

# Framework for *In Silico* Toxicity Screening of Novel Odorants

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SOT Abstract/Poster #: 3698/P183

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## Conflict Disclosure

- No conflict to declare
- Research funded by Monell Chemical Senses Center

# Background and Objective

## Background

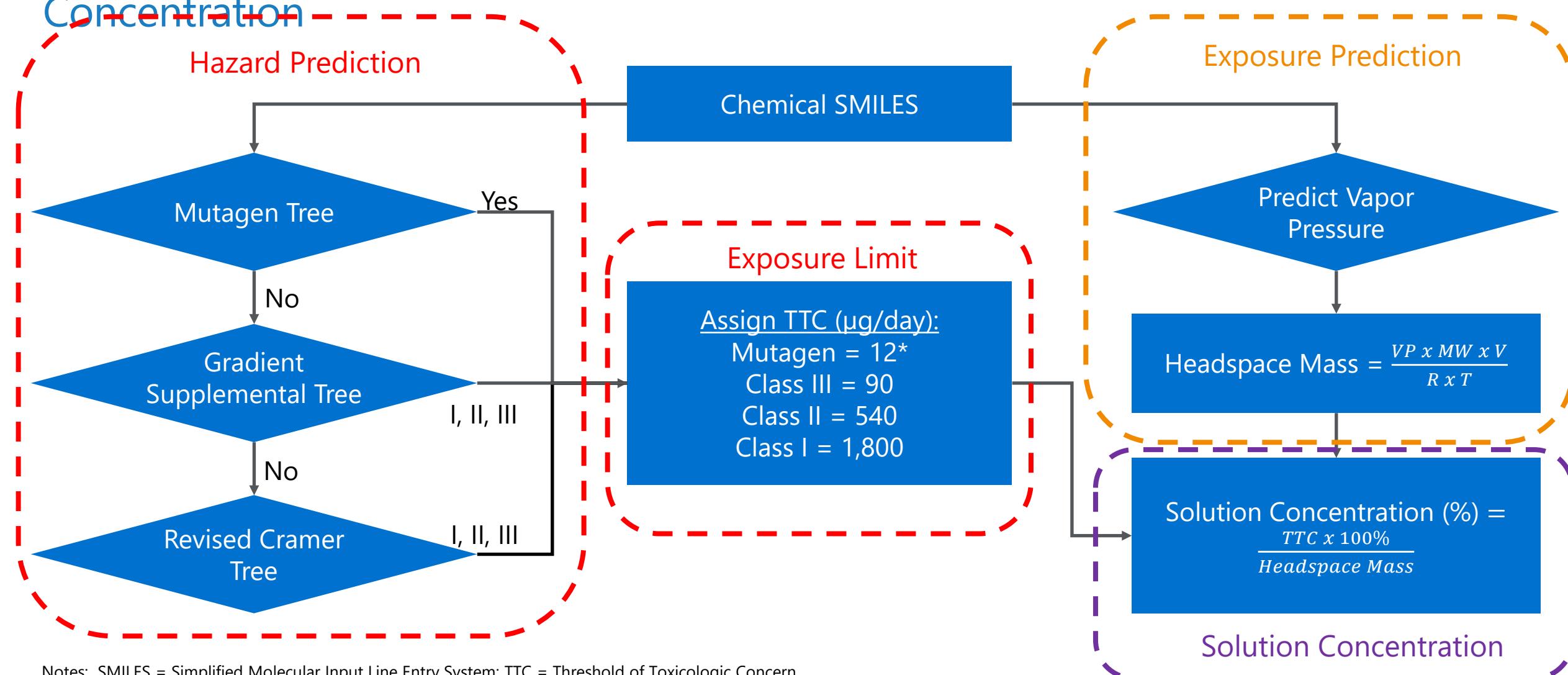
- This *in silico* approach was developed to support a psychophysical study of novel odorants, in which human volunteers sniffed the headspace of a solution in a vial (Lee *et al.*, 2023).
- Safety data lacking for novel odorants, restricts study.
- Develop a transparent *in silico* models to predict inhalation toxicity.
- Use this to predict allowable solution concentrations.

## Objective

- Derive toxicology-based maximum recommended solution concentrations for odorant chemicals, using chemical structure alone by an *in silico* approach.

Lee BK, Mayhew EJ, Sanchez-Lengeling B, Wei JN, Qian WW, Little KA, Andres M, Nguyen BB, Moloy T, Yasonik J, Parker JK, Gerkin RC, Mainland JD, Wiltschko AB. A principal odor map unifies diverse tasks in olfactory perception. *Science*. 2023 Sep; 381(6661):999-1006. doi: 10.1126/science.ade4401. Epub 2023 Aug 31. PMID: 37651511.

# Overview of *In Silico* Prediction of Inhalation Toxicity Hazard and Solution Concentration



Notes: SMILES = Simplified Molecular Input Line Entry System; TTC = Threshold of Toxicologic Concern.

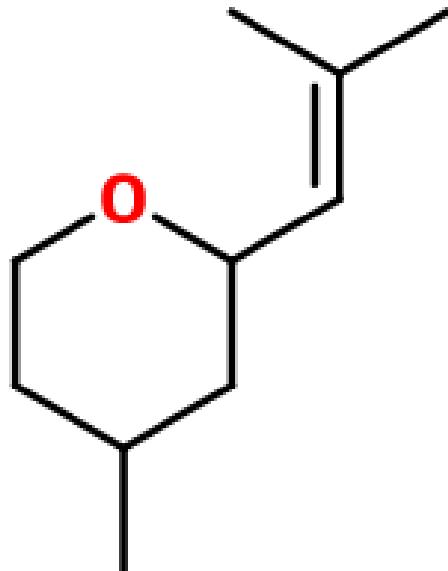
\* Based on ICH M7 TTC of 120 ug/day for  $\leq 30$  days exposure at 1:100,000 cancer risk level adjusted to 12 ug/day for 1:1,000,000 cancer risk level.

