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

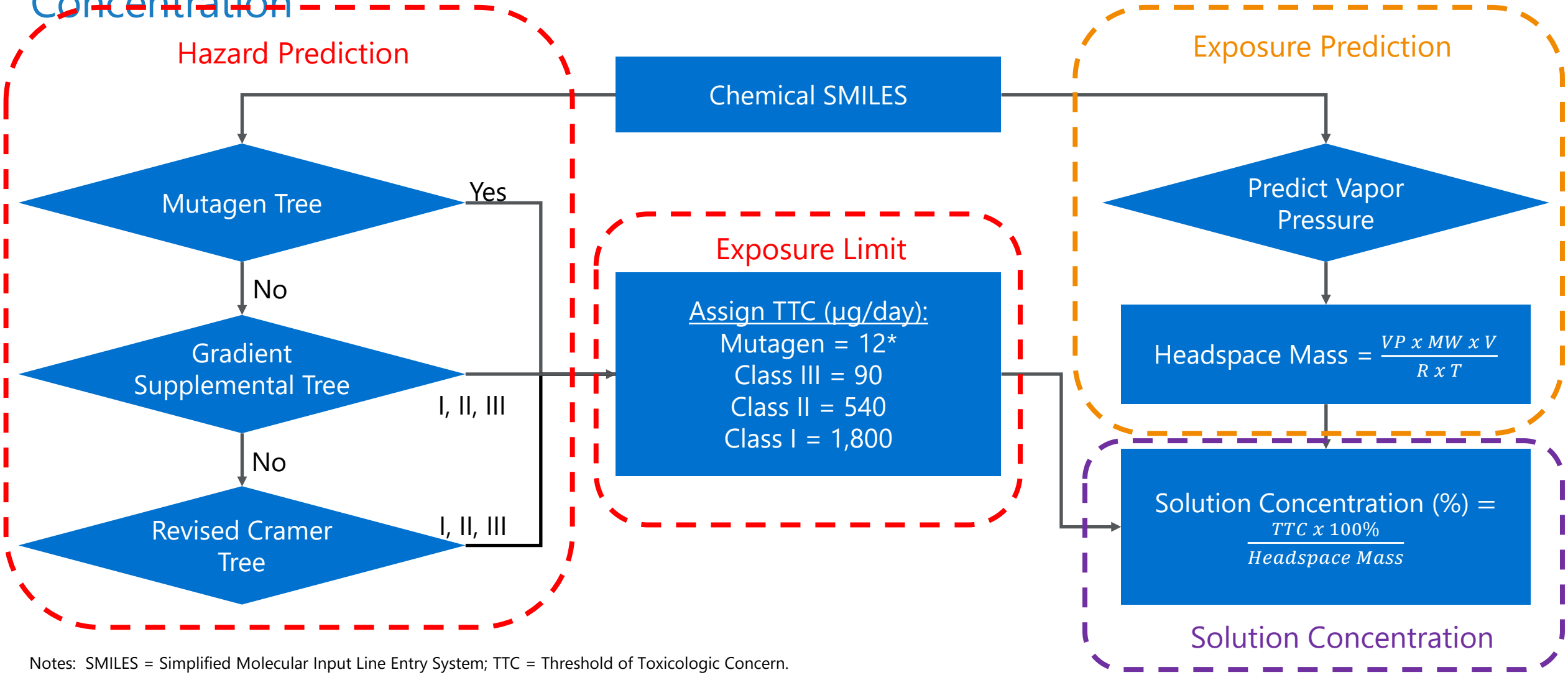
- This *in silico* approach was developed to support a psychophysical study of novel odorants, in which human volunteers sniffed the headspace of a solution in a vial (Lee *et al.*, 2023).
- Safety data lacking for novel odorants, restricts study.
- Develop a transparent *in silico* models to predict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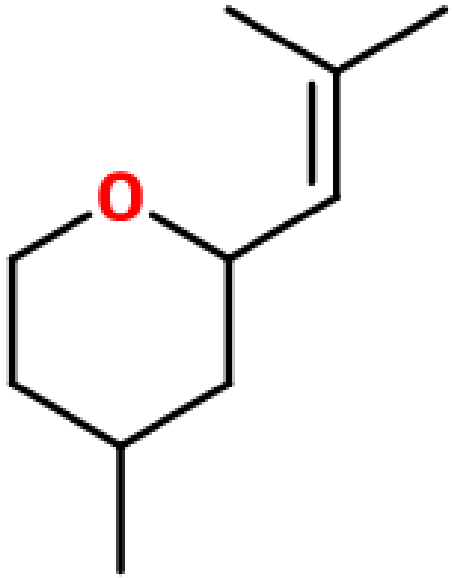
Chemical SMILES

