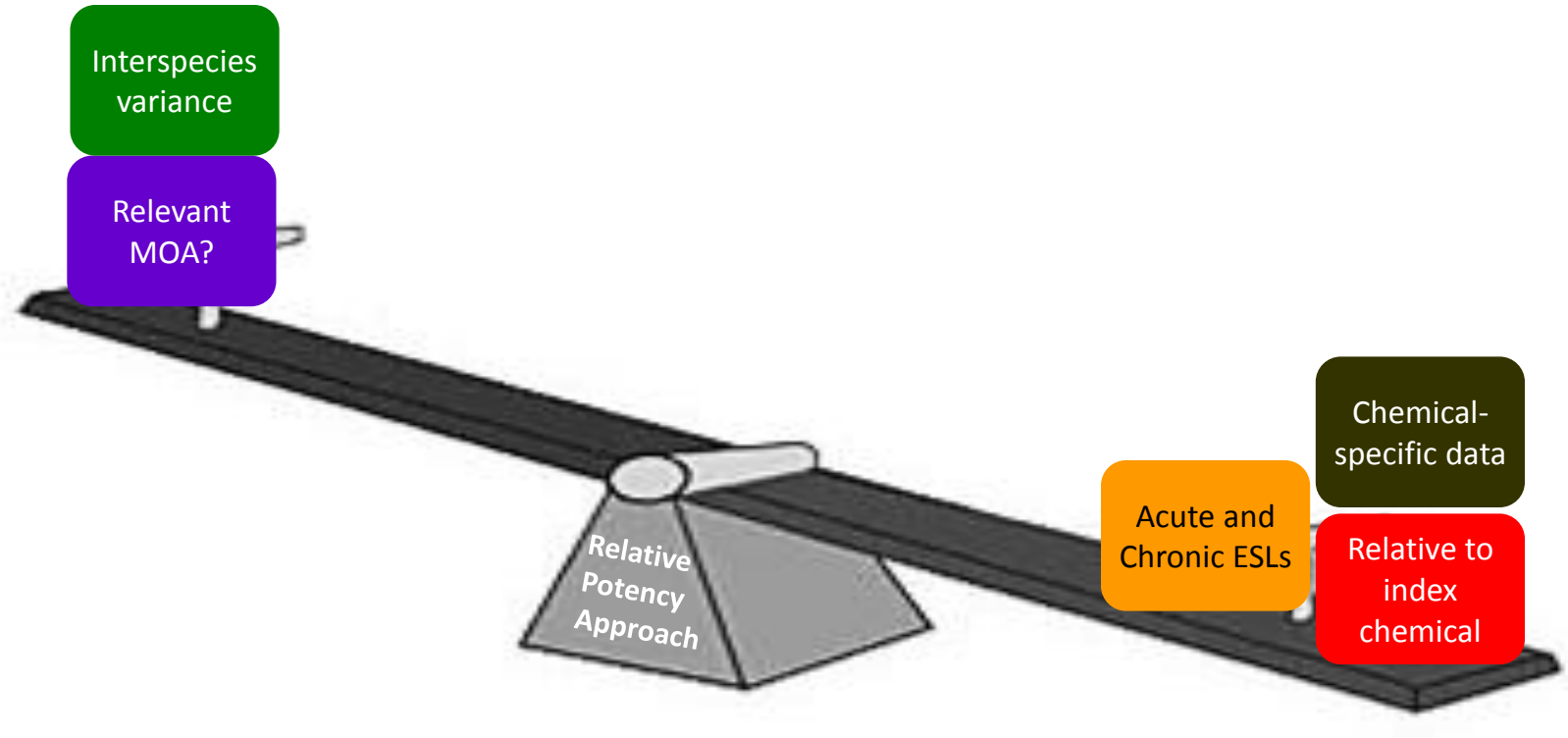
WOE Analysis: N-to L Ratio Approach



Uncertainties

Strengths

WOE Analysis: Relative Potency Approach



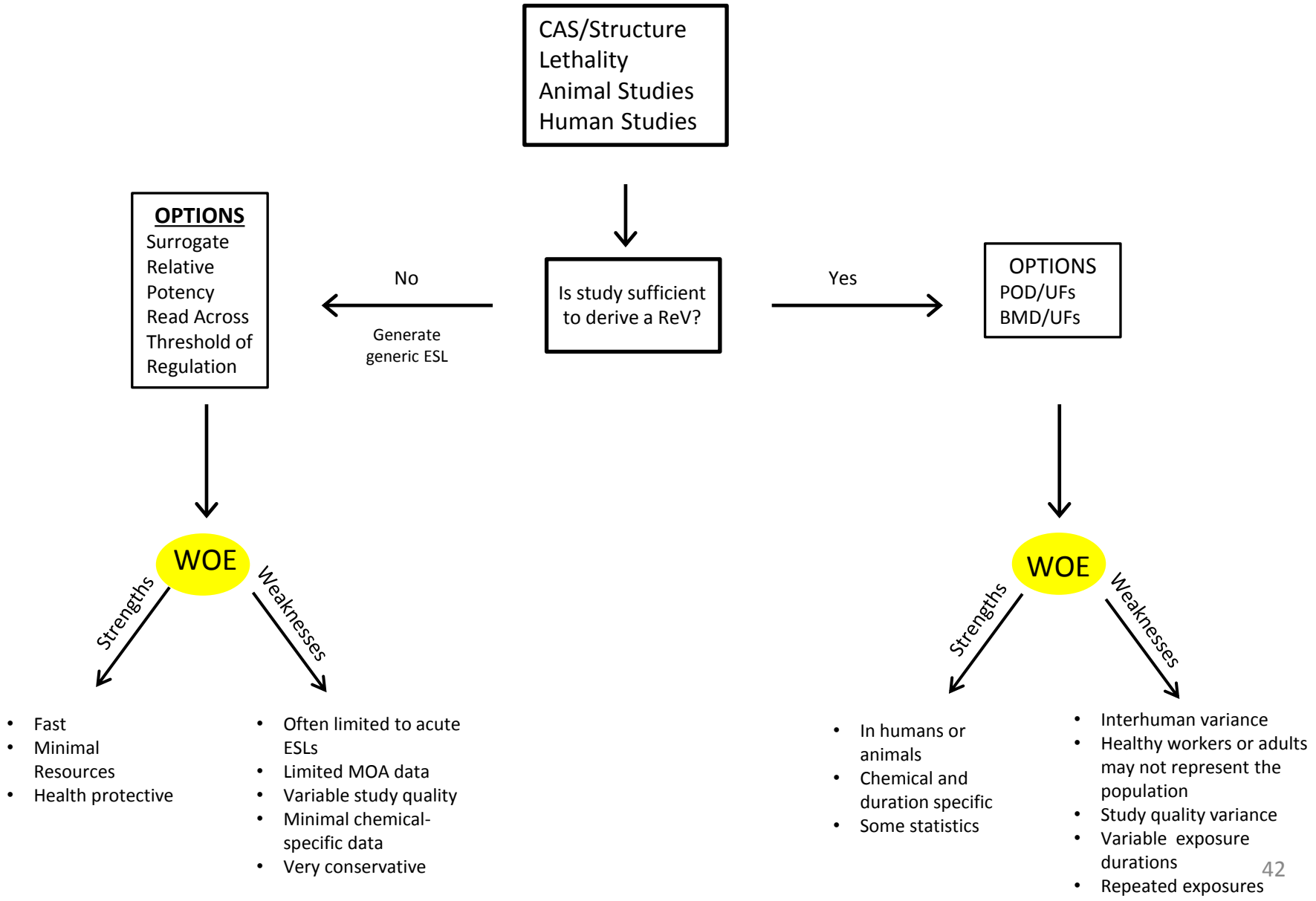
Uncertainties

Strengths

Summary and Conclusions

- Evaluation of the available evidence indicates MeOH as a surrogate may not be protective
- MeOH is a well-characterized chemical that may be used as an index chemical
- Chemical-specific data was limited to a few animal studies that could be applied to ESL generation (i.e., used for a ReV)
- A combination of surrogate, relative-potency, and chemical-specific approaches were used to derive ESLs for methoxysilanes

A Framework Approach



Acknowledgements

- TCEQ Toxicology Division
- Alliance for Risk Assessment
- TERA
- The Science Panel
- The Case Study TEAM

QUESTIONS???