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## Chemical SMILES

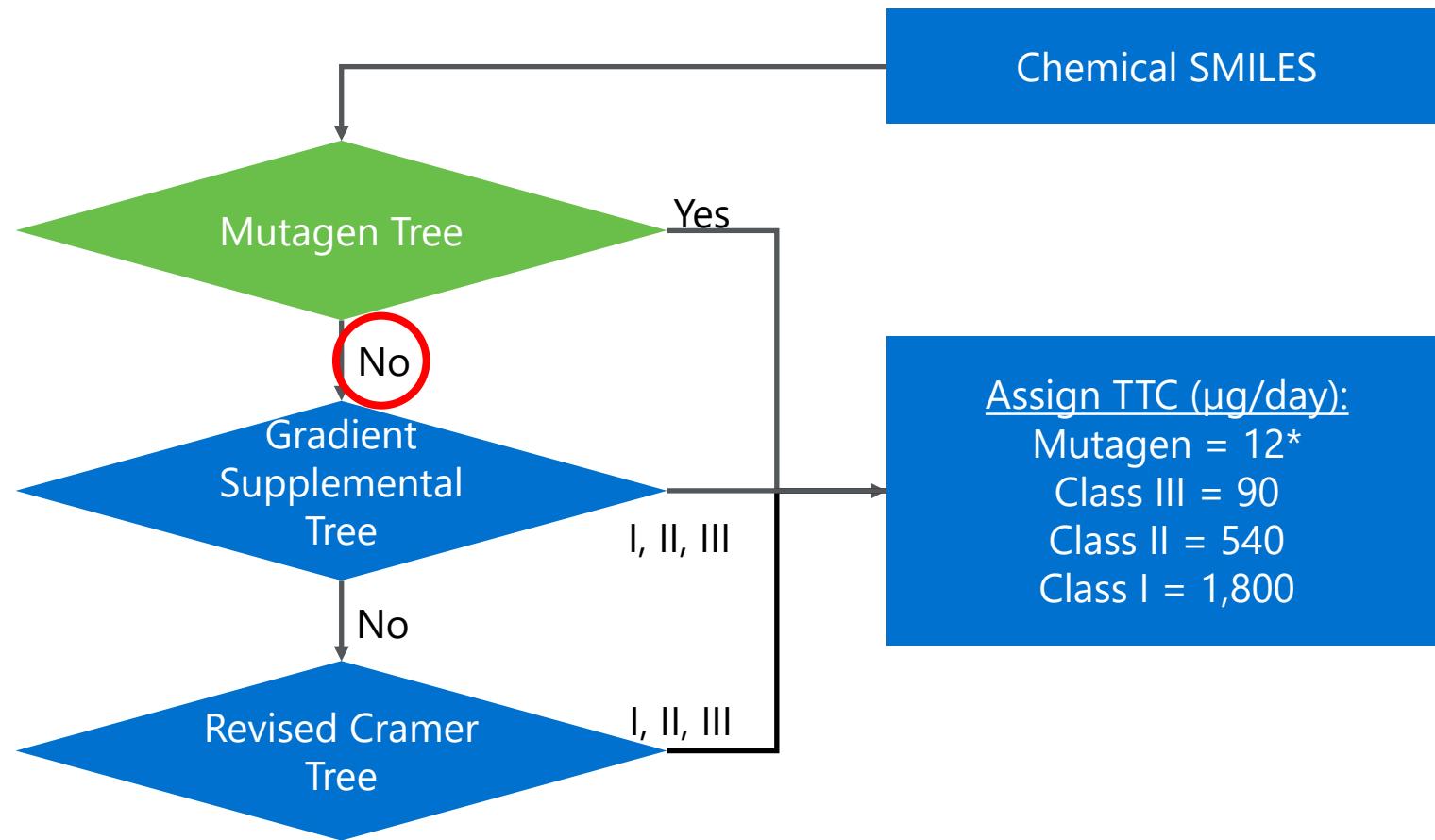
Rose oxide (CAS No. 16409-43-1)

CC1CCOC(C1)C=C(C)C

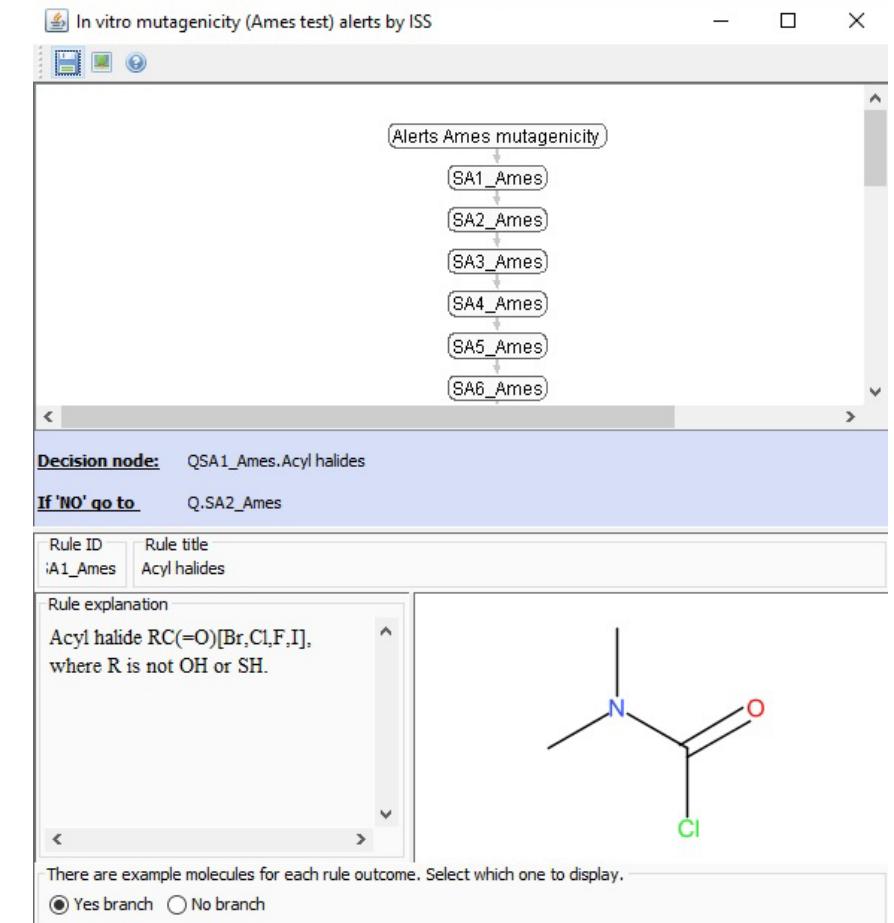


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<https://pubchem.ncbi.nlm.nih.gov/compound/27866>

