FIRST QSTR REPORT ON RAT'S CHRONIC AND SUB-CHRONIC TOXICITY OF DIVERSE CLASS OF CHEMICALS

Presented

by

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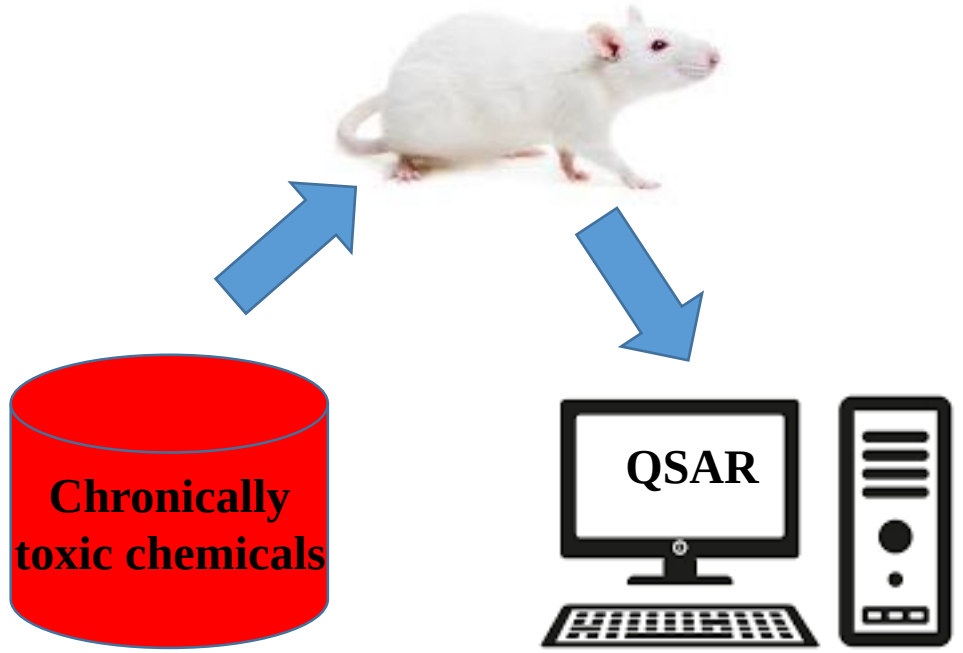
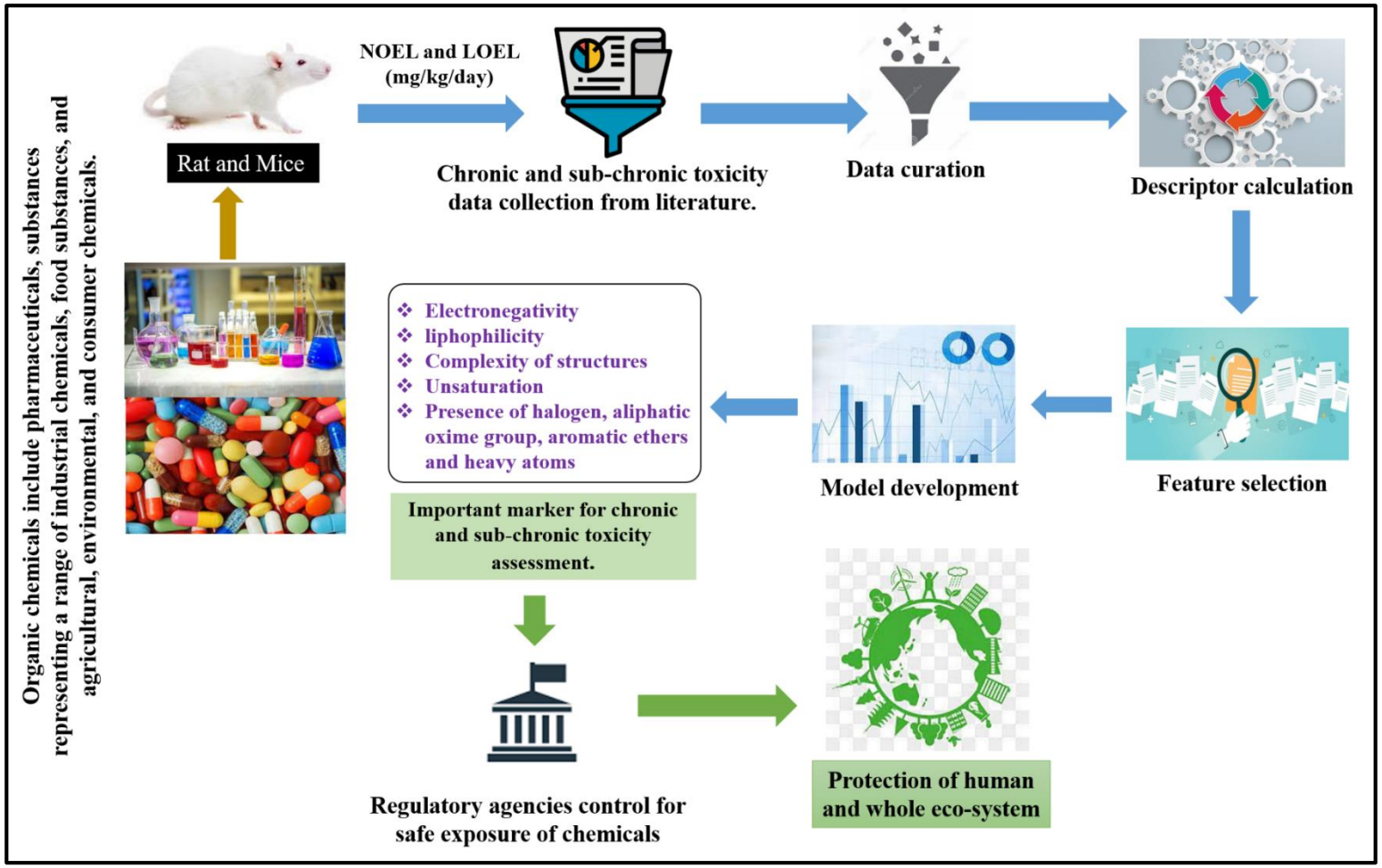
Introduction

