

## Novel Metabolic Descriptor Based on Xenobiotic Induced Cytochrome P450 Transcription for Carcinogenicity Prediction

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Cytochrome P450 (CYP) enzymes play an important role in carcinogen metabolism. They can help in detoxification by aiding elimination of potential carcinogens or facilitate toxicity by conversion of primary non-carcinogens (procarcinogens) into secondary carcinogenic metabolites. Cytochrome P450 enzymes are either expressed constitutively or induced by certain substrates. Induction is usually a protective mechanism and helps in detoxification, but it can also lead to increase in production of carcinogenic metabolites. It has been found that CYP1A1, CYP1A2, CYP2E1 and CYP3A4 enzymes are involved in the metabolism of procarcinogens. Also, CYP1B1, CYP1A1 and CYP2E1 expression has been found to be up regulated in certain cancer cells.

In this study, a strong correlation is identified between the ability of chemicals to induce simultaneous induction of CYP1A1, CYP1A2 and CYP3A4 enzymes in an in-vitro test (after exposure for 6 and 24 hrs) and their carcinogenic property. We use support vector machines (SVM) for classification of carcinogens based on expression change of these enzymes. Leave one out cross-validation results show that carcinogens can be classified with an accuracy of 88.24% and 81.25% from 6hr and 24hr data, respectively. Including this data as a metabolic descriptor in a hybrid QSAR model for carcinogenicity prediction improved the overall performance of the model. These correlation findings strongly recommend the use of expression changes of CYP1A1, CYP1A2 and CYP3A4 enzymes as a metabolic descriptor for QSAR studies for carcinogenicity prediction.

**Keywords:** Carcinogenicity, Hybrid QSAR model, Chemical descriptors, In-vitro descriptors, Cytochrome P450 induction, Support Vector Machine (SVM)