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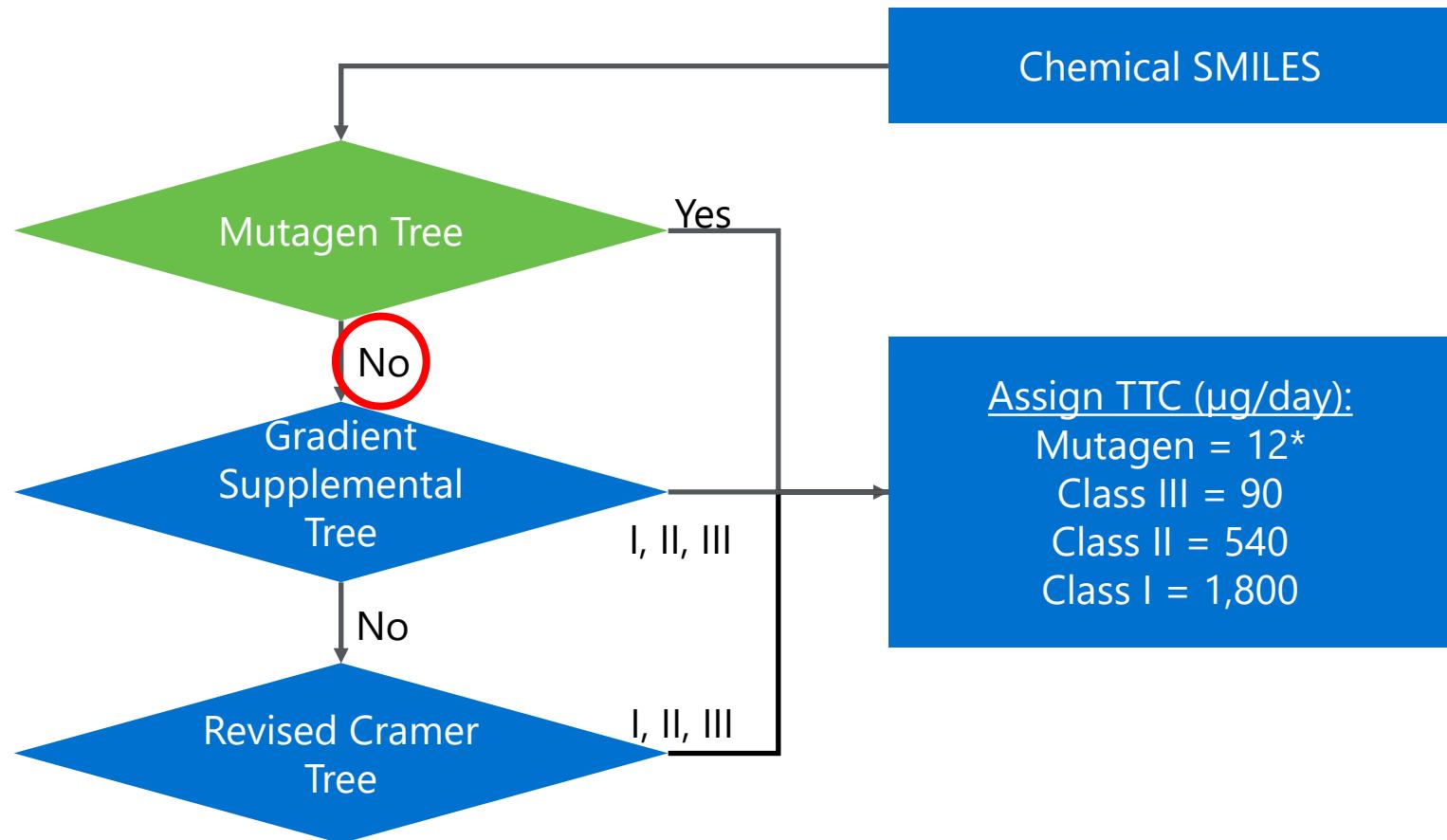


Toxtree software (version 3.1.0)



Ideaconult Ltd. 2018. "Toxtree - Toxic Hazard Estimation by decision tree approach (Version 3.1.0)." Accessed at <http://toxtree.sourceforge.net>.

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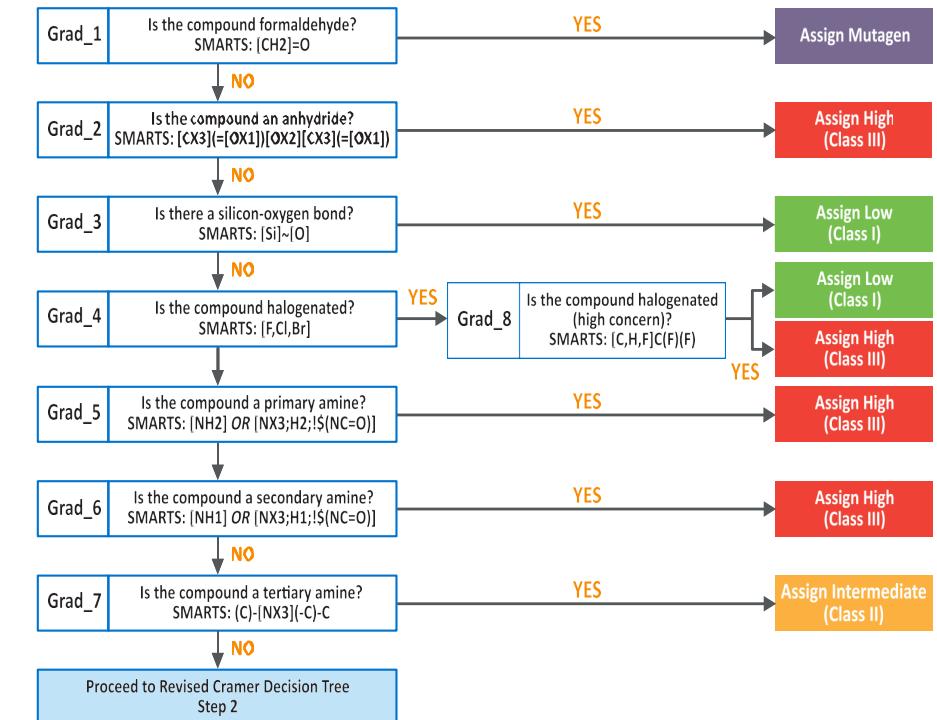
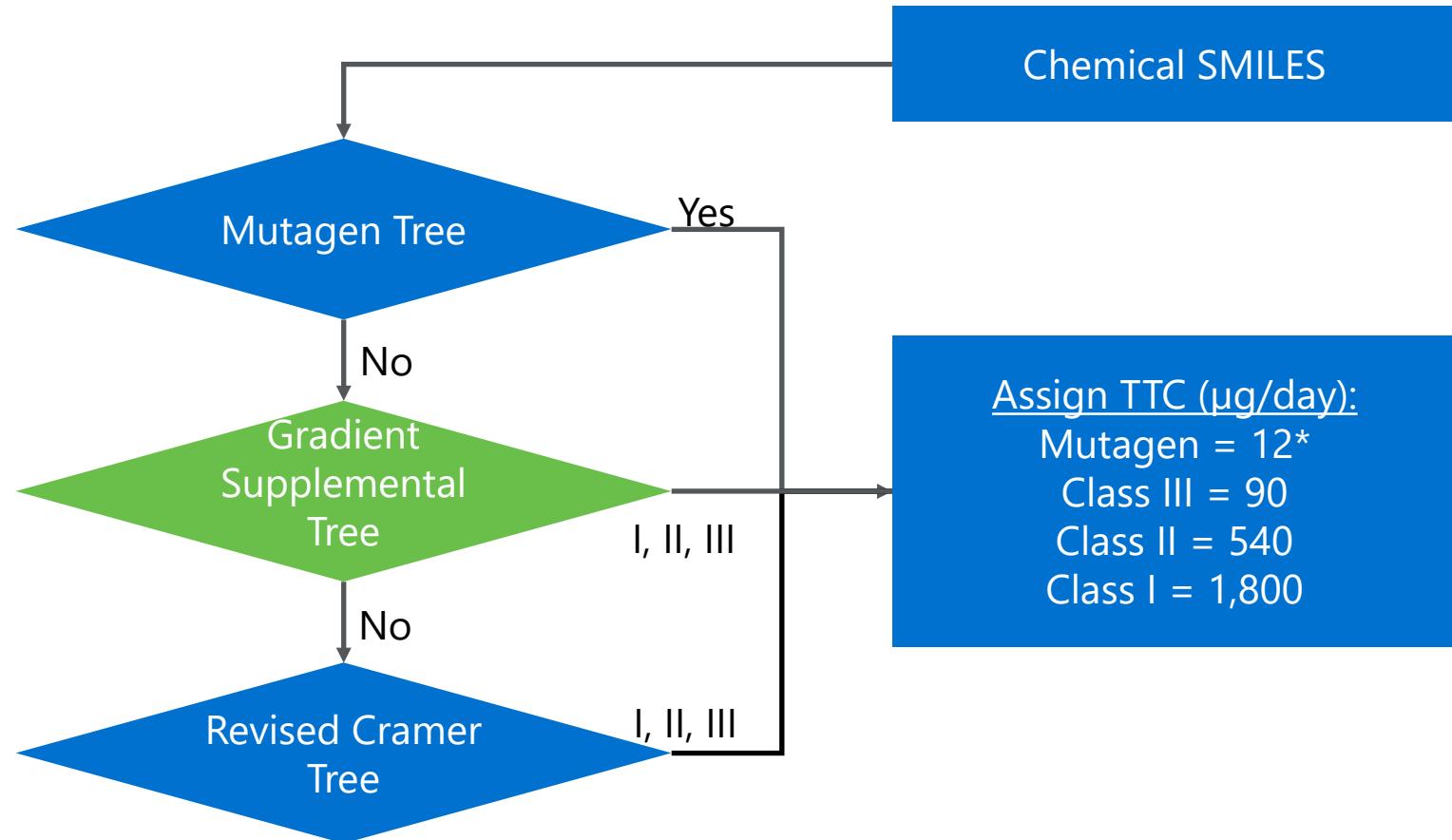
Toxtree software (version 3.1.0)

