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A rule-based method for comprehensive risk assessment of the mutagenic potential of drugs

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The genotoxic potential in any candidate drug is carefully assessed during the discovery and development of new drugs. This is commonly done using *in silico* screens early on and continued with *in vitro* and *in vivo* experiments as the drug progresses closer to regulatory submission. *In silico* screens have several purposes, selection of compounds for experimental testing and/or to get early warning of any potential risk associated with the compound in the form of *e.g.* alerting substructures. For this purpose, we have developed a comprehensive warning system for assessing the mutagenic potential of our compounds. This system is built on Ames assay data from public sources such as NTP and MultiCASE but also includes our internal data. The database that the system is built on comprises ~7000 compounds. Any molecule submitted to the system is passed through a series of steps and the output lists (i) structural near neighbours with experimental results (Positive and Negative), (ii) alerting substructures, and (iii) consensus QSAR results consisting of three different QSAR models. A set of rules that aid the interpretation of the output and enhance the overall predictive performance has been derived. The system provides a more complete picture of the information available when doing risk assessment of new compounds and allows a more realistic view of the underlying data. Using only QSAR predictions, accuracy is ~80-85% with sensitivity being slightly lower than specificity. The confidence for an individual prediction, however, varies depending on additional output from the complete system and can be used to give chemists an overall confidence index for each prediction.