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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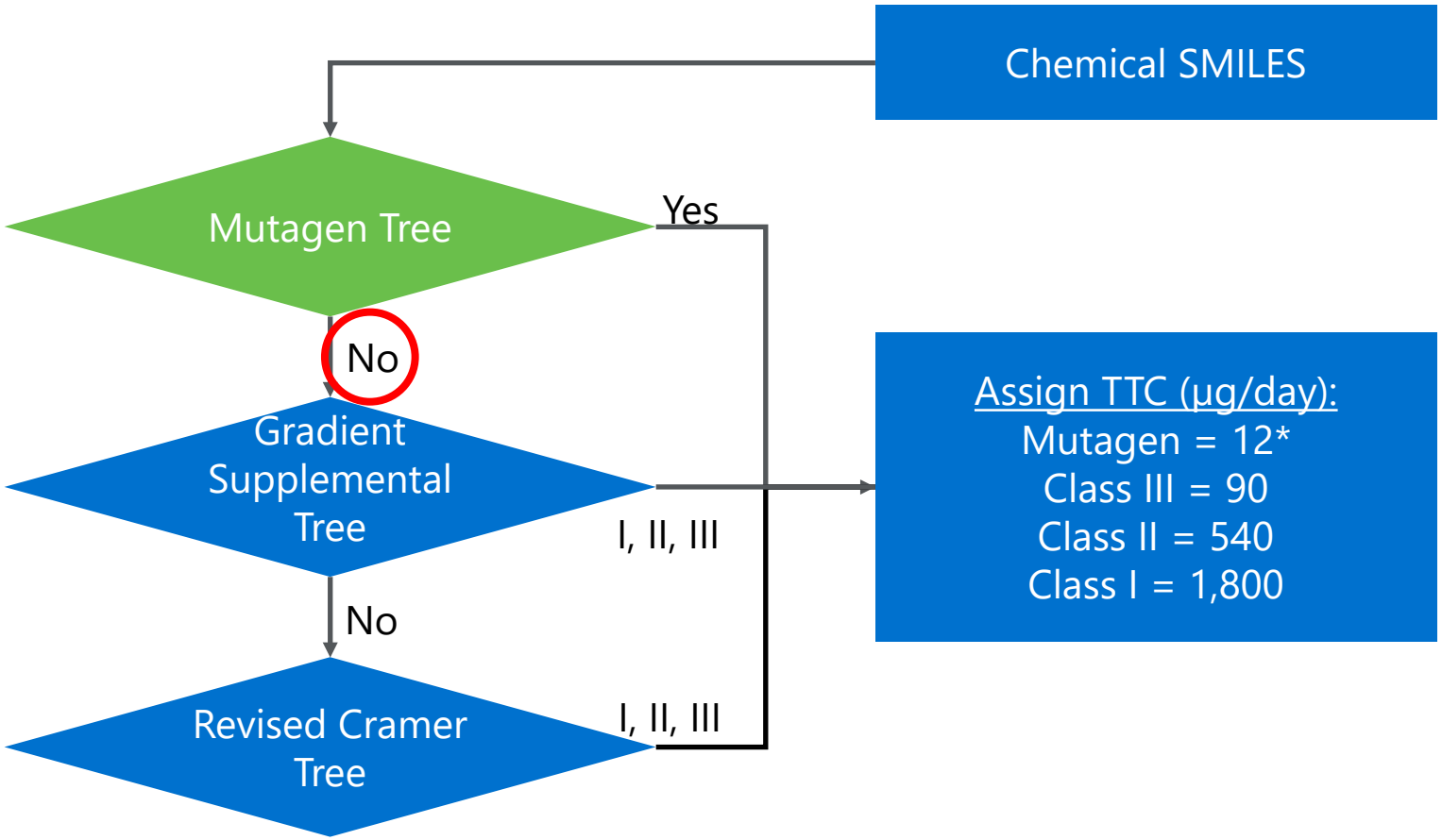
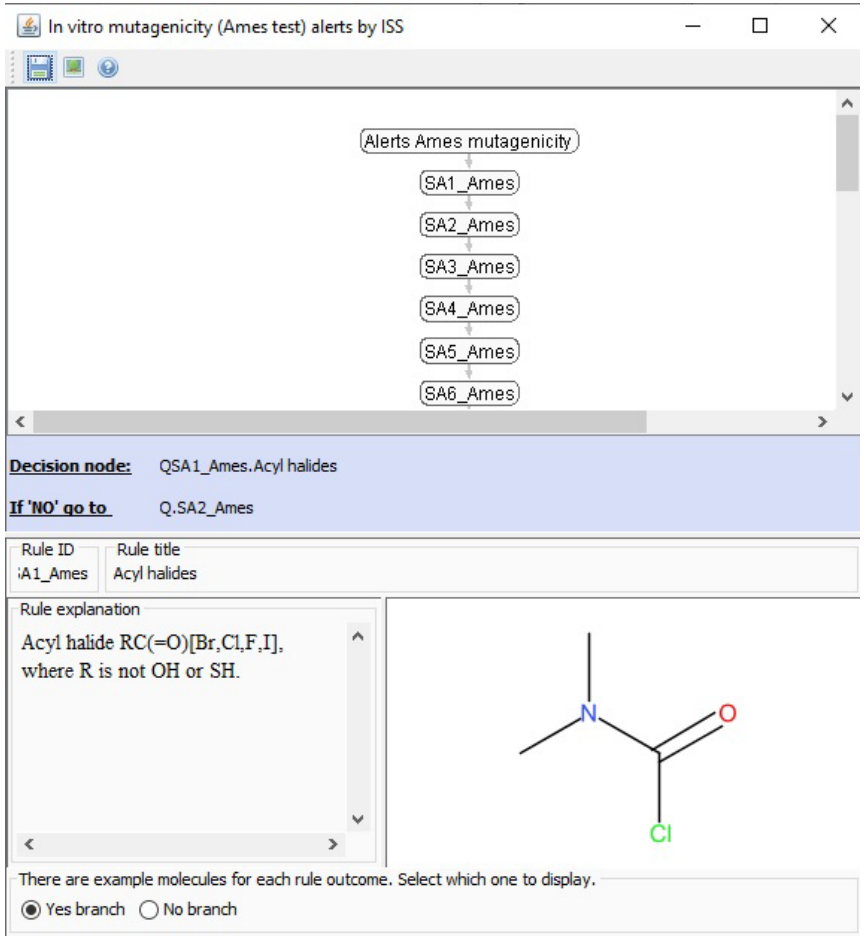


Toxtree software (version 3.1.0)



