2020 Webinar

ICH M7 Expert Review Workshop: Resolving common prediction scenarios using automated arguments in Nexus 2.3

Q&A Session

10th September 2020

Dr. Robert Foster

Leaders in the development of expert chemoinformatic systems and trusted curators of proprietary data.

ICH M7 Expert Review Workshop
Q&A Session

In example 3, why was this compound not excluded from Derek alert, based on the comments provided?

Example 3, N-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide, activates alert 352 "Aromatic amine or amide". The alert comments discuss a specific exclusion for aromatic amines/amides which have two substituents ortho to the amine/amide where neither of the substituents are considered to be "small", the understanding being that steric hinderance prevents N-hydroxylation which is required for the mutagenic mechanism of action of the chemical class. References supporting the exclusion include a systemic study showing that mutagenic activity is decreased with increasing substituent size, albeit mutagenicity is still present until diisopropylamine is reached. Given the available data, the alert has been implemented so that bis-substitution ortho to the amine/amide is allowed for certain substituents deemed to be "small" (e.g. methyl) and expected to still exhibit mutagenic activity.

I have an example of a negative prediction in Derek and Equivocal in Sarah, how should I approach this?

An equivocal prediction in Sarah is defined as one where "the confidence level is below which a prediction of positive or negative is unable to be made". In this situation, it is still possible to use the available Sarah training set examples, as well as additional knowledge, to make an assessment of whether any of the chemical features in the query are likely to be associated with mutagenic activity that were not predicted by Derek. However, it is important to remember that the negative prediction in Derek, even if there is a misclassified or unclassified feature, is still a valid prediction with high negative predictivity [Williams et al, 2016]. This is a similar situation to example 7 in the slides, although in that situation Sarah provided an outside domain prediction rather than equivocal.

Is it possible to remove the structures with exclamation mark and recalculate again by program as it was said in example 2?

This feature was implemented as a method to highlight to the user training set examples which require review, as they may not be relevant to the query, & where removal of these examples would result in a change to the generated prediction. It is not displayed if removal of the examples would not change the prediction. It has not been implemented in a way that automatically removes data from the model & changes the predicted result. It was considered that provision of the 'original prediction' & a 'recalculated prediction' may cause confusion on submission of results. Therefore, the decision was made to implement the feature without removing compounds automatically as a compromise that displays the information to the user while retaining the result generated by the statistical model.

Is it possible to access the list of all 61 expert review arguments so that the user can select arguments for themselves? This would be of particular interest if the automatically selected arguments are not considered relevant for the review.

After an ICH M7 prediction, only the most relevant expert review arguments are presented to the user following automatic selection by the program. This is designed specifically to improve the efficiency of the review, & standardisation of reporting arguments, rather than forcing the user to assess all 61 arguments for which situation may be the most relevant. Although not publicly available at present, Lhasa intend to publish on the development of this feature & this is likely to include the list in some format. Alternatively, please contact Lhasa in the meantime to discuss any requests directly.

You say these are common prediction scenarios but how often does each scenario occur in your experience?

Validation against a dataset of 1532 ICH M7-relevant impurities demonstrated that Derek & Sarah agreed with each other ~60% of predictions. Conversely, <10% of predictions were negative in Derek & either equivocal or outside domain in Sarah, which usually represent the most difficult situations to review. In agreement with these predictions, the most prevalent expert review arguments displayed are those stating "toxicophore identified by both systems cannot be adequately negated" or "no relevant toxicophore has been identified by either system".

Our Products

Derek® nexus — *Expert knowledge-based toxicity prediction software from Lhasa Limited.*

Sarah® nexus — *Statistical-based software for the prediction of mutagenicity.*

Setaria® — *A project-centric, knowledge-searchable database for storage of toxicity knowledge.*

Mirabilis® — *A tool for assessing the relative purging of mutagenic impurities.*

Zeneth® — *Expert decision support software for predicting the forced degradation pathways of organic compounds.*

Vitic® — *The chemical database and information management system, offering researchers and scientists rapid access to searchable toxicological information.*

Meteor® nexus — *Expert decision support software for predicting the metabolic fate of chemicals in mammals.*

Effiris™ — *A secondary pharmacology model suite leveraging value from federated learning.*

Kaptis™ — *A tool to support risk assessment in the context of adverse outcome pathways.*

Lhasa Limited Registered Office
Granary Wharf House, 2 Canal Wharf, Leeds LS11 5PS
Registered Charity (290866)

+44 (0)113 394 6020
info@lhasalimited.org
www.lhasalimited.org