CITATION
JOURNALS
HETEROGENEITY
DONORS
MEDICAL
HANDBOOK
APPRAISE
GROUP
BIOMEDICAL
SCIENCES
OCCUPATIONAL
STUDY
SYSTEMATIC
INFLUENTIAL
UNIVERSALLY
HIGH
INCLUDE
EPISTEMOLOGICAL
REHABILITATION
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DATABASES
CONFORMING
QUANTITATIVE
EVIDENCE
COLLABORATION
OBJECTIVE
SYNTHESIZE
HUMANITARIAN

BACKUP or POCKET SLIDES

- For additional reference
- To aid in answering questions

Data As A Spectrum of Information

judgment

Analogue good to fill data gaps

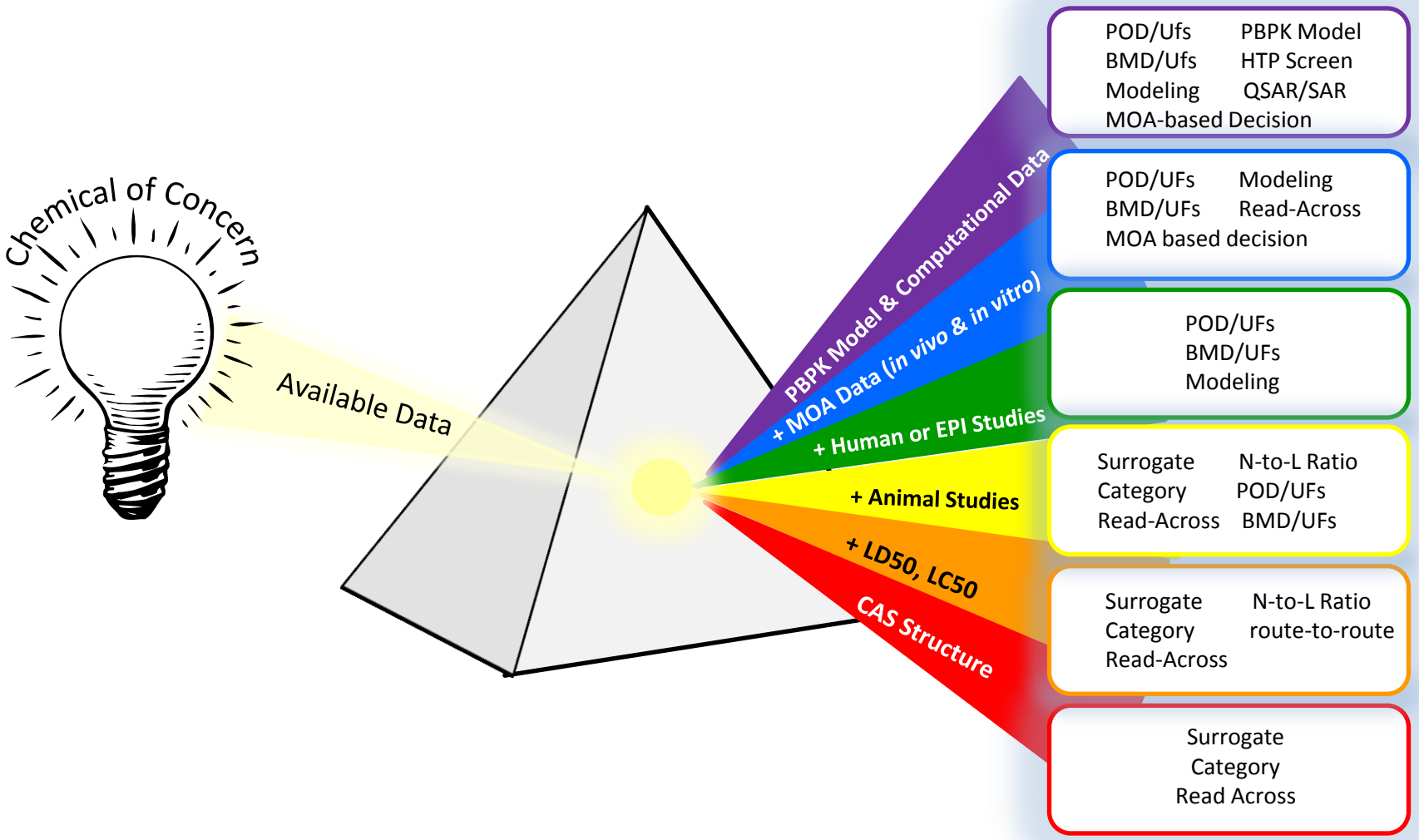
judgment

Human Relevance
MOA
Extrapolation from high dose

judgment

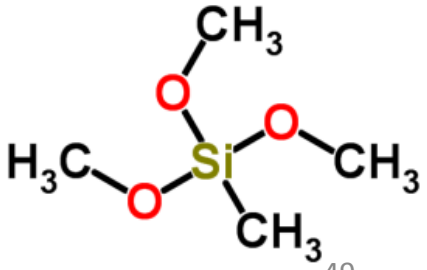
Human Relevance
MOA
Kinetics/Dynamics
Population Variance

The Data Spectrum



Methyltrimethoxysilane (MTMS) ESL

- No acute studies for ESL derivation
- 90-day subchronic study 6 hr/day, 5 day/week
- Concentrations: 0.14, 0.56, 2.2, and 8.9 mg/L
- NOAEL 0.56 mg/L (100 ppm)
- LOAEL 2.2 mg/L (400 ppm)
- Increased urinary bladder calculi and kidney dilation
- POD_{HEC} = 17.8 ppm (intermittent to continuous, HEC)
- Chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)
  = 17.8 ppm / (10 x 3 x 1 x 3)
  = 0.198 ppm
  = 200 ppb or 1,100 µg/m^3
- ESL = ReV x 0.3 = **60 ppb (330 µg/m^3)**