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

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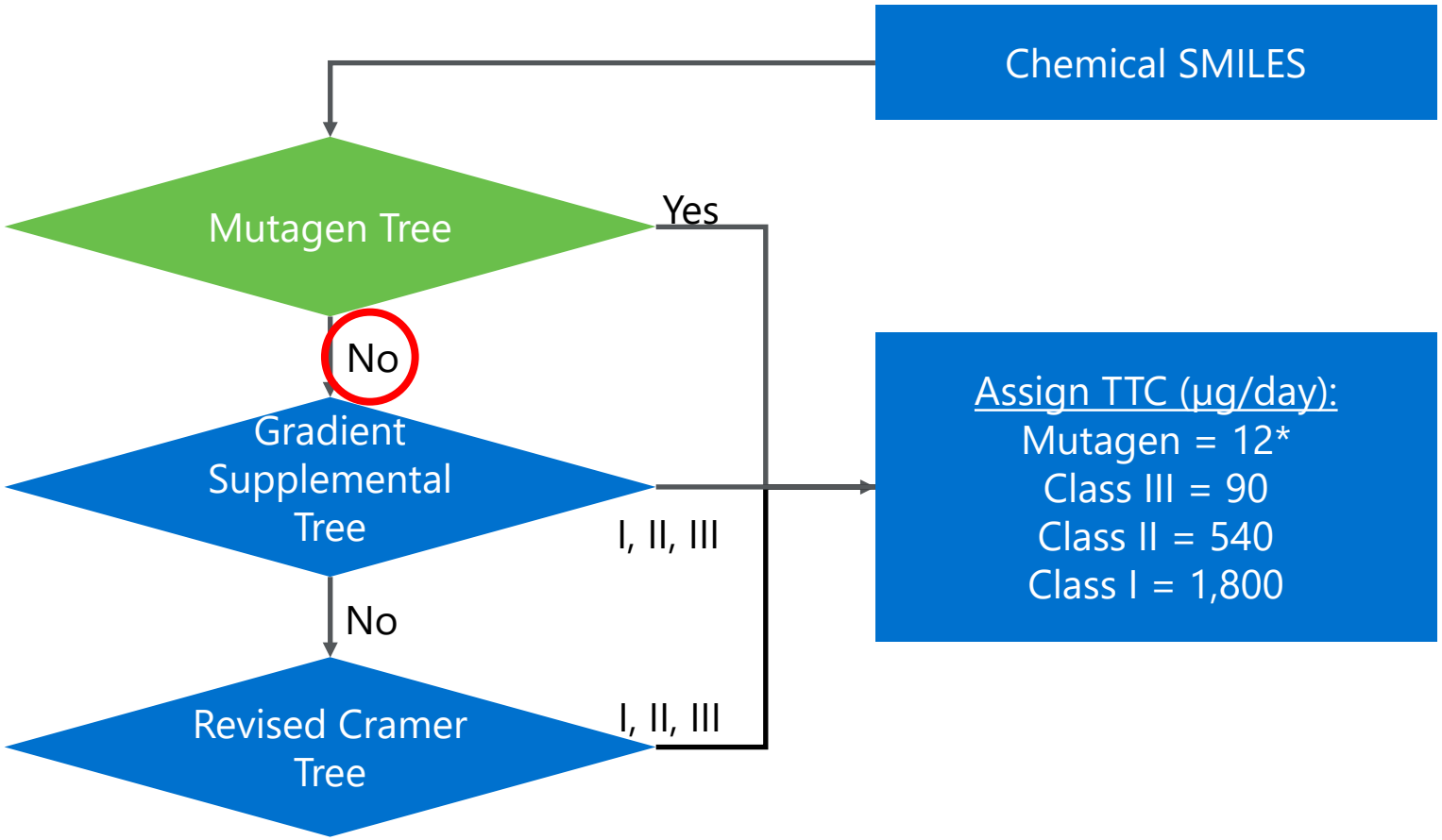

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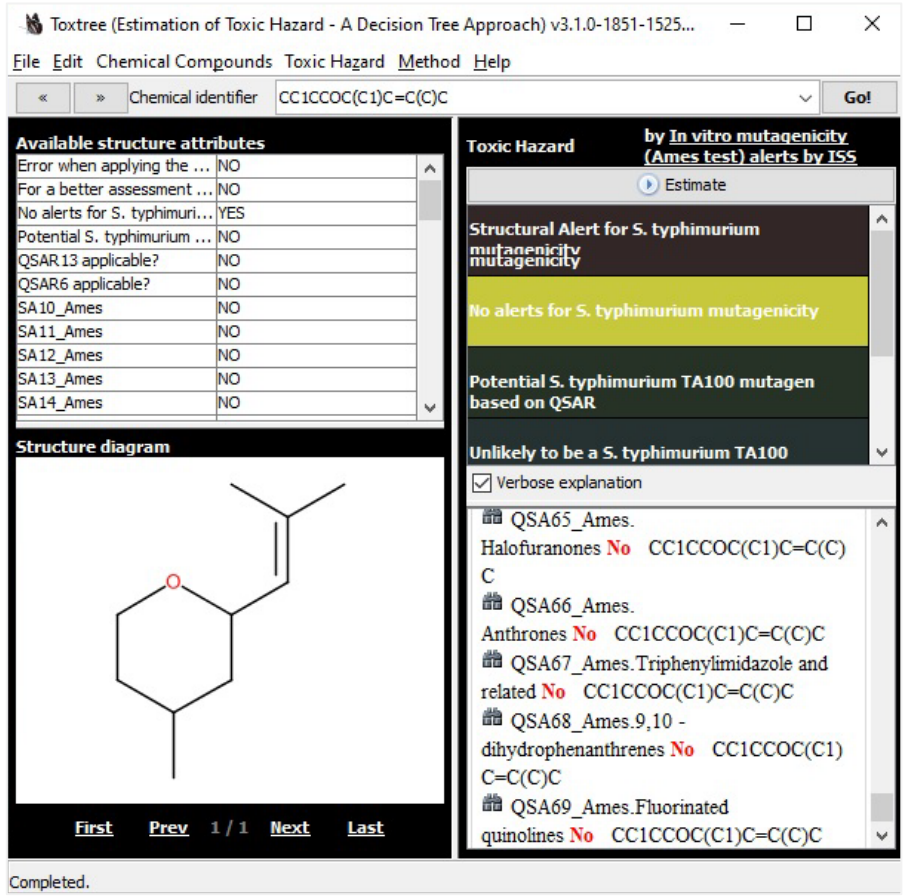

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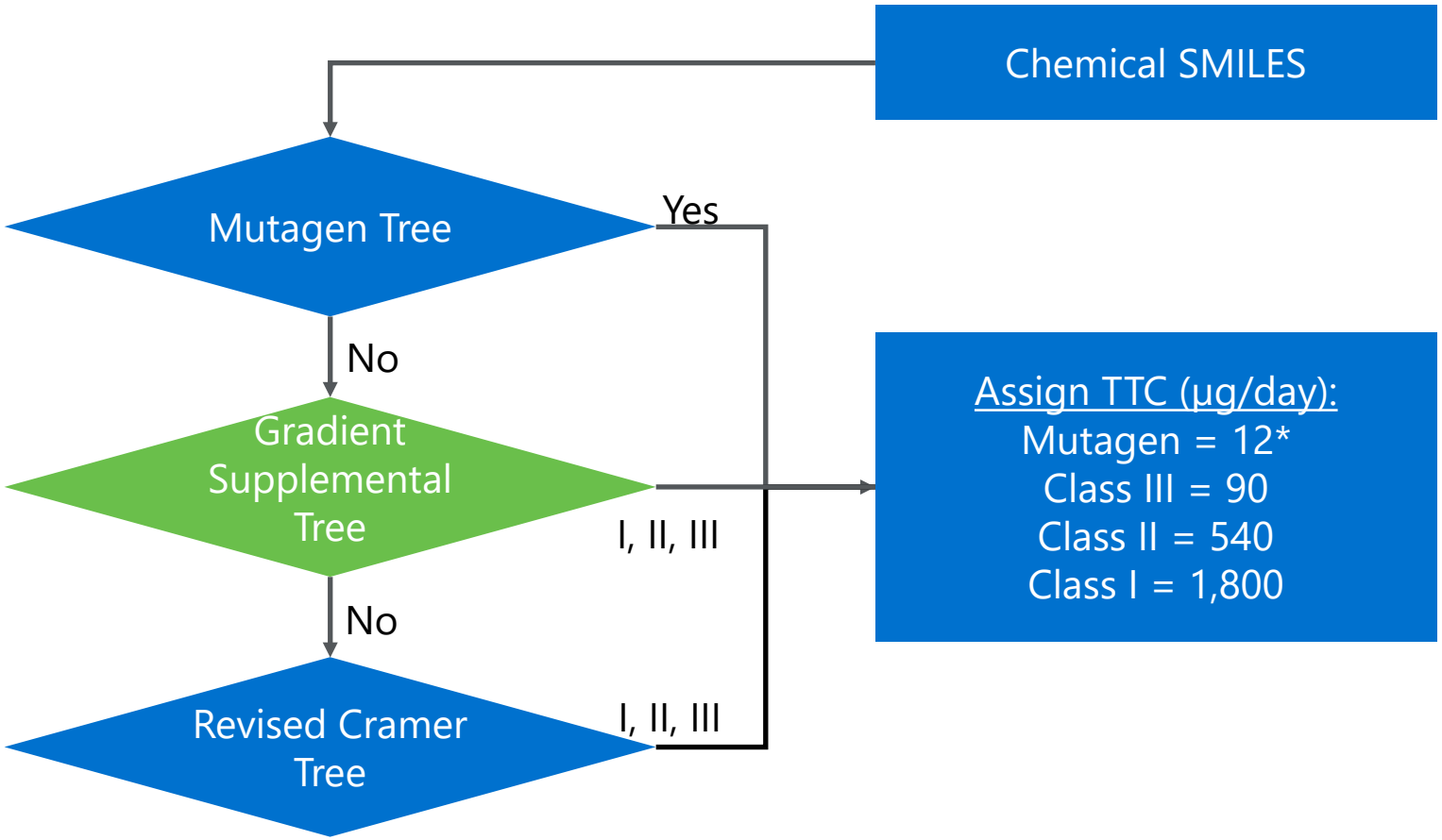

