

Investigating false predictions in mutagenicity QSAR models: What are we missing?

C. Hasselgren¹

S. Boyer¹

¹*AstraZeneca, Mölndal, Sweden*

Mutagenicity is the ability of a compound to induce permanent, heritable alterations in DNA sequence. The most common experimental test is the Ames¹ assay which is used as a predictor of carcinogenicity. The use of QSAR models to predict mutagenicity is current practice not only in the pharmaceutical industry but also in the manufacturing of industrial chemical and food additives etc. Numerous QSAR models have been published and report predictivities ranging from 60 to 85% depending on the dataset.

We have previously reported a rules-based system for risk assessment of mutagenicity. This comprises QSAR results, experimentally tested structural near neighbours and the presence of substructural alerts.² The overall predictivity of this system based on the QSAR alone was reported to be around 80-85% with sensitivity being slightly lower than specificity.

In this study, we report the temporal validation of this system based on data generated within AstraZeneca after the system was built. The aim is to assess true model predictivity on external data. In addition, work directed at understanding why some compounds are not correctly predicted by our QSAR models is presented. Emphasis was placed on experimentally active compounds which were falsely predicted as inactive, as these are of critical importance to guide experimental testing. Poor sensitivity has previously been discussed in terms of non-covalent interactions and poor structural coverage.³

The work includes various methodologies, such as assessing local structural environments in the dataset around the classified compounds, using a variable kNN approach. This was done to identify poor/variable coverage in the dataset. Also, separately modelling subgroups of the dataset, based on the presumed mechanism of interaction with DNA, was explored to investigate if non-covalently interacting agents could be modelled using electrostatic surfaces or pharmacophore/shape based methods.

The temporal validation shows that the models do not perform as well on an external dataset for active compounds but inactive predictions have high confidence. A number of public compounds were also included in the analysis and will be used to illustrate modelling results.

1. Ames, B. N.; McCann, J.; Yamasaki, E., Methods for detecting carcinogens and mutagens with the salmonella/mammalian-microsome mutagenicity test. *Mutat. Res.* **1975**, 31, (6), 347-63.
2. Hasselgren, C.; Carlsson, L.; Boyer, S., A rule-based method for comprehensive risk assessment of the mutagenic potential of drugs. *Manuscript*.
3. Snyder, R. D.; Smith, M. D., Computational prediction of genotoxicity: room for improvement. *Drug Discovery Today* **2005**, 10, (16), 1119-1124.