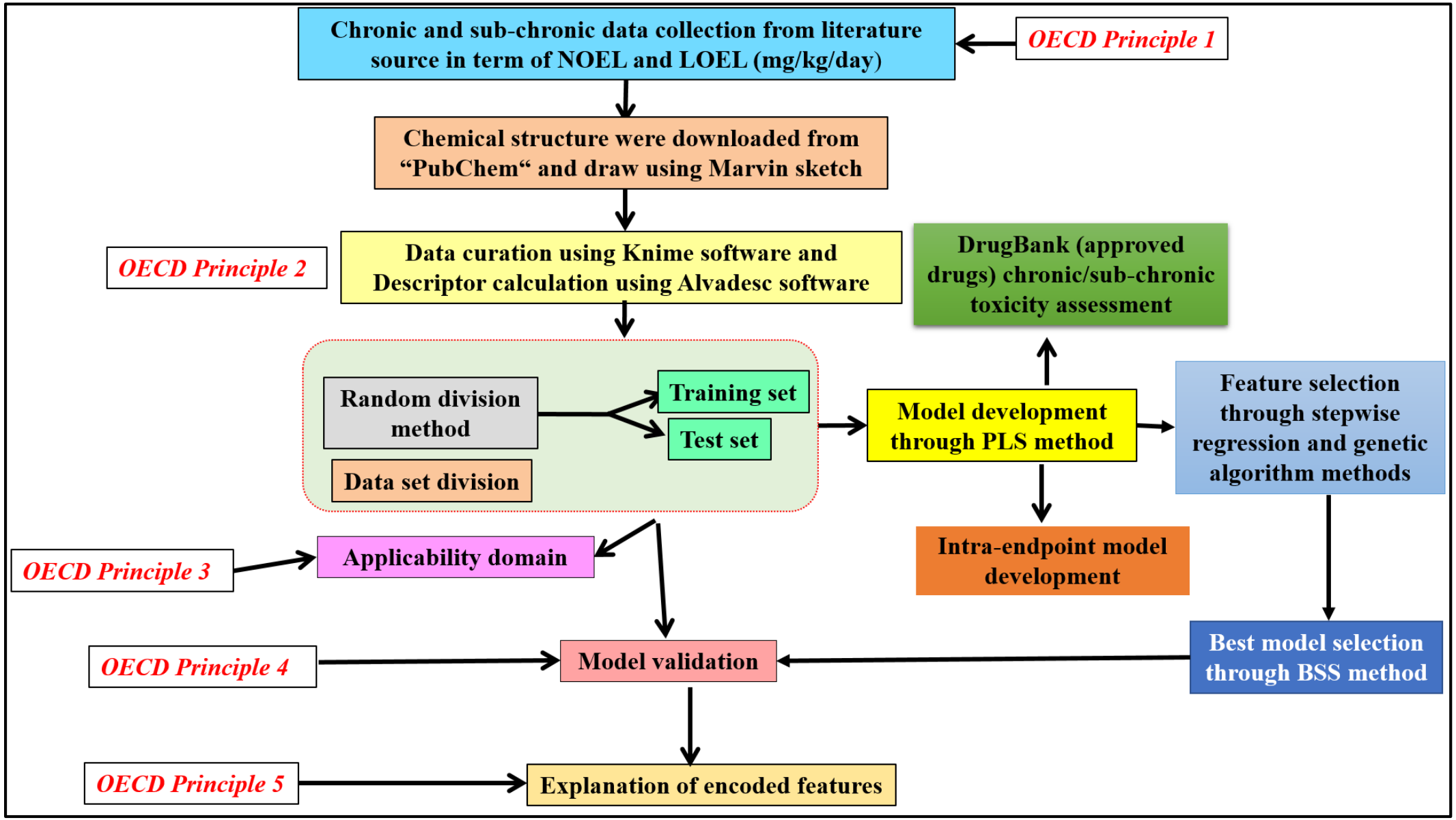
- Humans and other living species of the ecosystem are constantly being exposed to a wide range of chemicals of natural as well as synthetic origin.
- A wide multitude of compounds exerts profound long-term detrimental health effects.
- The chronic toxicity profile of chemicals is of utmost importance for long-term risk assessment.
- Several regulatory agencies, researchers, and organizations are deeply concerned about the chronic/sub-chronic toxicity of chemicals. Since there is a large gap in chronic/sub-chronic toxicity data owing to limited experimental data, QSAR modeling can be used as an alternative.



