PROCEEDINGS OF THE IADIS INTERNATIONAL CONFERENCES

INTERFACES AND HUMAN COMPUTER INTERACTION 2013

and

GAME AND ENTERTAINMENT TECHNOLOGIES 2013

Prague, Czech Republic
JULY 22 - 24, 2013

Organised by
IADIS
International Association for Development of the Information Society

Co-Organised by

Volume Editor:
Katherine Blashki

Computer Science and Information Systems Series Editors:
Piet Kommers and Pedro Isaías

Associate Editor: Luís Rodrigues

ISBN: 978-972-8939-90-8

ISBN: 978-972-8939-90-8 © 2013 IADIS

OVERTAKING BARRIERS BETWEEN TOXICOLOGISTS AND COMPUTERS: THE EXAMPLE OF VEGA

Emilio Benfenati[1], Giuseppa Raitano[1] and Giuseppina Gini[2]
[1]*Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, Milano*
[2]*Politecnico di Milano, DEIB, Piazza Leonardo da Vinci 23, Milano*

ABSTRACT

Computer simulation and predictive models are widely used in engineering. Computer models are often criticized as a black box, which produces results without a reasoning scheme. In case of computer models for toxicity predictions, this reduces the acceptance of the results, because the predictions seem without a theoretical basis, and possibly obtained by chance. We will present here an initiative aimed to establish a dialogue within the community of scientists, regulators, industry representatives, offering a common platform which combines the predictive capability typical of computer models, with reasoning and explanation tools, which may be convincing and helpful for human users to derive a conclusion. Such a community is rapidly growing and is close to one thousand users.

KEYWORDS

Computer models; acceptability; transparency; understanding; toxicity; regulatory use.

1. INTRODUCTION

The concept of "Structure-Activity Relationship" (SAR) is that the biological activity of a chemical in the human body and the environment (including its toxicity) can be related to its molecular structure and physico-chemical properties. When quantified, this relationship is known as "QSAR". A QSAR model makes use of existing experimental toxicity data for a series of chemicals. By using potentially complex algorithms, the model correlates experimentally observed toxicity with aspects of molecular structure and physico-chemical properties across a series of related compounds in order to predict the toxicity of further chemicals with related molecular structures. When toxicologists use one of the leading platforms they receive predictions and supporting information from one or several QSAR models relevant to the particular compound and the particular toxicological endpoint (Gini et al. 1999).

Computer models may offer a powerful way to cope with the problems of toxicity evaluation of the many tens of thousands of chemicals present in the modern society. A series of regulations require to produce information about the safety of the chemical substances, such as the European legislation in the field, called REACH (Registration, Evaluation, Authorization and restriction of Chemicals). This regulation states that for each chemical circulating in the European territory, a complete dossier on physico-chemical, biological and toxicological properties has to be compiled. In order to prevent an over-usage of animal testing, REACH (ECHA 2008) regulation foresees and promotes the use of alternative methods, including use of predictive programs. These programs are often called *in silico* models, because this recalls the classical methodology used in toxicology (in vivo methods), referring to the use of the computer with the expression "*in silico*".

Besides various commercial systems, in the QSAR community there are a few examples of free models offered as web services or embedded into applications. The most notable are the systems developed by the USA EPA (Environmental Protection Agency), and the data base navigation tool developed by OECD (Organization for Economic Cooperation and Development). None of them has spent much effort in the user interface, and only to start the OECD toolbox requires reading a manual of 45 pages (OECD 2013).

Some *in silico* models have proved to be predictive, and able to offer a scientifically valuable alternative to the classical *in vivo* methods (Benfenati et al. 2007). Nevertheless, most of the *in silico* models are not trusted by their targeted users. This depends on many factors, including the property to be modeled, and the model itself. However, even for good models, there is a high skepticism about the models them selves, for several reasons (Benfenati et al. 2011):

1. Some human experts fear to loose a role;
2. Some users fail to recognize within the new methodology the structure and the intrinsic nature of the information, which is virtual and not experimental;
3. Some users judge the *in silico* models as a kind of black box;
4. The lower cost of the *in silico* methodology may represent a competing market for the laboratories and consultants offering traditional approaches.

Thus, the reasons are psychological, cultural, and economic. This mixture of factors against the use of the computer as a resource needs a complex strategy, involving several aspects. We proposed to cope with this issue through a platform, which is dedicated to the community of stakeholders potentially interested in the use of *in silico* models.