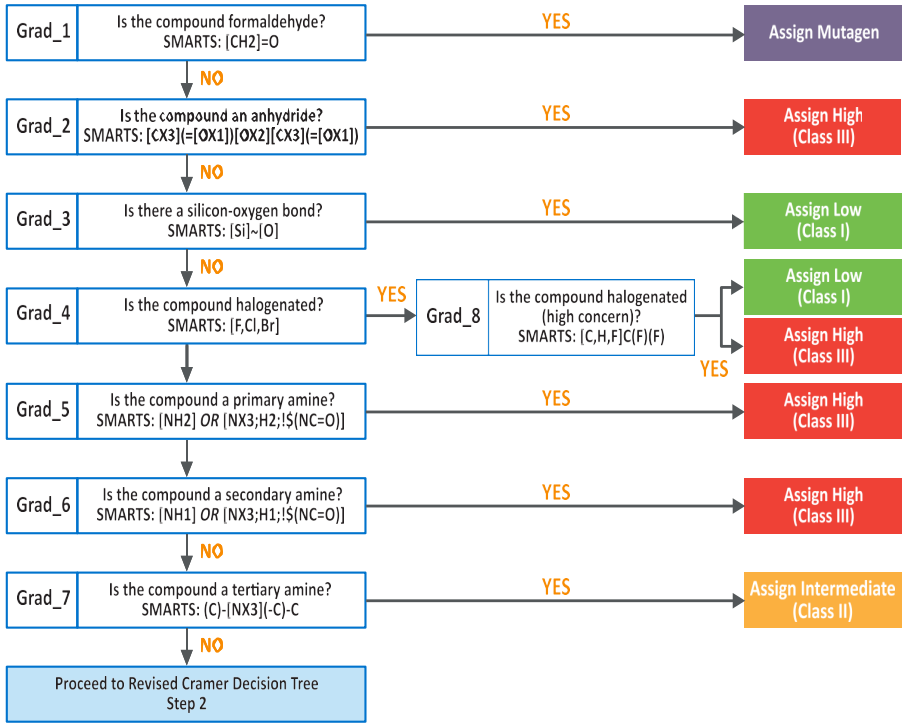

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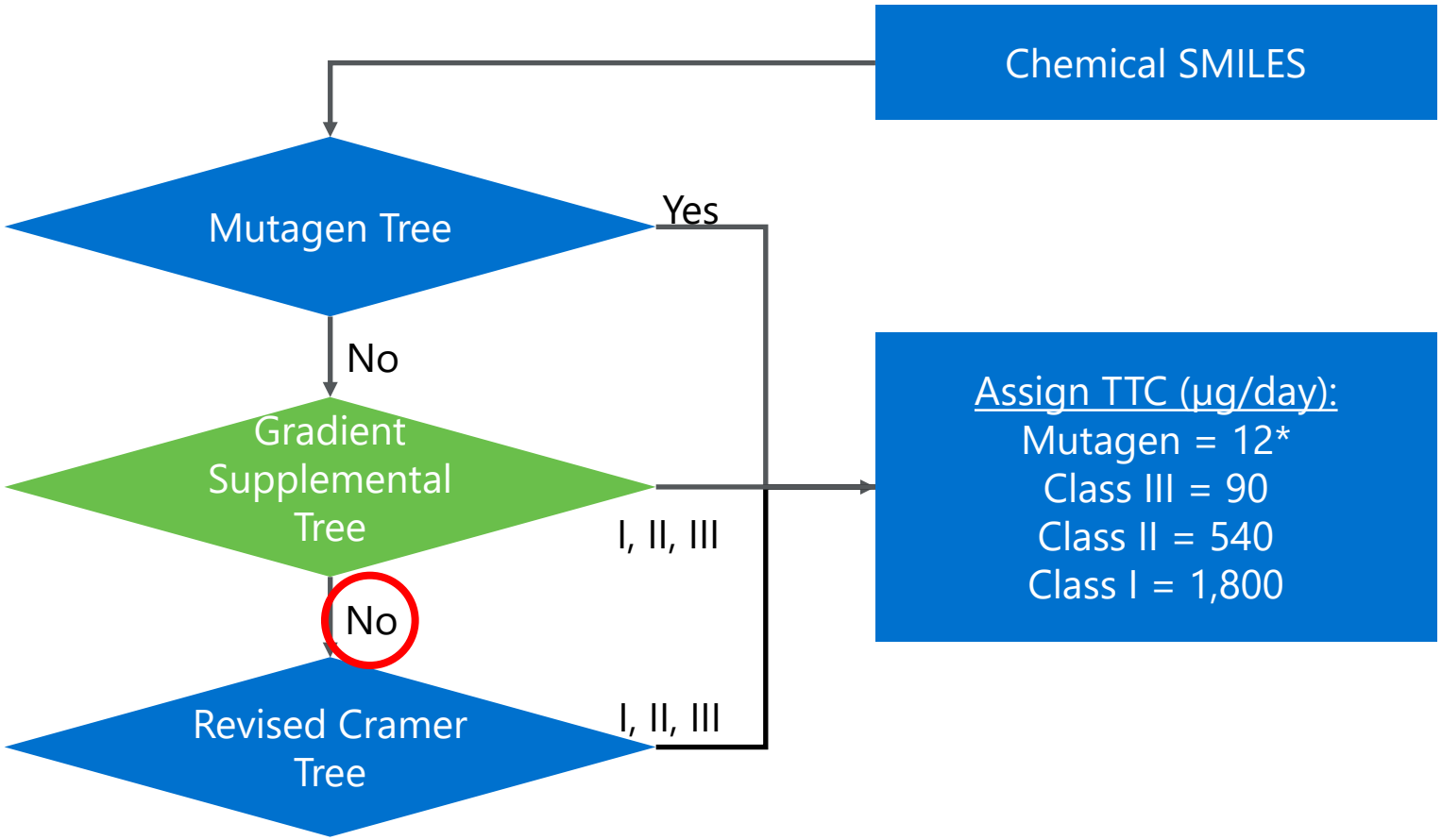