- Experimental testing of chronic toxicity of compounds, apart from being resource intensive in terms of time, limited availability of experimental data, and associated cost, is not always a feasible option considering the magnitude of the number of chemicals, which necessitates utilizing in-silico approaches to overcome the associated limitations.
- Herein, QSAR (Quantitative Structure-Activity Relationship) models were developed employing the regression-based PLS method with strict adherence to the OECD guidelines.



Method and materials



Result and discussion

IM1: pLOEL chronic toxicity

$$\boldsymbol{pLOEL} = -17.04182 + 0.18387 \times \text{nHM} + 39.64332 \times \text{Eta\_epsi\_3} - 0.13193 \times \text{nCb} - -0.90898 \times \text{nArCOOH} - 0.58155 \times \text{nOHp} - 0.37378 \times \text{C} - 007 + 0.53198 \times \text{B01[N} - \text{O]} + 0.47263 \times \text{B06[C} - \text{N]} + 0.79515 \times \text{B06[C} - \text{Cl]} + 1.71437 \times \text{B01[S} - \text{P]} - 0.45704 \times \text{nArCOOR} + 0.88359 \times \text{nRSR}$$

IM2: pNOEL chronic toxicity

$$\boldsymbol{pNOEL} = 0.7256 + 0.26063 \times \text{nHM} + 0.63801 \times \text{C} - 019 - 0.36212 \times \text{O} - 058 + 1.5621 \times \text{B03[C} - \text{P]} + 0.86576 \times \text{B04[C} - \text{N]} + 0.60945 \times \text{nArOR}$$

IM3: pLOEL sub-chronic toxicity

$$\boldsymbol{pLOEL} = -1.81023 - 0.15185 \times nO + 0.55685 \times nCsp + 0.18064 \times X4v + 2.50839 \times nRCNO + 0.10683 \times H - 048 - 0.37199 \times MaxdssC + 0.54049 \times MaxssssC + 2.97984 \times B01[C - F] - 0.89772 \times B05[O - S] + 0.5201 \times SAscore + 0.08844 \times C - 026 + 0.18375 \times nCconjX$$

IM4: pNOEL sub-chronic toxicity

$$\boldsymbol{pNOEL} = -2.04357 + 0.98599 * nCrq - 0.25671 \times H - 051 - 1.09359 \times minssCH2 + 1.84276 \times B01[C - C] - 0.71667 \times B03[C - C] + 0.76782 \times B04[N - N] + 0.81005 \times B05[C - O] + 1.10367 \times F01[S - P] - 0.32873 \times F02[O - O] + 0.36323 \times B07[C - C] + 3.75617 \times Eta\_alpha\_A - 0.69496 \times nRCONR2$$

Model IM5:

pNOEL = 0.69211+1.0005 ×pLOEL

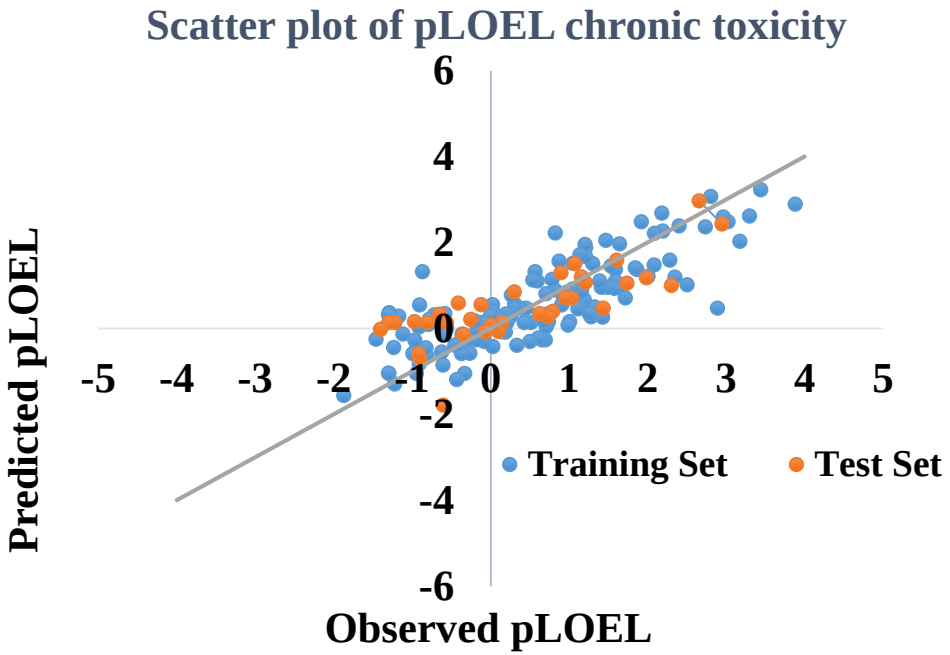
Model IM6:

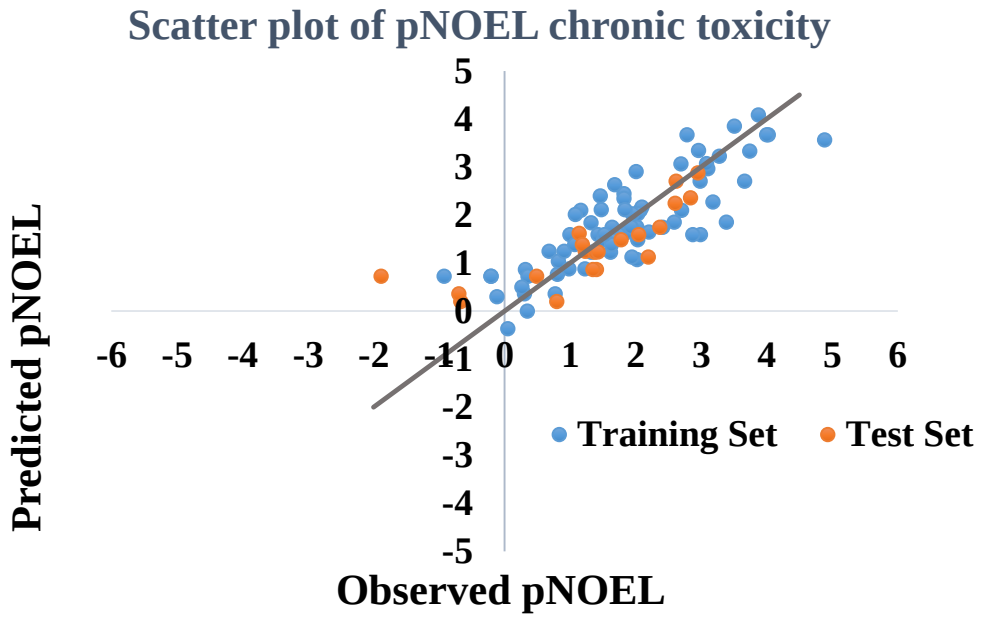
pNOEL = 0.54434+1.01288×pLOEL

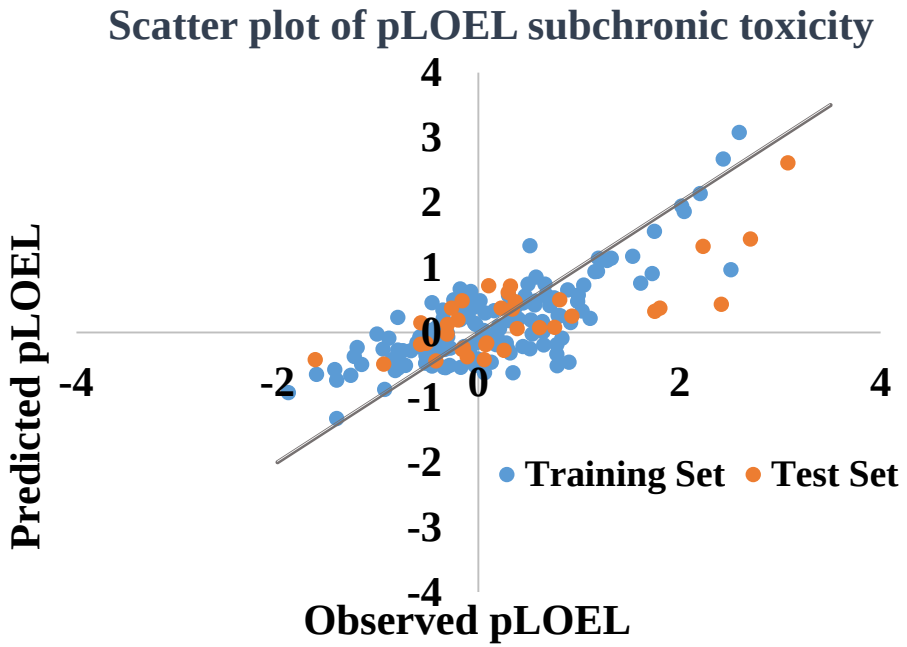
Table : Validation metrics of the developed models