This paper analyses the premises and the developed computer platform. The user needs, captured several time during workshops, interviews and exercises carried on through four recent European projects (DEMETRA, CAESAR, ORCHESTRA and ANTARES) have strongly guided the development of the platform. According to the users requirement that have to keep as confidential the chemical structures, our solution is implemented both as a web-based application and as a downloadable software application.

2. THE WORKFLOW IN VEGA

The platform we developed is called VEGA, which stands for Virtual Evaluation of chemicals within a Global Architecture. The first page presents different buttons; the most important function in it, using QSAR, is located where attention focuses (near the top-left corner).

The QSAR page, in Figure 1, lists all the different available models clustered in toxicological categories. This view is targeted to toxicologists, that start usually from the problem of knowing everything of a set of substances, or prioritize them for subsequent analysis, or assessing their classification as PBT (Persistent Bioaccumulative Toxicant) or very Persistent and very Bioaccumulative, or CMR (carcinogenic, Mutagenic, or toxic for Reproduction). Each of those choices will coherently activate all the single models. The user can instead make a more restricted study selecting in the following rows the toxicology endpoint of interest. The toxicity endpoints have been selected to fulfill the requirements of the REACH regulation.

To start the study the user has to follow the arrow that opens a new page for inserting the chemical structure(s). The steps of the workflow are clearly indicated for each model. Sequentially the steps are: insert the list of the molecules identifiers, choose where to send the prediction output, call the classifier, analyze the results. The input can be given in different standard formats used in the chemical domain, including SMILES and SDF files (Weininger 1988).

The software allows processing one single molecule, or a batch of many substances. For one chemical it takes a few seconds on a common computer. The downloadable version is what the user typically prefers, because it allows working on confidential structures without the use of the internet. This is convenient for industrial users, but also for regulators, who have to deal with confidential information.

So far about one thousands users downloaded the system world wide, and their number is constantly increasing.

Let us see the example of the result of the mutagenicity models. The user has selected two models to study this endpoint: one, called CAESAR (Ferrari et al. 2010), is an integration of statistics and expert defined rules derived from Toxtree (Toxtree 2012); the other, called SARpy (Ferrari et al. 2011), is a data miner that extracts relevant fragments from the analysis of their correlation with the endpoint. Both of them give a binary output: mutagenic or not mutagenic. Illustrated in Figure 2 is the output of the CAESAR model; the prediction is given with the draw of the checked molecular structure; the rest of the page shows the most similar compounds with their experimental values as available in the model training data.

