Improving the Predictivity of QSAR Models to Evaluate Rodent Carcinogenicity

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Introduction

Carcinogenicity is considered one of the most important toxicity endpoints to evaluate concerning human safety. The high costs associated with rodent carcinogenicity studies and the time required to perform them render the amount of experimental data available limited, thus presenting challenges for QSAR modeling.

Our previously reported rodent carcinogenicity QSAR models were built with public data collected in collaboration with the FDA's Center for Drug Evaluation and Research. To further improve the predictive performance of rodent carcinogenicity QSAR models, the size of the dataset was increased by processing current data from FDA drug labels using natural language processing techniques.

This approach of adding new compounds increased the accuracy of models. However, to characterize the effect of the updates on the structural composition and diversity of the models, a deeper analysis was performed comparing the updated models with the original ones.

Model Comparisons

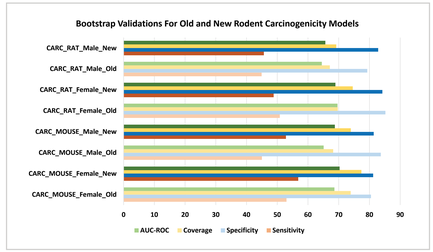
Existing and Updated Rodent Carcinogenicity Models

Updated carcinogenicity models were built with CASE Ultra software. These models improved the number of descriptors (structural alerts) and covered several additional classes of rodent carcinogens.

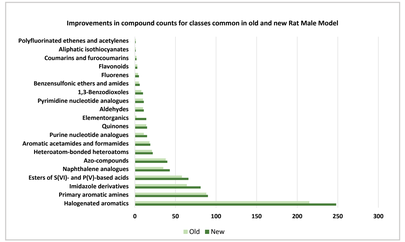
Data from current FDA drug labels processing added new chemicals ranging from 79 - 131 for various male and female mouse and rat models.

	Data set size		Newly added data		
Model Name	Old	New	Positives	Negatives	Total
MOUSE FEMALE	1279 (545/734)	1361 (546/815)	8	77	85
MOUSE MALE	1266 (510/756)	1342 (511/831)	9	70	79
RAT FEMALE	1387 (566/821)	1507 (575/932)	17	110	127
RAT MALE	1397 (624/773)	1523 (645/878)	24	107	131

There is significant improvement in the sensitivity, specificity, coverage, and accuracy of the models.



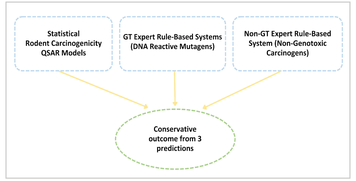
This update not only increased the compounds count per chemical classes that are present in old models, but also added new classes of compounds (for example Aryl hydroxamates and Catecholamines in Rat Male model). This analysis helped us identify the chemical classes that need improvement.



Methodology for Improving Predictions

To reduce the number of inconclusive and out of domain predictions obtained from the newly developed carcinogenicity models, we identified an approach of using GT Expert Rule-Based (DNA Reactive Mutagens) and Non-GT Expert Rule-Based (Non-Genotoxic Carcinogens) SAR model predictions in addition to statistical rodent carcinogenicity QSAR models.

After obtaining predictions from both statistical and expert rule-based systems, the outcome should be based on a conservative approach where a positive result in either statistical or expert rule-based model gives an overall positive prediction.



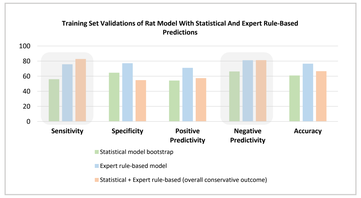
Results and Discussion

We considered rat male model to test this approach. Bootstrap validations (10% out of 100 times) were performed on the training set. Compounds that are consistently mispredicted as either "inconclusive" or "out of domain" were identified from these validations. These compounds are then predicted against the GT Expert Rule-Based system (DNA Reactive Mutagens) and Non-GT Expert Rule-Based system (Non-Genotoxic Carcinogens) which resulted in resolving the majority of the out of domain/inconclusive calls that are obtained from statistical model predictions. Thus, subjecting the compound to prediction against all three models (Statistical, GT Expert, and Non-GT Expert Rule-Based systems) resolved all the out of domain/inconclusive calls except for two compounds, abrocitinib and silicone dioxide (shown right).

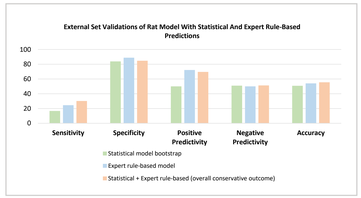
Abrocitinib
Experimental Activity: Negative

Silicone Dioxide
Experimental Activity: Negative

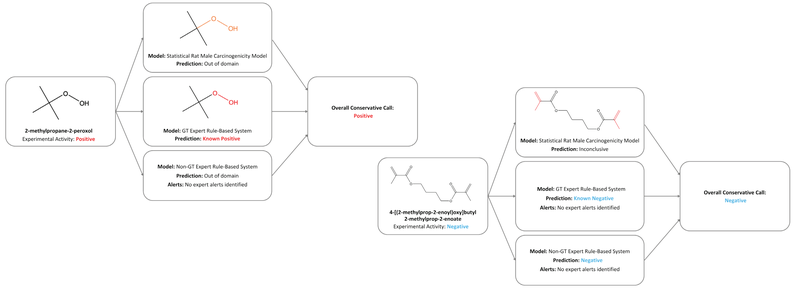
Prediction accuracies are also improved with this approach. There is a drastic improvement in the sensitivity and negative predictivity of the models.



To further verify the approach, a small external set of 110 compounds obtained from ECHA is subjected to validation against all three models (Statistical, GT Expert, and Non-GT Expert Rule-Based systems). The external set validations also show an improvement when predicted against three models versus using just the statistical rat model.



Examples of compounds with predictions improved by the technique:



Conclusion

This approach of joint use of statistical and expert rule-based systems can aid in resolving out-of-domain and inconclusive predictions, thereby providing highly interpretable and reasonably accurate (Q)SAR models for predicting rodent carcinogenicity. In addition, the analysis of existing and updated QSAR models helped us identify structural gaps, defining the direction of future improvements to the chemical space of the models.

Conflicts of Interest

Roustem Saiakhov and Mounika Girireddy were employed by MultiCASE, Inc. at the time of this study.