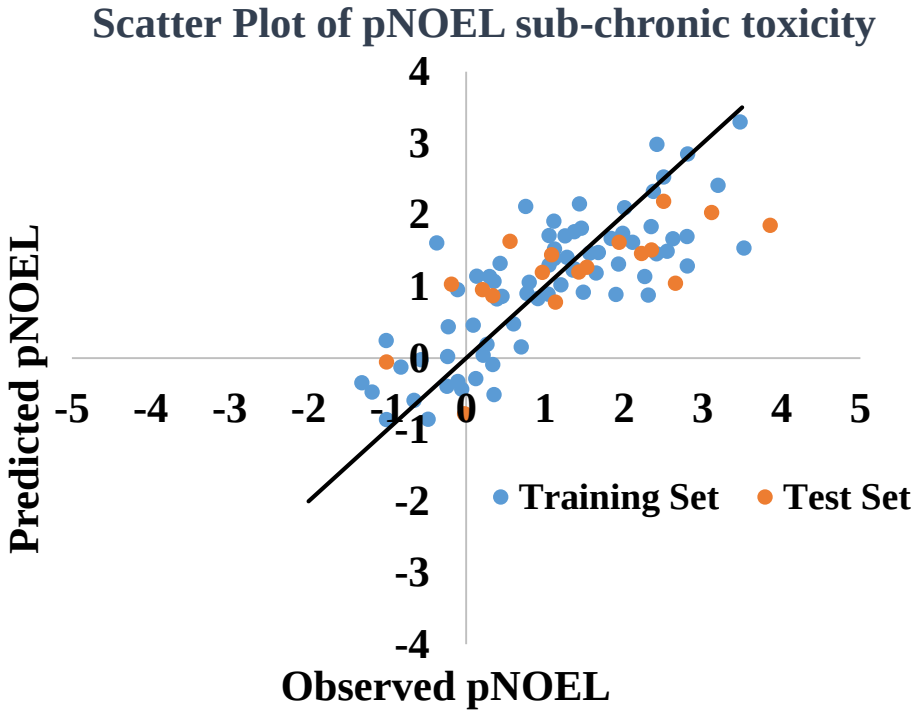
Types of models	LVs	Number of descriptors	**Training set statistics**			**Test set statistics**		
			Model R^2	Model $Q^2_{(LOO)}$	MAE_{LOO}	R^2_{pred} or $Q^2_{(F1)}$	$Q^2_{(F2)}$	MAE_{Test}
IM1 (CHRONIC_ LOEL)	2	12	0.673	0.624	0.575	0.618	0.606	0.559
IM2 (CHRONIC _NOEL)	2	6	0.711	0.604	0.545	0.658	0.598	0.542
IM3 (SUB CHRONIC _LOEL)	4	12	0.607	0.547	0.464	0.562	0.537	0.546
IM4 (SUB-CHRONIC_ NOEL)	4	12	0.632	0.513	0.639	0.523	0.50	0.730
IM5 (CHRONIC_ NOEL+LOEL)	-	1	0.9196	0.914	-	0.946	0.945	-
IM6 (SUB-CHRONIC_NOEL +LOEL)	-	1	0.964	0.961	-	0.936	0.935	-