The screenshot shows the Toxtree software interface (version 3.1.0) with the chemical SMILES CC1CCOC(C1)C=C(C)C entered. The software displays the following information:

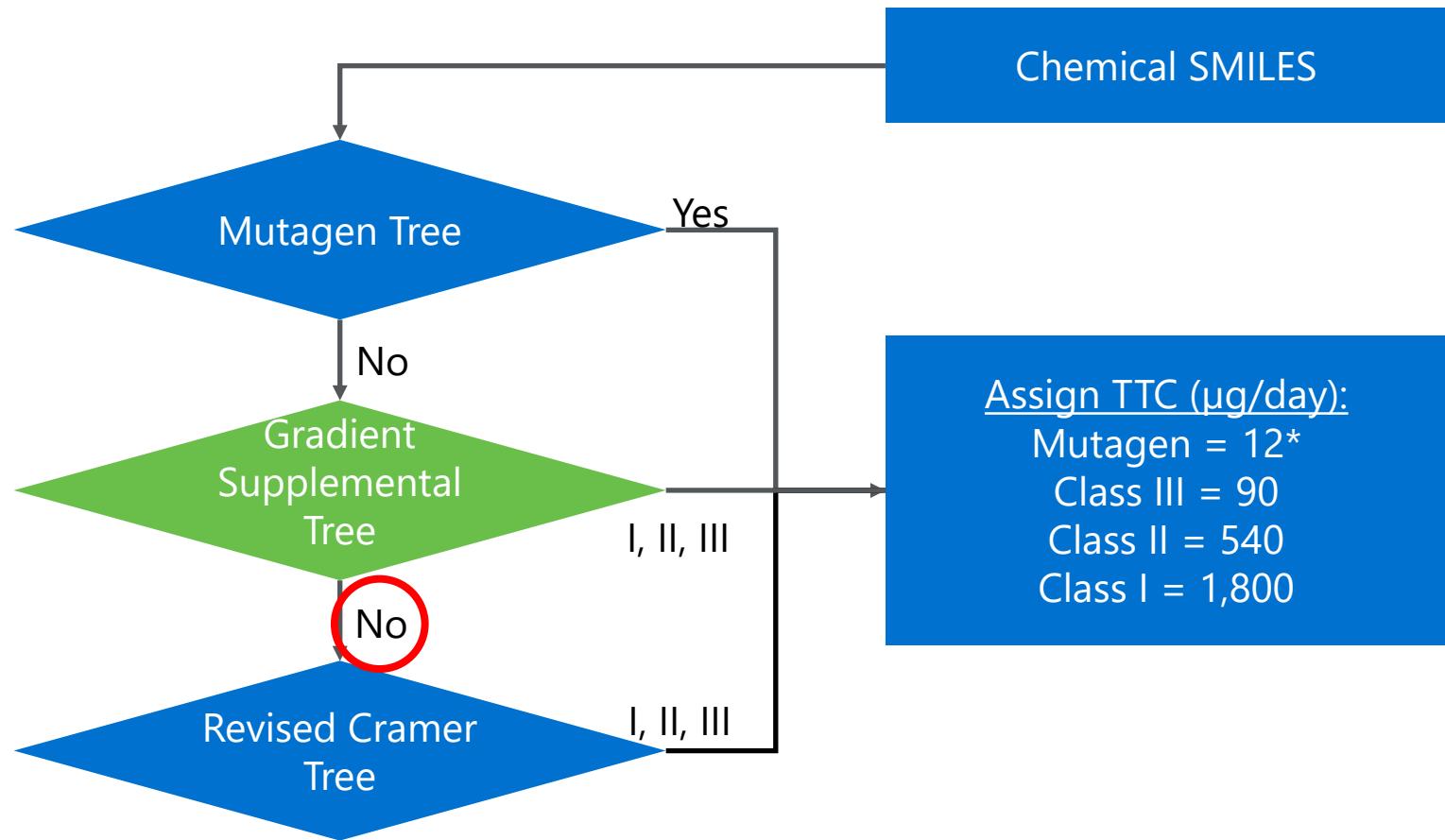
- Available structure attributes:**
  - Error when applying the ... NO
  - For a better assessment ... NO
  - No alerts for *S. typhimuri* ... YES
  - Potential *S. typhimurium* ... NO
  - QSAR13 applicable? NO
  - QSAR6 applicable? NO
  - SA10\_Ames NO
  - SA11\_Ames NO
  - SA12\_Ames NO
  - SA13\_Ames NO
  - SA14\_Ames NO
- Toxic Hazard:** *In vitro mutagenicity (Ames test) alerts by ISS*
  - Structural Alert for *S. typhimurium* mutagenicity mutagenicity
  - No alerts for *S. typhimurium* mutagenicity
  - Potential *S. typhimurium* TA100 mutagen based on QSAR
  - Unlikely to be a *S. typhimurium* TA100
- Structure diagram:** A chemical structure diagram of the input SMILES: CC1CCOC(C1)C=C(C)C.
- QSAs:**
  - QSA65\_Ames: Halofuranones **No** CC1CCOC(C1)C=C(C)C
  - QSA66\_Ames: Anthrones **No** CC1CCOC(C1)C=C(C)C
  - QSA67\_Ames: Triphenylimidazole and related **No** CC1CCOC(C1)C=C(C)C
  - QSA68\_Ames: 9,10 - dihydrophenanthrenes **No** CC1CCOC(C1)C=C(C)C
  - QSA69\_Ames: Fluorinated quinolines **No** CC1CCOC(C1)C=C(C)C

Ideaconsult Ltd. 2018. "Toxtree - Toxic Hazard Estimation by decision tree approach (Version 3.1.0)." Accessed at <http://toxtree.sourceforge.net>.