Tetramethoxysilane (TetMS)

- 28-day study available to derive acute and chronic ESLs
- Rats exposed 6 hr/day, 5 days/week for 28-days
- NOAEL of 10 ppm
- Acute ReV =

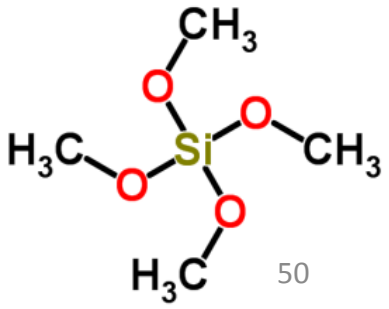
  POD_{HEC} / (UF_H x UF_A x UF_D)

  = 18.2 ppm / (10 x 3 x 3)

  = 0.202 ppm

  = 200 ppb or 1,200 µg/m^3

- ESL 60 ppb (360 µg/m^3)



Tetramethoxysilane (TetMS)

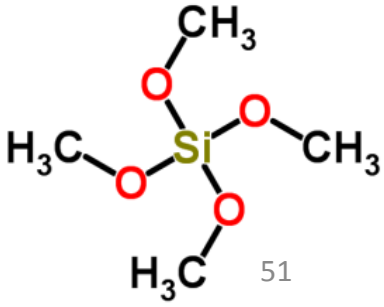
- Rats exposed 6 hr/day, 5 days/week for 28-days
- NOAEL of 10 ppm
- Chronic ReV

  = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)

  = 1.79 ppm / (10 x 3 x 1 x 3)

  = 0.02 ppm

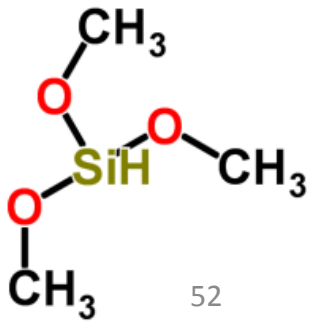
  = 20 ppb or 120 µg/m^3
- Chronic ESL = 6 ppb (36 µg/m^3)
- ReV multiplied by a HQ of 0.3



Trimethoxymethylsilane (TMS) ESL

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)

- The 9-day NOAEL is lower than the 90-day NOAEL
- The variance in NOAELs increases uncertainty in which study would be appropriate for ESL derivation.
- If the 9-day NOAEL is less than the 90-day NOAEL, it is unlikely that the 90-day study would be considered reliable for ESL derivation.
- 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.



WOE Analysis

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*