Initiatives For The Sharing Of Toxicity Data

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Introduction

Much high-quality toxicity information is held within organisations rather than being in the public domain. Indeed, after it has fulfilled the purpose for which it was generated, toxicology data is often just filed away and forgotten when it could be a valuable resource for other projects. Transferring data from toxicological reports to a structure-searchable database offers immediate benefits to a company as the data is then available for more effective internal use. Organisations would also benefit from sharing this data with each other in a reciprocal manner where commercial sensitivity issues allow. Participants gain new data which can be used to avoid repetition of experiments for established chemicals and to provide data to develop and evaluate models for predicting the toxicity of new ones.

Vitic, a structure-searchable toxicity database, has recently been used as the basis for a number of such proprietary data sharing initiatives. Consortia include those interested in the sharing of toxicity data on excipients, intermediates and impurities. This poster outlines the work of the intermediates and impurities data sharing group (Box 1) and illustrates how the data shared by it has been used to evaluate alerts in the Derek for Windows toxicity prediction system.

Box 1: Overview of the intermediates and impurities data sharing group.

Participating organisations:	Bayer Schering Pharma GlaxoSmithKline Hoffmann La Roche Novartis Pfizer
Description:	Sharing structures and toxicity data for impurities, intermediates and other non-commercially sensitive structures
Objective:	To facilitate successful response to legislation such as REACH and new rules surrounding the assessment of impurities

Method

Members of the intermediates and impurities data sharing group met to discuss the quantity and nature of data to be contributed by each participating organisation. In the first instance, it was agreed that Ames test mutagenicity data would be shared and that this data must not have been published previously in any peer reviewed journal or otherwise be easily accessible in a public domain forum. A template was then circulated providing guidance on the format and content of the data to be provided. The resulting data contributions received from each organisation were entered into a single Vitic database using the Vitic data entry tool in such a way that all of the data could be subsequently redistributed to each of the participating organisations.

Members of the intermediates and impurities data sharing group gave permission for their shared data to be used for the validation of Ames test mutagenicity alerts in Derek for Windows, a knowledge-based expert system for the prediction of toxicity. The chemical structures in the intermediates and impurities data sharing group database were exported in SDfile format and processed in Derek for Windows. The number of chemicals activating each Derek for Windows alert for Ames test mutagenicity was determined and, by comparison with the experimental data, the proportion of these chemicals which were in practice mutagenic in the Ames test. In this way, positive predictivity values were calculated for each alert and included in its associated Validation Comments display using the Derek for Windows editor.

Figure 3: The Validation Comments display for Derek for Windows alert 329. The performance metrics presented include positive predictivity values determined using data from the intermediates and impurities data sharing group.

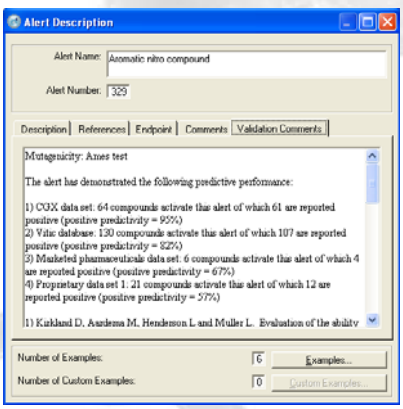


Figure 1: Example search of intermediates and impurities data sharing group data in Vitic 4. The search identifies compounds containing a nitrophenyl group which gave a positive response in the Ames test.

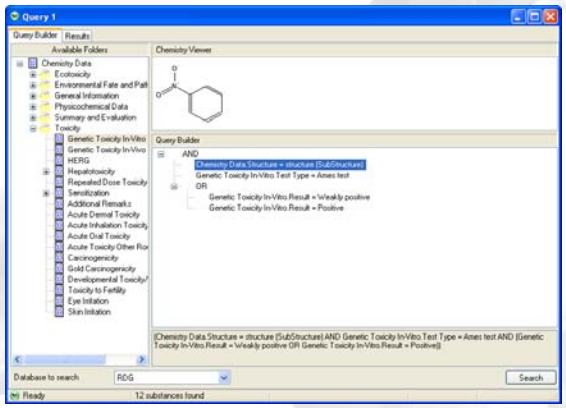
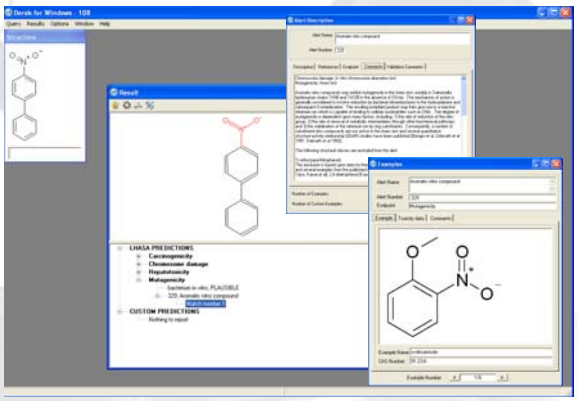


Figure 2: Example prediction for an aromatic nitro compound in Derek for Windows 10.0.2. The prediction for mutagenicity is based on the presence of alert 329, describing the mutagenicity of aromatic nitro compounds. The location of the alert is shown in the structure highlighted in red.



Results

Proprietary Ames test mutagenicity data contributed by a consortium of pharmaceutical companies has been entered into a Vitic database, allowing the data to be shared between them. Use of Vitic for this purpose ensures the standardisation of the data in a common format and its ease of searching, including by structure (Figure 1). As a result, exact chemicals of interest or their analogues suitable for read-across assessment can be readily identified.

The shared data has also been used to assess the predictive performance of Derek for Windows alerts for Ames test mutagenicity. A framework for the use of such alerts in the assessment of the genotoxicity of pharmaceutical impurities has been described (Dobo et al). Figure 2 shows an example Derek for Windows prediction. In addition to the comments, references and examples provided in previous versions, each alert for Ames test mutagenicity is now associated with a Validation Comments display which provides an assessment of the positive predictivity of the alert, including for the shared data described here (Figure 3). This information provides additional guidance to the user in the interpretation of predictions.

Conclusion

The Vitic structure-searchable toxicity database has recently been used as the basis for a number of proprietary data sharing initiatives. A consortium of pharmaceutical companies, for example, has been successfully established to share toxicity data for intermediates, impurities and other non-commercially sensitive structures. Plans for further expansion of this data sharing group to include additional data and more member organisations are currently under discussion. Data shared to date has been made available to each participating organisation in readily-searchable, Vitic database format and is being used to provide guidance on the performance of Derek for Windows alerts for the prediction of Ames test mutagenicity.

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References

Dobo K.L. et al, *Regulatory Toxicology and Pharmacology* 44 282-293 2006.