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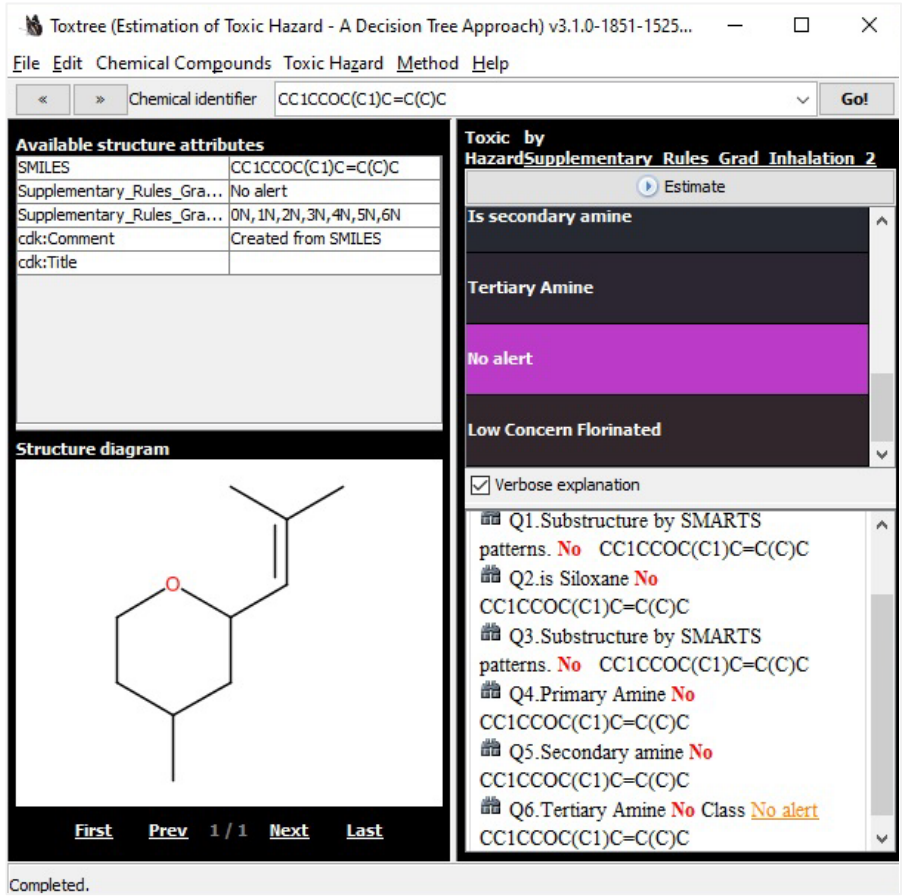

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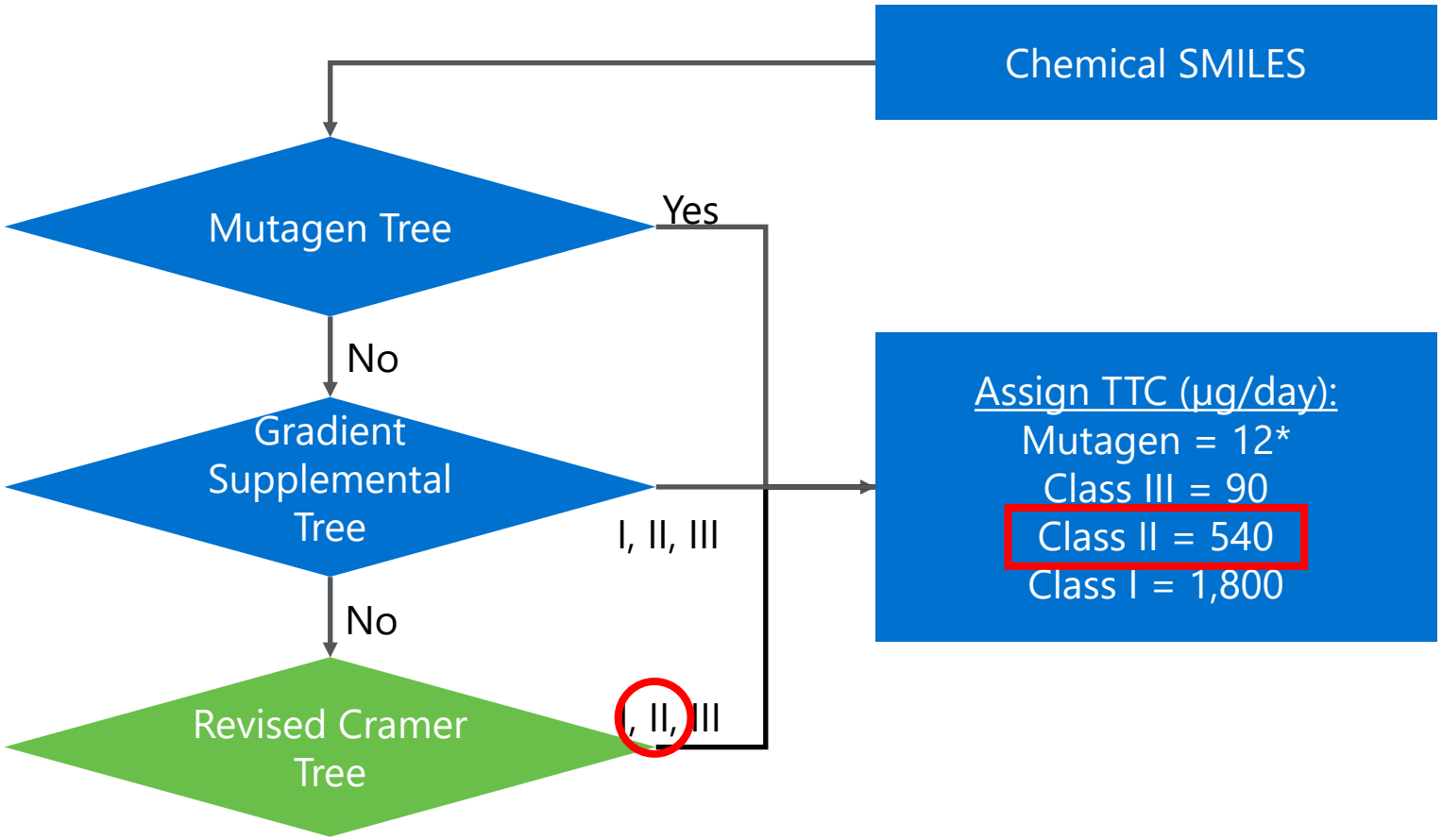

