Computer Software for Risk Assessment

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LHASA UK Ltd. is well established in the field of expert computer systems for chemists and toxicologists. A rule-based expert system approach is currently being used successfully in industry for the prediction of toxicological hazard. Each rule contained in the rule-base describes the relationship between a structural feature or "toxicophore" and its associated toxic effect. These rules are derived by an evaluation of toxicological, mechanistic, and physico-chemical data. New computer software for the risk assessment of chemical toxicity is now being developed as a collaborative project which includes a qualitative assessment of risk for each predicted hazard. This is achieved by an argumentation-based approach using general toxicological and physico-chemical concepts. The results of the assessment are presented to the user in a clear and standardized format. This novel approach improves the assessment of risk under uncertainty and aims to make the nature and potential impact of risks easier to understand.

INTRODUCTION

The assessment of toxicological risk has long been an important factor in new chemical design. Globally, the chemical industry spends millions of dollars in testing potential products for adverse health effects. The ability to predict the potential risks both quickly and accurately would save not only time and money but also laboratory animals as well, an increasingly significant issue in public relations. Computer software has proved to be both adept and useful in handling large quantities of chemical information and is now a routine part of the process for new chemical design. It is therefore logical to use computers to predict the toxicity of chemicals.

Current commercial software for toxicity prediction can be classified as either mechanistic or correlative. However, all such systems use structure−activity relationships (SAR) and/or quantitative structure−activity relationships (QSAR) to some extent in the prediction of chemical toxicity. Correlative systems take molecular descriptors, biological data, and chemical structures and by the use of statistical analysis of data sets represent these in mathematical models. The models describe the relationships between structure and activity and can be used to predict toxicity. In contrast, the mechanistic approach involves human experts who make a considered assessment of the mechanism of interaction with a biological system, taking the molecular properties, biological data, and chemical structures into account. From this structure−activity relationships are devised, and these are then used as prediction tools. DEREK is one example of computer software that takes a mechanistic approach to toxicity prediction.

Both methods have advantages and disadvantages. The correlative approach uses an unbiased assessment of the data to generate relationships and predict toxicity. It is capable of discovering potentially new SARs[1] and can lead to new ideas in the human assessment of mechanisms by which chemicals interact with biological systems. It is most useful for congeneric data sets or where there is a large amount of good data but little mechanistic knowledge. However, it can also generate relationships that have little chemical or biological plausibility, and the results obtained are heavily dependent upon the quality of the data used to build the model. For these reasons careful validation is required for its effective use.[1]

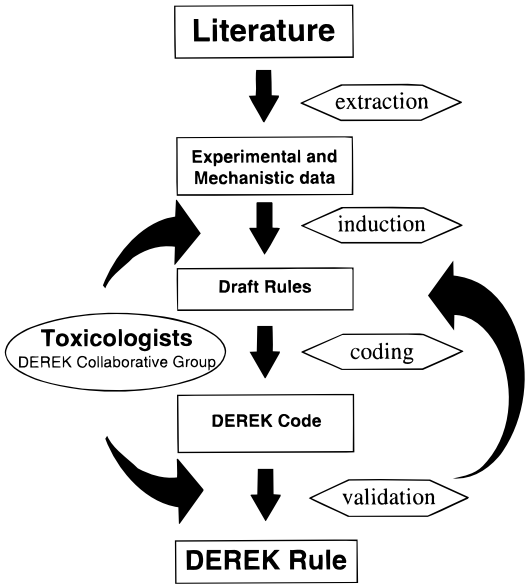

Figure 1. The DEREK rule development process.

The advantage of the mechanistic method is that it is based on an understanding or hypothesis of the mechanisms of molecular interactions that determine the activity, i.e., there is some human input into the system of SAR generation. However, systems using this approach are restricted to human knowledge, being incapable of discovering new relationships automatically. As a consequence of this, they also have a tendency to be biased toward current ideas about mechanisms of action.