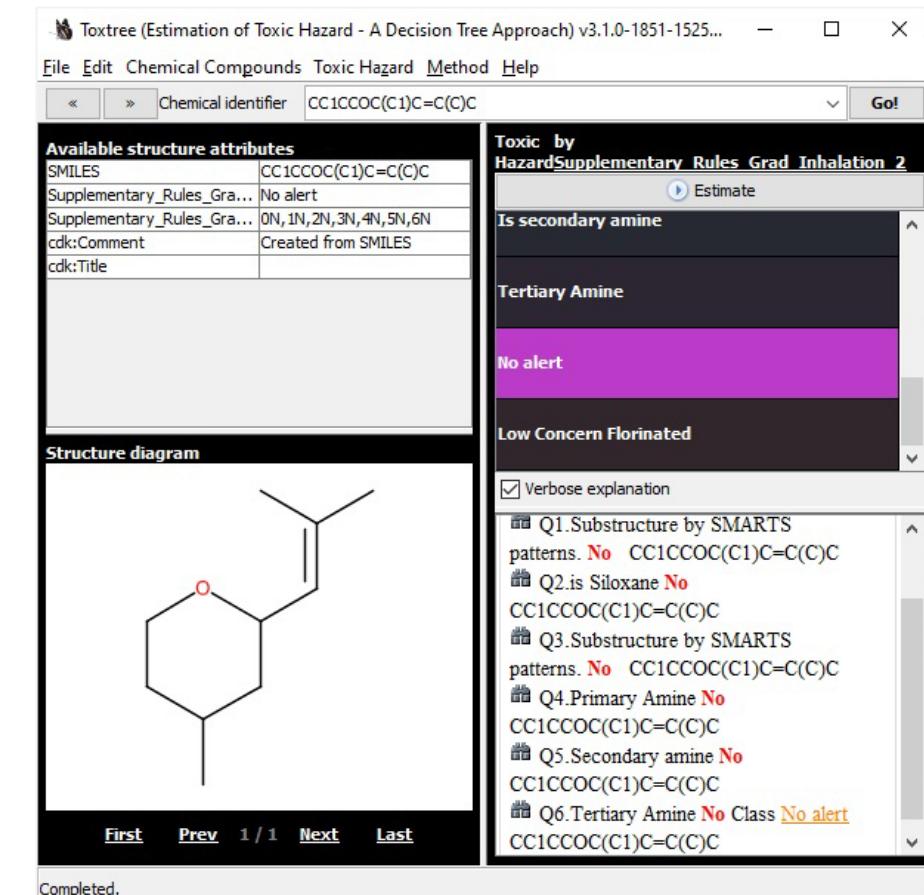
# Overview of *In Silico* Prediction of Inhalation Toxicity Hazard and Solution Concentration



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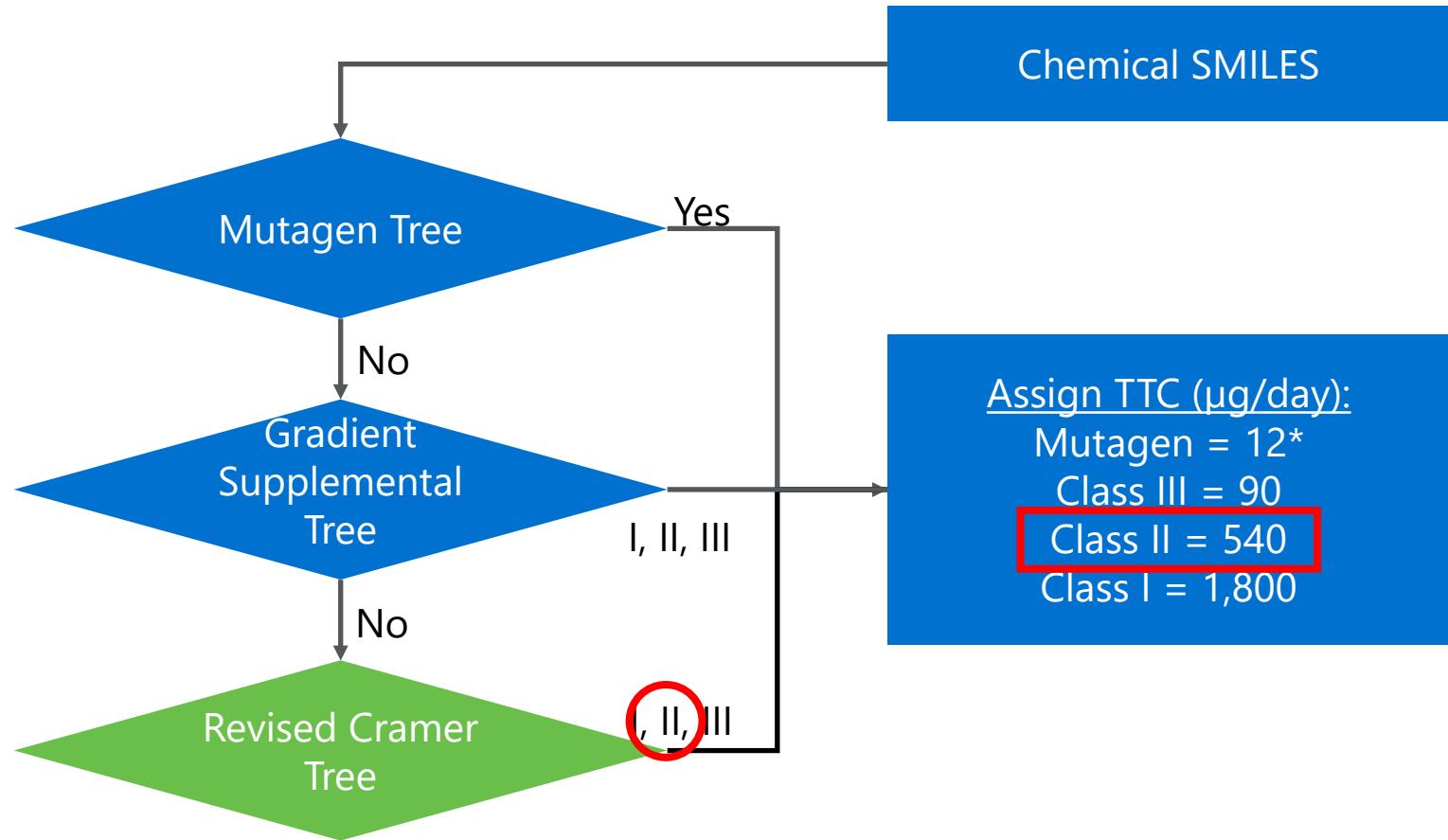