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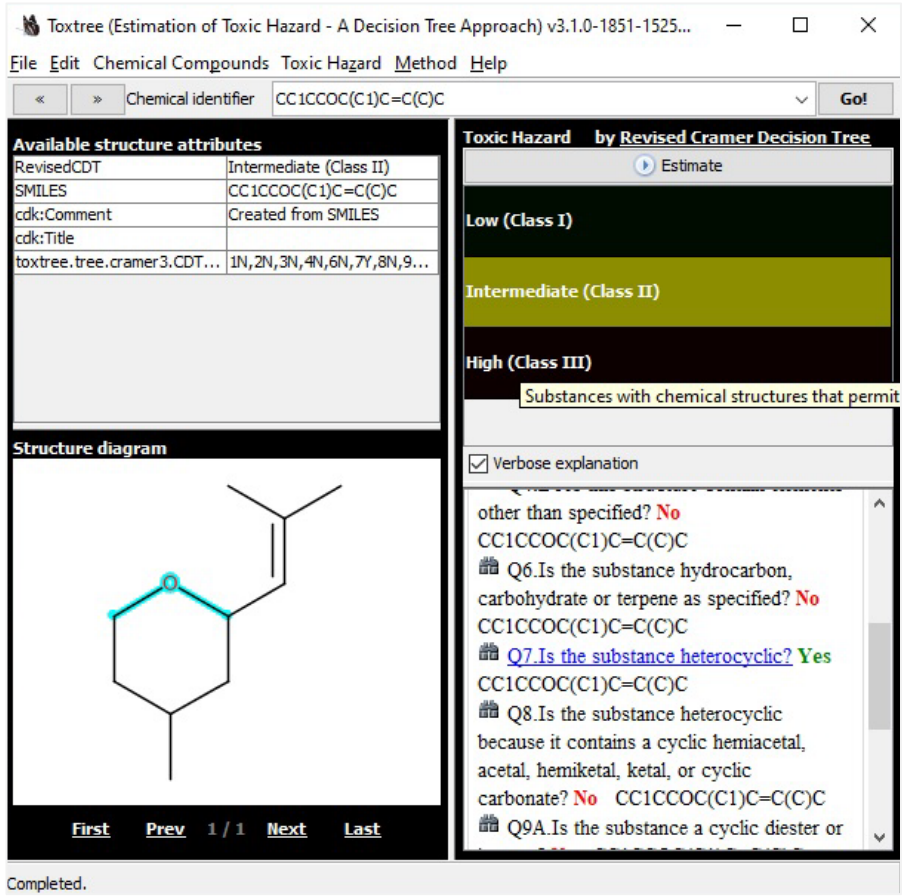

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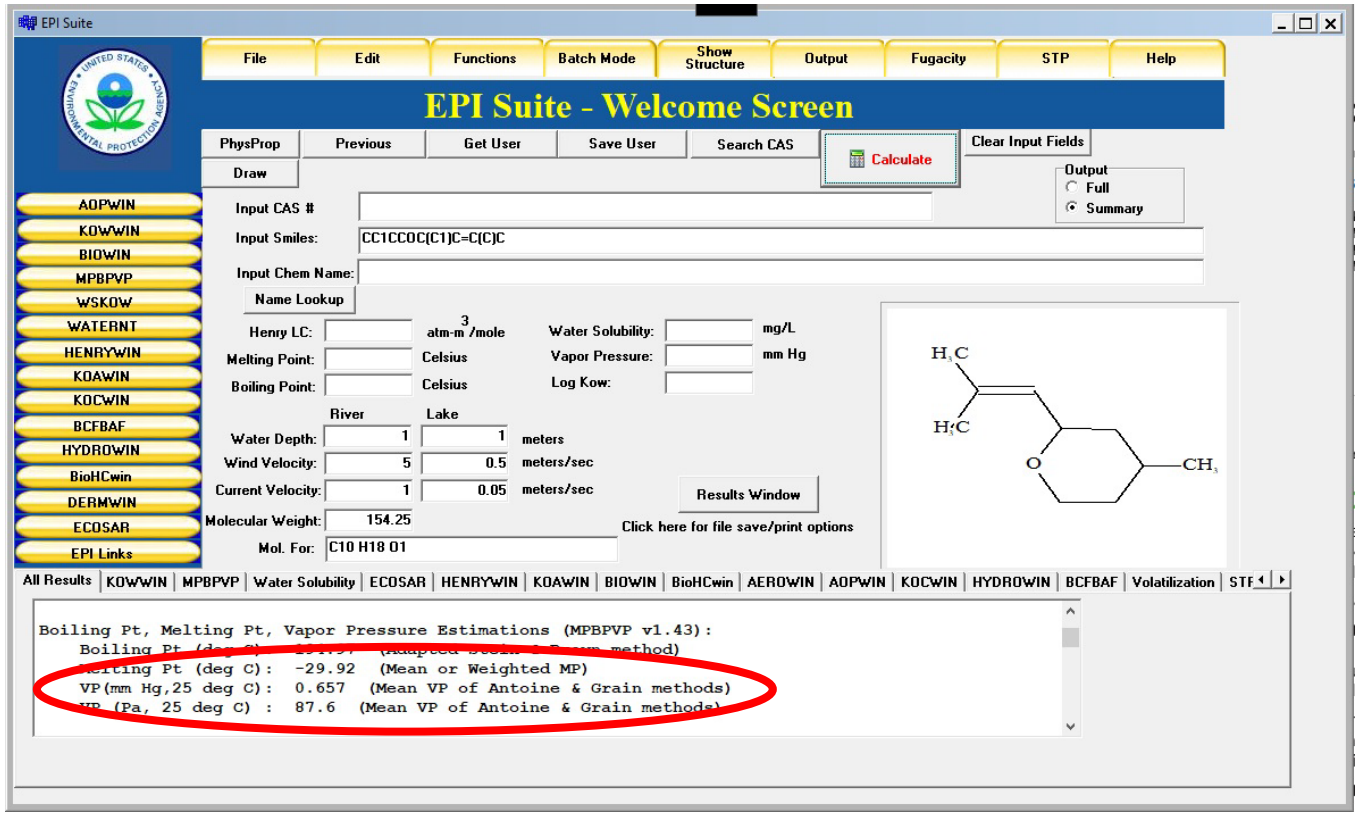
Chemical SMILES