DEREK−A MECHANISTIC APPROACH TO TOXICITY PREDICTION

Since 1989 LHASA UK has been actively developing and promoting a computer system for toxicity prediction called DEREK. Originally devised at Schering Agrochemicals

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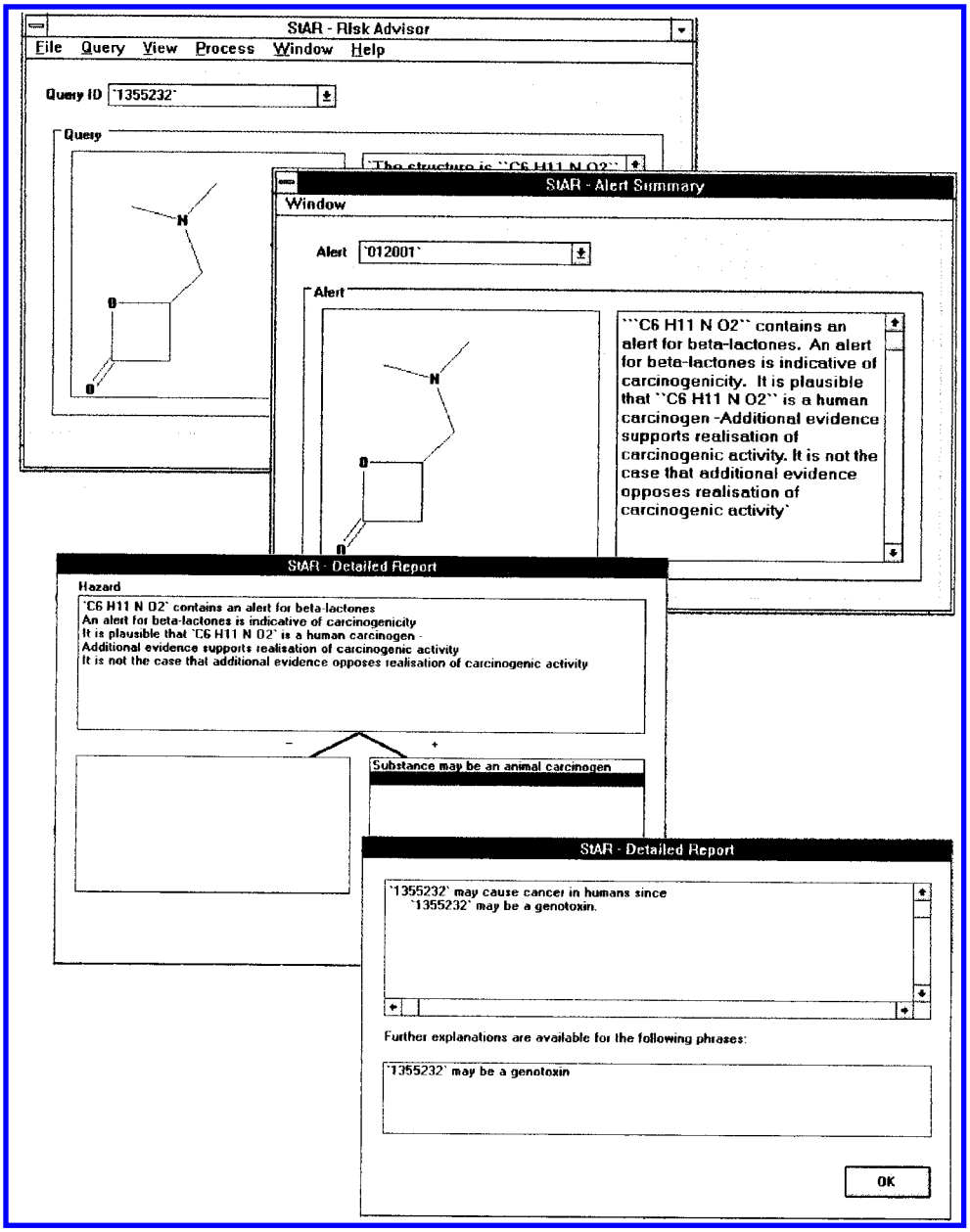

Figure 2. Example screens from the StAR project prototype.

Limited,[2] DEREK is a rule-based expert system designed to give a qualitative assessement of the potential hazards associated with a chemical structure. It uses rules to link structural features of chemicals to toxic endpoints. These rules are also capable of discriminating between different chemical environments around the toxicophore when assessing the query structure. The software is now licensed by over 15 chemical manufacturing and research organizations world-wide.

The program has a simple graphical interface for the input of structures and display of results. The results consist of the query compound being shown with the structural fragment, or "toxicophore", suspected of being the cause of the toxicity shown highlighted along with a statement of the associated hazard. Reference screens are available to the user which summarize the reasoning behind the prediction and in most cases provide literature citations for further reading.

The current DEREK rule-base covers a broad range of toxicological endpoints[3] including mutagenicity, carcinogenicity, and skin sensitization. However, the rules can easily be extended to cover any form of biological activity by adapting the existing rules or generating new ones. Sources of information used to generate new rules include published results and ideas along with suggestions and opinions for toxicological experts in industry, regulatory bodies, and academia. All the rules are based on hypotheses relating to the mechanisms of action, and the ideas generated are discussed by a collaborative group of toxicologists who represent LHASA UK's DEREK customers. The rule development process (see Figure 1) is a continual cycle of validation and refinement using data sets and expert opinions to optimize the predictions made by the system.