Toxtree software (version 3.1.0)



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Toxtree software (version 3.1.0)

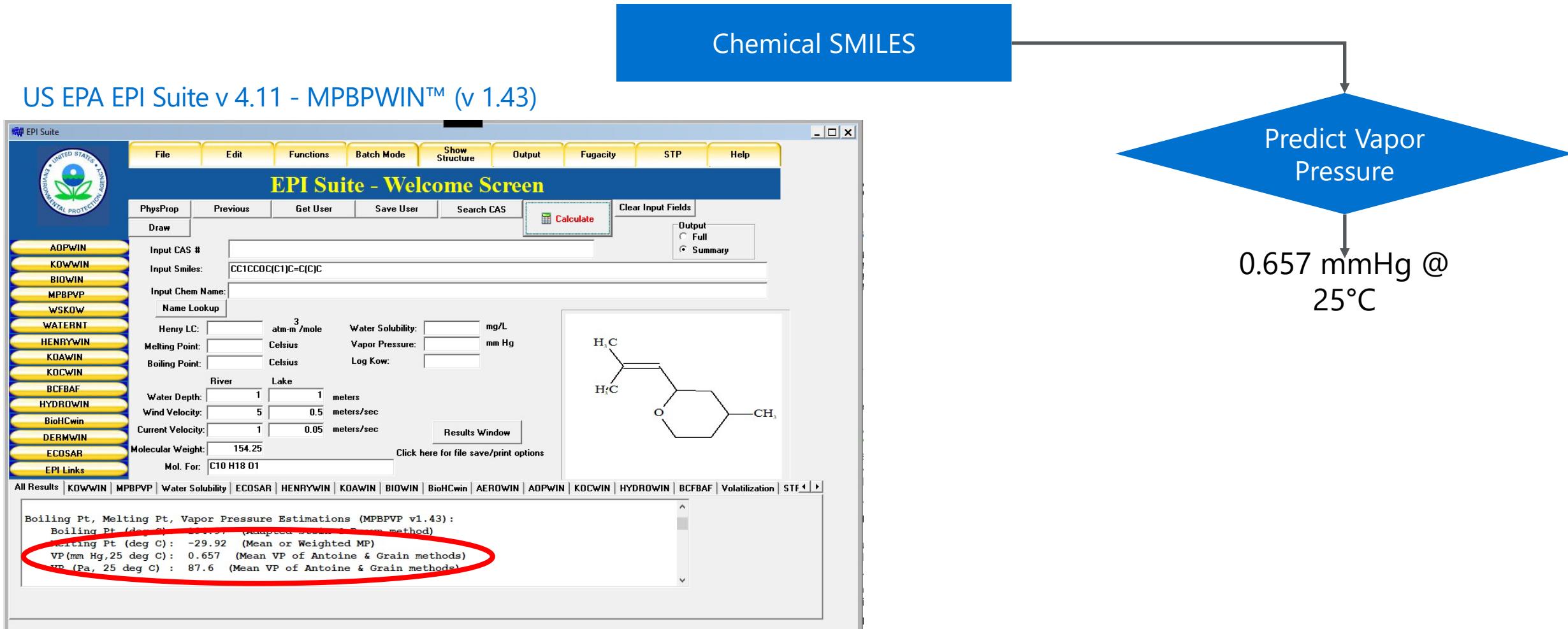
The screenshot shows the Toxtree software interface with the following details:

- Top Bar:** Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) v3.1.0-1851-1525...
- Menu Bar:** File, Edit, Chemical Compounds, Toxic Hazard, Method, Help
- Search Bar:** Chemical identifier CC1CCOC(C1)C=C(C)C
- Available structure attributes:**

RevisedCDT	Intermediate (Class II)
SMILES	CC1CCOC(C1)C=C(C)C
cdk:Comment	Created from SMILES
cdk:Title	
toxtree.tree.cramer3.CDT...	1N,2N,3N,4N,6N,7Y,8N,9...
- Toxic Hazard by Revised Cramer Decision Tree:** Shows categories: Low (Class I), Intermediate (Class II), and High (Class III). The chemical is assigned to Class II (Intermediate).
- Structure diagram:** Displays the chemical structure CC1CCOC(C1)C=C(C)C.
- Text Area:** Substances with chemical structures that permit other than specified? **No**  
CC1CCOC(C1)C=C(C)C  
Q6. Is the substance hydrocarbon, carbohydrate or terpene as specified? **No**  
CC1CCOC(C1)C=C(C)C  
Q7. Is the substance heterocyclic? **Yes**  
CC1CCOC(C1)C=C(C)C  
Q8. Is the substance heterocyclic because it contains a cyclic hemiacetal, acetal, hemiketal, ketal, or cyclic carbonate? **No** CC1CCOC(C1)C=C(C)C  
Q9A. Is the substance a cyclic diester or
- Buttons:** Estimate, Go!, First, Prev, 1 / 1, Next, Last