Predict Vapor Pressure

0.657 mmHg @ 25°C

US EPA EPI Suite v 4.11 - MPBPWIN™ (v 1.43)



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

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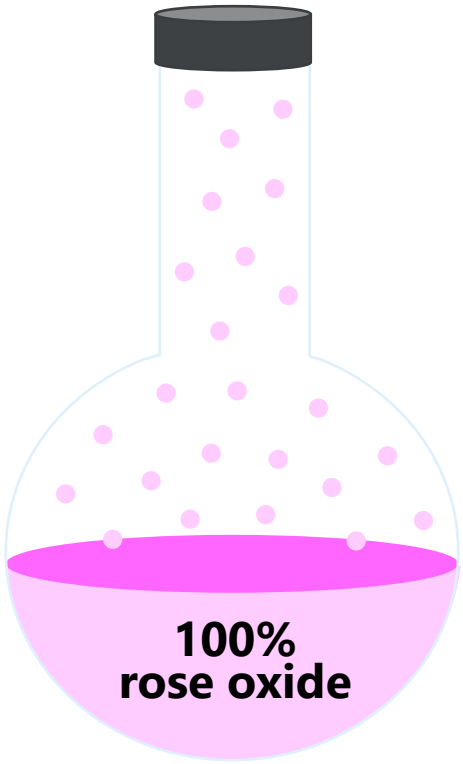

Chemical SMILES

Predict Vapor Pressure

Headspace Mass = $\frac{VP\ x\ MW\ x\ V}{R\ x\ T}$

$$\frac{(0.657\ mmHg)\ x\ (0.001316\ \frac{atm}{mmHg})x\ (154.25\ \frac{g}{mol})\ x\ (0.1\ L)\ x\ (1E6\ \frac{\mu g}{g})}{(0.082\ \frac{L\ atm}{K\ mol})\ \ x\ (298\ K)} = 546\ \mu g$$

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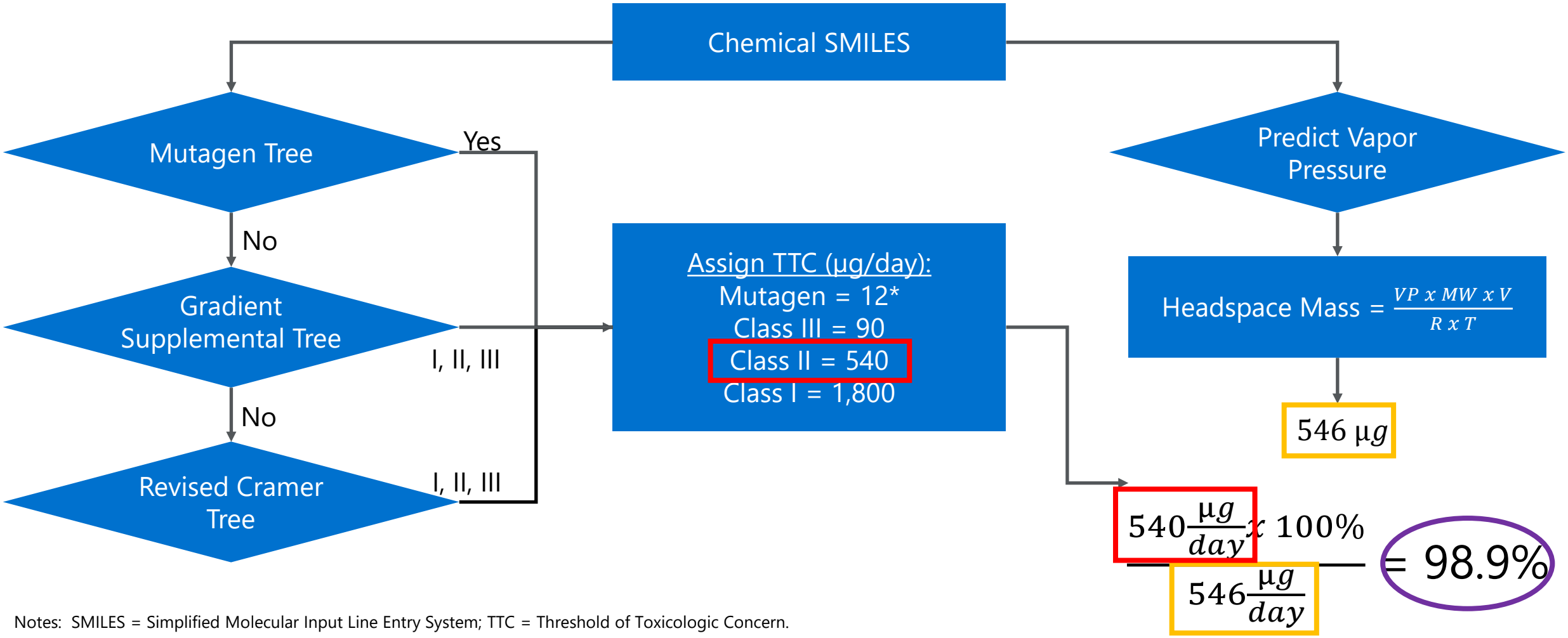