The performance of the rules in DEREK has been explored using published data sets for the various toxicological end points, and the rules have also been reviewed by members of the collaborative group. For example, for a set of 250 chemicals from the National Toxicology Program (NTP) salmonella mutagenicity database, DEREK correctly predicted 98% of the 112 Ames positive compounds as being

genotoxic and 70% of the 138 Ames negative compounds as not being genotoxic. A study of the 2% of Ames positive compounds that DEREK missed is currently taking place.

There are several causes of the "false positives" in this exercise, firstly, some classes of genotoxic compounds do not give positive results in the Ames test for reasons such as high cytotoxicity. Secondly, some rules in DEREK over predict as because, although a structure−toxicity relationship is correctly identified, other factors affect the expression of the toxic effect. Lastly, for some SARs there is a lack of biological data which results in some rules not being fully developed and which is reflected in over prediction. This exercise used DEREK version 14.2 and development work to improve the prediction rate further is ongoing. Similar validation exercises have been reported elsewhere in the literature.[3]

The next release of DEREK, version 16.1, scheduled for the end of 1996 contains significant improvements to the user interface design with the intention of making the program even easier and faster to use. The program now has true client/server architecture which will improve the automatic processing of large data sets of compounds. The program can now import many different types of file formats, including SD and SMILES, and the reporting of results has been improved. The rule-base has also continued to receive substantial development work with new rules being added along with refinements to the existing rules where required.

THE WAY FORWARD—THE STAR PROJECT

Of over 5 million known chemical substances, only 30 are definitely linked with cancer in humans, and only 7000 have been tested for carcinogenicity: the rest is darkness.[4]

In vivo tests involve regular and often very high doses of the substance under study to be delivered to a population of test animals. The relative increase in tumor incidence with respect to a control population, as a function of dosage, is then used as the basis for an estimate of the increased risk to humans through exposure to the same substance.[5]

From the above statements it is clear that there are large gaps in the knowledge of chemical carcinogenicity in humans. It is therefore reasonable to say that it is not possible to accurately quantify the risk to humans posed by a chemical for 99.9% of cases. There is an obvious need for effective qualitative approaches to risk assessment.

LHASA UK has been collaborating in research into ways of assessing chemical risk in circumstances where there is not enough information to use mathematical models. The StAR (Standardized Argument Report) project started in October 1993 in collaboration with Imperial Cancer Research Fund, Logic Programming Associates, and City University. It set out to design a PC-based computer system for risk assessment of chemical carcinogenicity.

The StAR system has taken advantage of new methods of reasoning based on the Logic of Argumentation[6,7] (LoA) which overcomes the difficulties encountered when information cannot be quantified numerically and hence does not allow the application of conventional probability theory. The LoA theory has drawn upon work done on the development of a model for reasoning under uncertainty based on the simple intuitive notion of constructing arguments "for" and "against" a hypothesis.[6] The full details of the semantics and syntax of the formal model for LoA have been reported elsewhere.[7]

The project team includes psychologists who are studying the ways in which people perceive, and communicate about, risk. It is expected that from the results of this work we will be able to improve our understanding of the strengths and weaknesses of human judgement and hence build better systems and interfaces for computer risk assessment.

The system has been designed to run under Microsoft Windows on IBM compatible PCs and communicates to the user through graphical and textual representations (Figure 2). It assesses risks on the basis of knowledge stored in a knowledge base but is capable of retrieving supporting information from databases or through dialogue with the user. The user can then question the decisions made by the program and receive explanations in an appropriate fashion (see Figure 2).

A chemically intelligent user interface has been provided by Hampden Data Services, and the project was supported financially by the Department of Trade and Industry and the Engineering and Physical Sciences Research Council in the United Kingdom. Although the project is scheduled for completion in December 1996, a commercial version of the program is not expected until March 1997.

CONCLUSIONS

Current knowledge about the risks to human health from exposure to chemical substances is not sufficient to facilitate accurate mathematical modeling of chemical toxicity. Techniques should be rigorously validated and applied only where appropriate. Only by joint cooperation between industry, academia, and regulatory authorities can we shed light on the subject. LHASA UK Ltd. is working together with these bodies to generate new ideas and techniques for the computer assessment of chemical risk.

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