Abstract # 2640

**Making a Prediction of a Compound’s Biological Activity Based on Its Chemical Structure**

...Uses the results of actual laboratory testing or clinical outcomes to determine if a compound meets a Threshold of Toxicological Concern (ToTC) or be shown to lack mutagenic potential. Agencies recommend that these impurities be controlled to an acceptable level (e.g., in commercial manufacturing intermediates, which often continue to be present at low levels in a finished drug product). Consequently, may provide information for read-across when query molecule is chemically analogous to known mutagens.

**Evaluation**

Analyzing the structural features of a query compound for mutagenic potential...that the impurity could have mutagenic potential. Two complementary (Q)SAR methodologies were employed to derive different alert structures for the same impurity. (Q)SAR was deemed inappropriate for...coordinates even if alerts differ. Post-training validation experiments, as well as demonstrate that the model training set structures are...as (Q)SAR software. Based on the irrelevance of this alert, the positive prediction was overruled and the negative prediction was reported...models used, raw model predictions, and an explanation of any conclusions that are...from two complementary (Q)SAR methodologies. Expert models have...toxicological concerns, and no further testing is recommended (see Table 1 in Ref. 9)."}

**DISCLAIMER**

One should not assume that the results reported herein are applicable to a (Q)SAR assessment performed on a different (Q)SAR software. Based on the irrelevance of this alert, the positive prediction was overruled and the negative prediction was reported. A review of the training set structures used to derive the alert revealed that many structural features of the query compound were not present in the training set structures. Consequently, may provide information for read-across when query molecule is chemically analogous to known mutagens.

**Case Study 1**

An impurity in was flagged by CDER safety review staff due to the presence of a 1,2-diaryl ethylene structure within the impurity. The (Q)SAR was deemed inappropriate for...three different mutagenicity data points...the Ames data for those examples, (Q)SAR was deemed inappropriate for...and no further testing is recommended (see Table 1 in Ref. 9)."}

**Case Study 2**

The case studies presented in the section below have been anonymized and specific (Q)SAR models have been removed to avoid embarrassment of any particular (Q)SAR software.

**Case Study 1**

**Alert**

**Evidence**

...based on an expert rule-based and statistical (Q)SAR methodology. Under the ICH M7 guideline, sponsors may submit (Q)SAR analyses performed using commercially available models or in-house proprietary models. In these cases, predictions are currently verified using models available to regulators.

**Model Applier Leadscope, Inc. Expert Alert System Leadscope, Inc. Sarah Nexus Lhasa Limited Derek Nexus Lhasa Limited**

The table below describes some of the frequently encountered cases and proposed expert analyses. Any one prediction is...in reliability of this prediction and provide a rationale to support the final conclusion. Although there are some obvious limitations to expert analysis, it is routinely performed by FDA/CDER, as well as regulatory agencies. Consequently, may provide information for read-across when query molecule is chemically analogous to known mutagens.

**SUMMARY**

Under the newly finalized ICH M7 guideline (Q)SAR models may be utilized for regulatory (Q)SAR assessments under ICH M7 through the presentation of non-proprietary examples. Under the newly finalized ICH M7 guideline (Q)SAR models may be utilized for regulatory (Q)SAR assessments under ICH M7 through the presentation of non-proprietary examples. Reviewing the training set structures used to derive the alert revealed that many structural features of the query compound were not present in the training set structures. Consequently, may provide information for read-across when query molecule is chemically analogous to known mutagens.

**REFERENCES**

M. R., et al., Boronic acids—A novel class of bacterial mutagen,...cm-1 (R1). The impurity was predicted to be positive for two complementary (Q)SAR workflows. The impurity was predicted to be negative for two complementary (Q)SAR workflows. The impurity was predicted to be negative for two complementary (Q)SAR workflows. Based on the irrelevance of this alert, the positive prediction was overruled and the negative prediction was reported. A review of the training set structures used to derive the alert revealed that many structural features of the query compound were not present in the training set structures. Consequently, may provide information for read-across when query molecule is chemically analogous to known mutagens.