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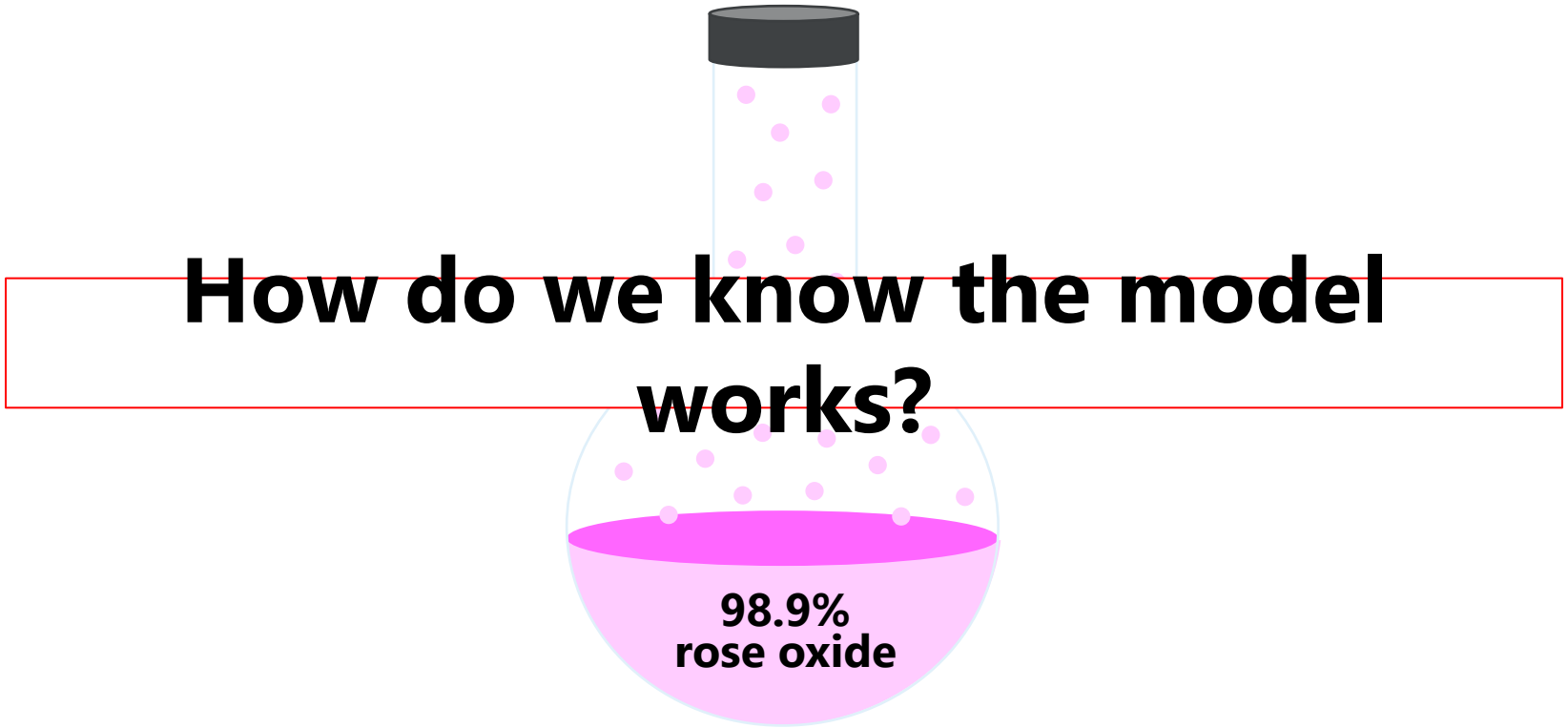
Overview of *In Silico* Prediction of Inhalation Toxicity Hazard and Solution Concentration

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



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 (µg/day) by:
  - $NOAEL\ \left(\frac{\mu g}{day}\right) = NOAEC\ \left(\frac{mg}{L}\right) x\ RMVrat\ \left(0.2\frac{L}{min}\right) x\ \mathrm{t}\ \left(360\frac{\mathrm{min}}{\mathrm{day}}\right) x(1000\frac{\mu g}{mg})$
- 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:

$$Safety\ Margin = \frac{Experimental\ Inhalation\ Study\ NOAEL\ (\frac{\mu g}{day})}{Acceptable\ Predicted\ Exposure\ from\ Headspace\ Mass\ (\frac{\mu g}{day})}$$

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.

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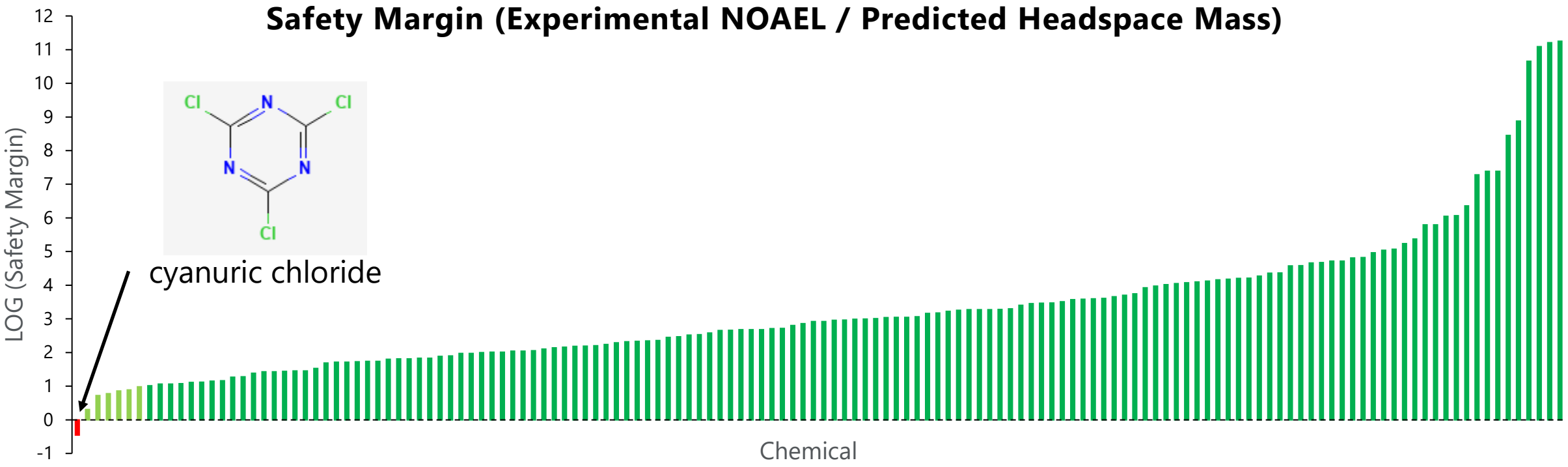

$$Safety\ Margin = \frac{Experimental\ Inhalation\ Study\ NOAEL\ (\frac{\mu g}{day})}{Acceptable\ Predicted\ Exposure\ from\ Headspace\ Mass\ (\frac{\mu g}{day})}$$

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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