Scatter plot of developed models

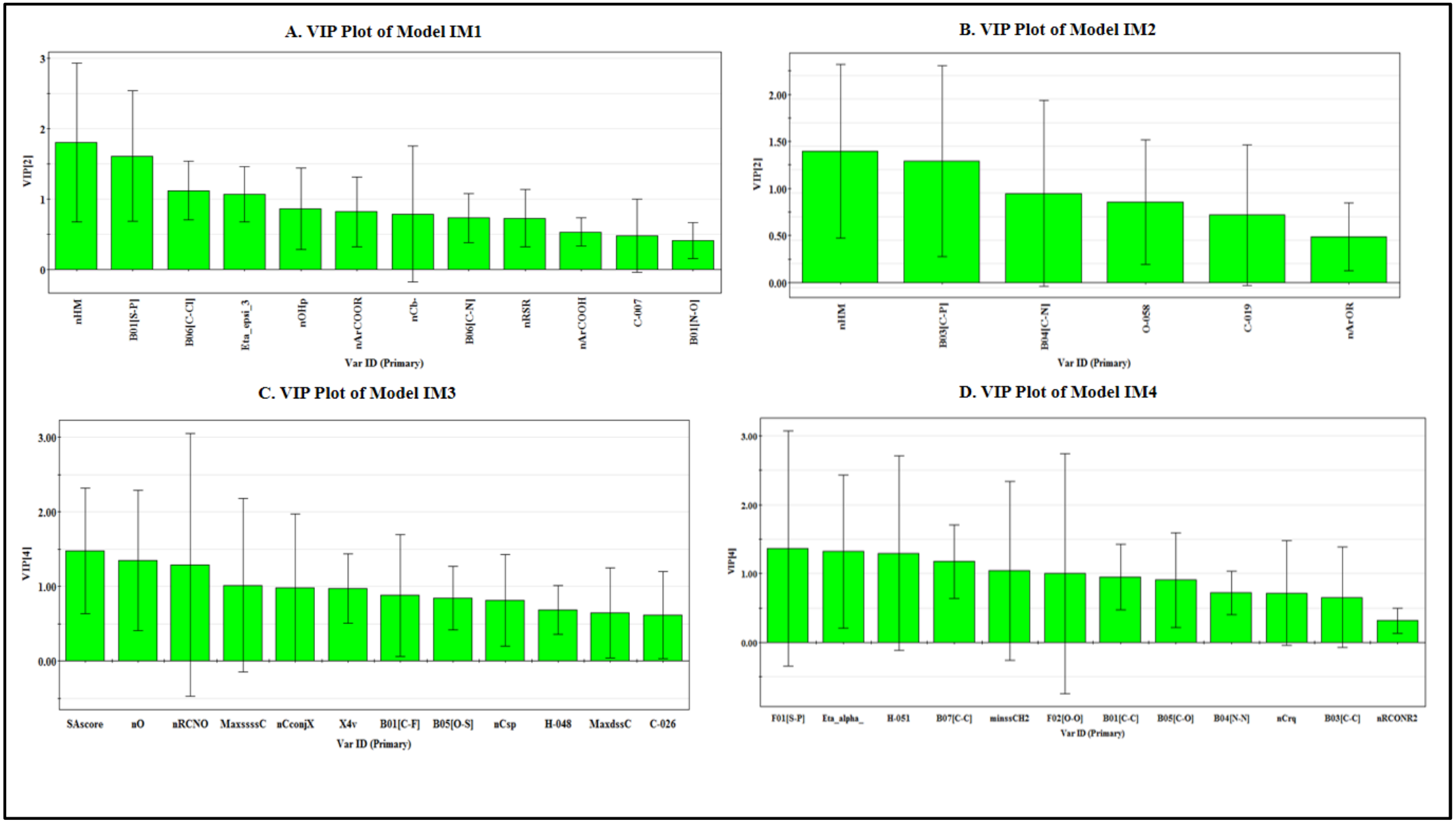




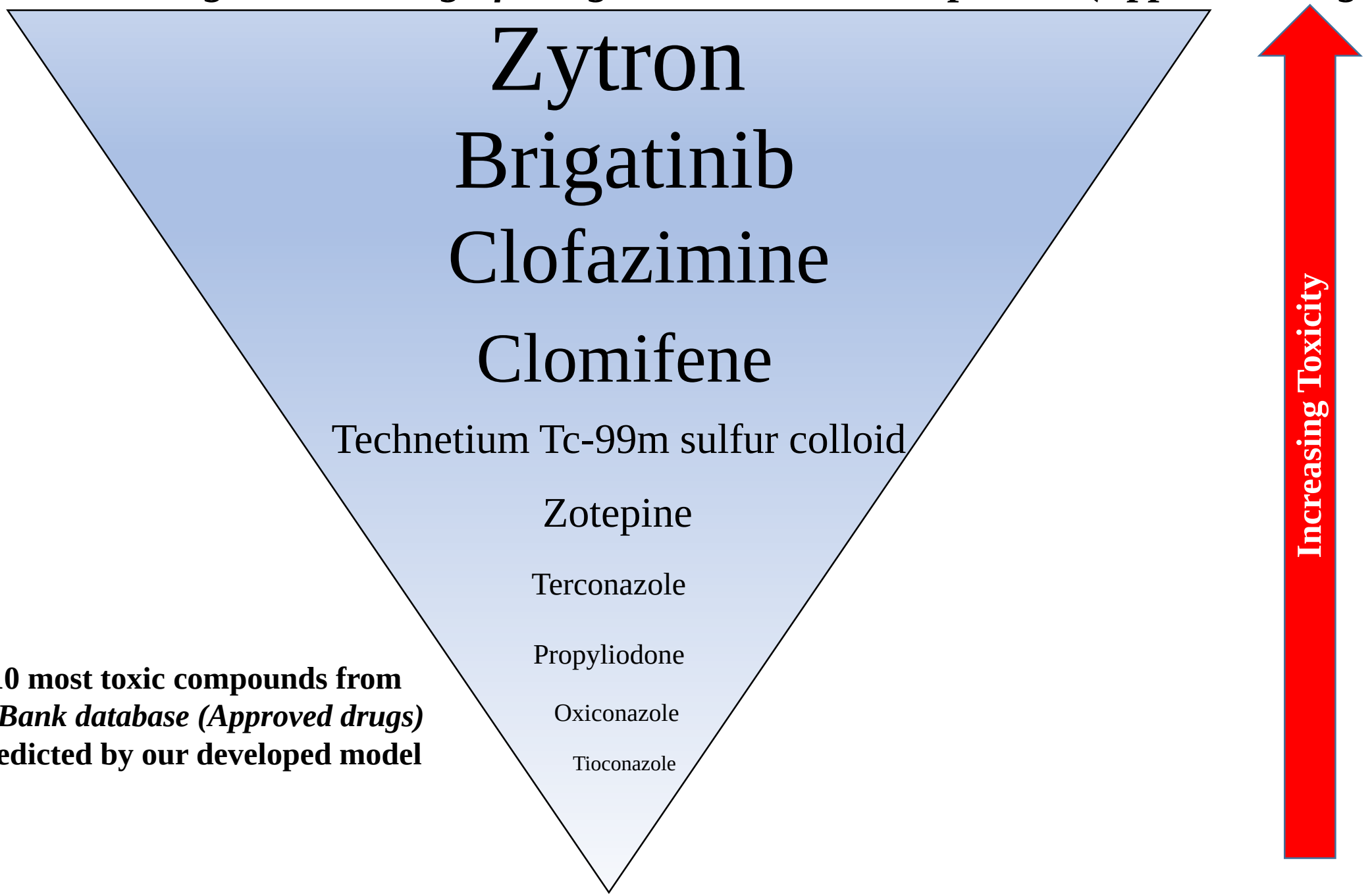




Variable importance plot



Screening and Ranking of DrugBank database compounds (Approved drugs)



Top 10 most toxic compounds from *DrugBank database (Approved drugs)* as predicted by our developed model

Conclusion

- Important features **increasing chronic and sub-chronic toxicity**: lipophilicity, electronegativity, aromatic ethers or aliphatic oxime group, the complexity of structures, unsaturation in molecules, presence of halogen and heavy atom (phosphate, sulphur, etc.).

- Features **decreasing chronic and sub-chronic toxicity**: polar and hydrophilic groups

- Models developed→ toxicity prediction and assessment of chemicals as well as data-gap filling → fulfill the strict guideline of ECHA to provide toxicity assessment of all existing chemicals.

- Validated models → screening, and prioritization of chemicals, pharmaceuticals, and other compounds inside the chemical space (AD) of the developed models.

- DrugBank database (Approved Drugs) → screening and ranking was performed → top 10 compounds with chronic and sub-chronic toxicity was detected

- Thus, the developed model will help to reduce the time, cost, resources, and frequency of animal testing strictly catering to the “RRR” (reduction, refinement, and replacement) principles.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