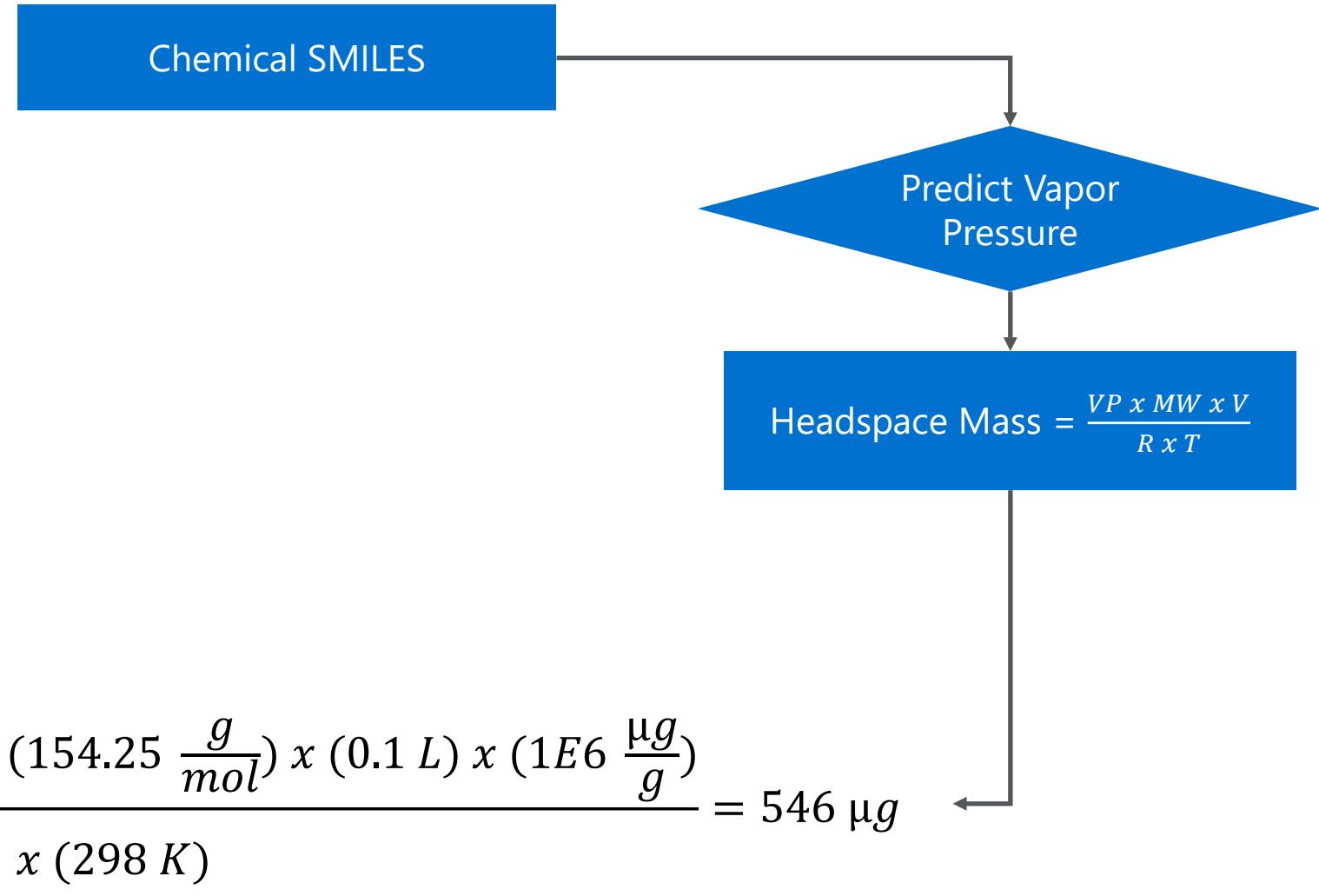
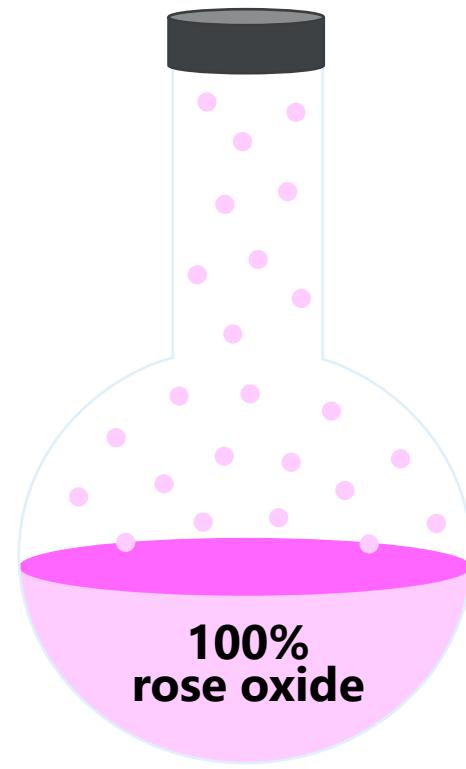
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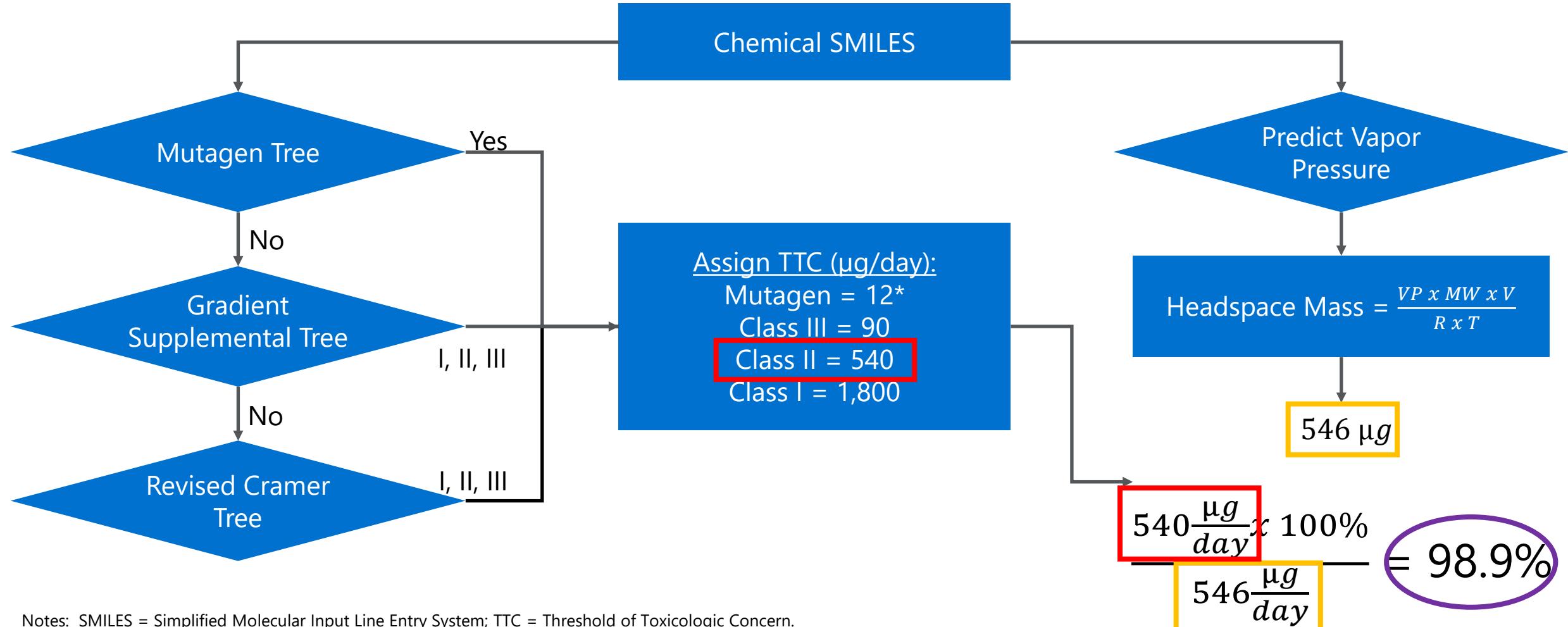


US EPA. 2012. "EPI Suite v4.11." November. Accessed at <http://www.epa.gov/opptintr/exposure/pubs/episuitesdl.htm>.

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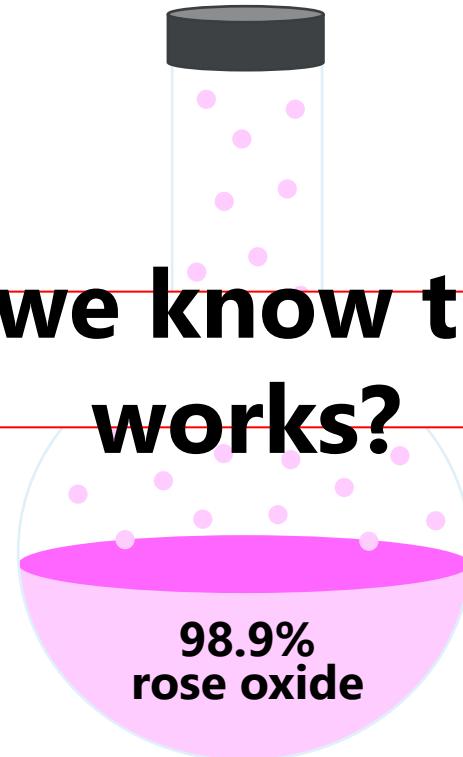
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# Overview of *In Silico* Prediction of Inhalation Toxicity Hazard and Solution Concentration

- Model predicts that inhalation of a 0.1-L headspace of a 98.9% rose oxide solution would not exceed the assigned TTC.

**How do we know the model works?**

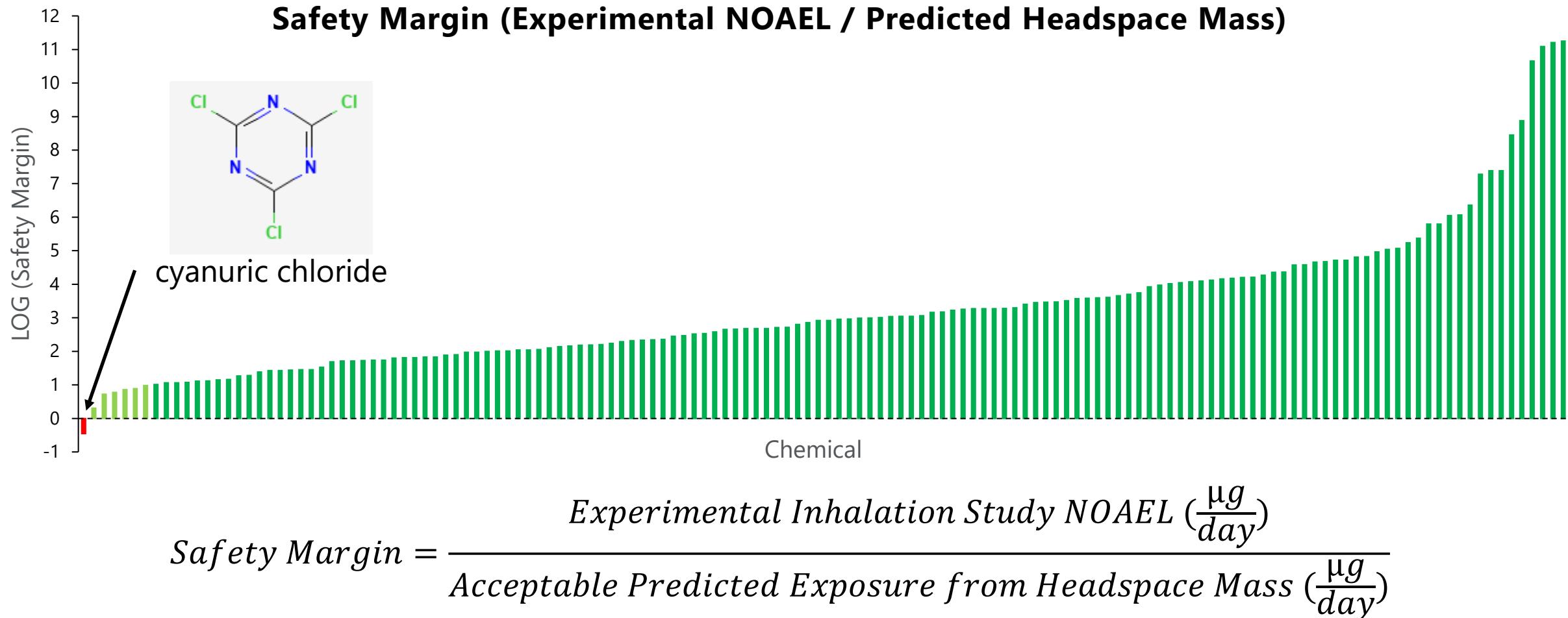


## Model Validation Against Inhalation Toxicity Dataset (Shin *et al.* 2019)

- Inhalation toxicity data for 143 compounds (90-day studies in rats) (Shin *et al.* 2019).
- Converted NOAEC (mg/L) to NOAEL ( $\mu\text{g}/\text{day}$ ) by:
  - $NOAEL \left( \frac{\mu\text{g}}{\text{day}} \right) = NOAEC \left( \frac{\text{mg}}{\text{L}} \right) \times RMV_{rat} \left( 0.2 \frac{\text{L}}{\text{min}} \right) \times t \left( 360 \frac{\text{min}}{\text{day}} \right) \times (1000 \frac{\mu\text{g}}{\text{mg}})$
- Used our model to predicted acceptable solution concentrations based on SMILES.
- Estimated inhalation exposure (*i.e.*, headspace mass) based on predicted solution concentration (in water) assuming Raoult's Law applied.
- Compared NOAEL to exposure:
$$Safety\ Margin = \frac{Experimental\ Inhalation\ Study\ NOAEL \left( \frac{\mu\text{g}}{\text{day}} \right)}{Acceptable\ Predicted\ Exposure\ from\ Headspace\ Mass \left( \frac{\mu\text{g}}{\text{day}} \right)}$$

Shin, JH; Lee, BH; Lee, SK. 2019. "Development of QSAR model for subchronic inhalation toxicity using random forest regression method." Bull. Korean Chem. Soc. 40(8):819-825. doi: 10.1002/bkcs.11835.

# Model Validation Against Inhalation Toxicity Dataset (Shin *et al.* 2019)



Safety Margin was above 1 for 99.3% of chemicals and above 10 for 95% of chemicals.

# Conclusions

- The in silico approach was developed as a transparent and health-protective tool
- Risk-based approach integrates predicted hazard and predicted inhalation exposure
- The approach showed robust performance in validation test
- Approach is conservative
  - TTCs are for repeated daily exposure while odorants will have acute / limited exposure
  - Validation used NOAEC values from 90-day repeated exposure studies
- Useful to exclude odorants where the concentration would be too low to allow reliable perceptual ratings
- Useful to flag certain (potentially toxic) chemicals for additional evaluation

## Limitations

- Cramer/Kroes TTC values derived from oral toxicity data (but for chronic daily exposure)
- Mutagenicity TTC does not apply to high potency mutagenic carcinogens (e.g., N-nitroso, alkyl azoxy, aflatoxin-like)
- Does not identify potential asthmagens (but asthmatics excluded from study)
- Does not identify potential irritants (but irritation would likely be transient)
- Validation conducted with relatively small dataset that may not be representative of odorants

# Questions?

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*Principal Scientist / Toxicologist*



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