ISBN: 978-972-8939-90-8 © 2013 IADIS

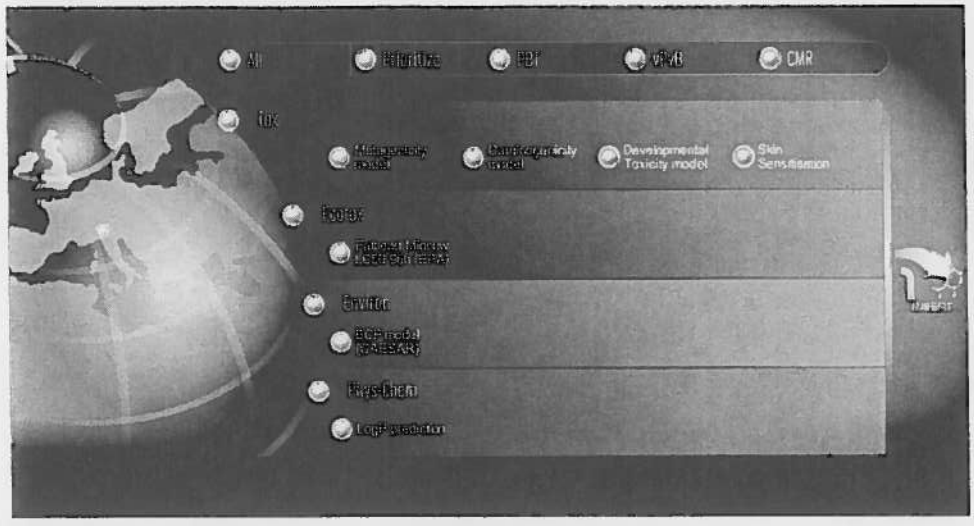

Figure 1. Menu with the list of available modeled endpoints

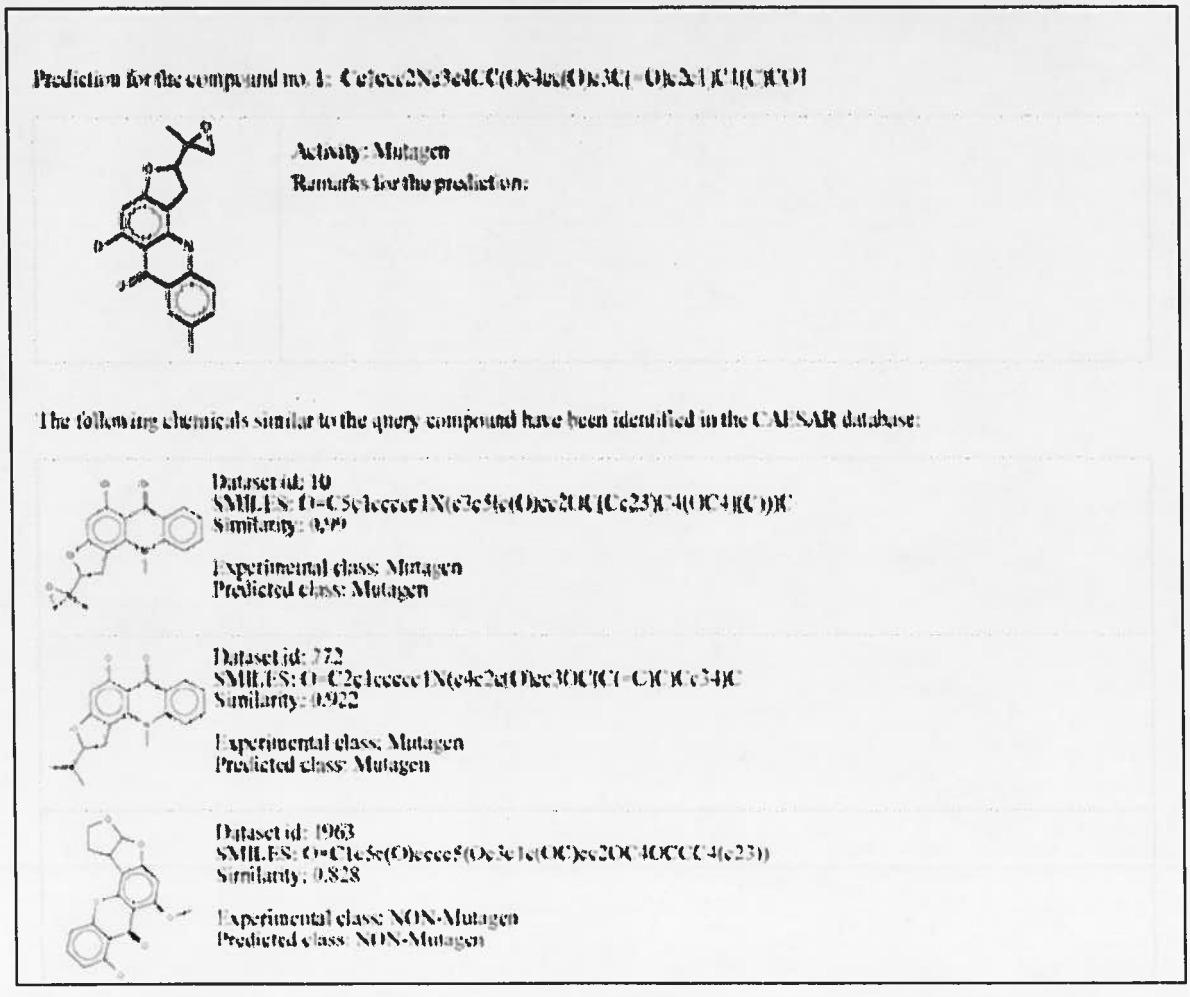

Figure 2. The prediction of the CAESAR model for mutagenicity shows the most similar structures available in the training data of the model.

A different case is illustrated in Figure 3, showing a part of the prediction of the bioconcentration factor (BCF) model (Lombardo et al. 2010). BCF is a dose value, expressed in logarithmic units. However for regulation classes are assigned according to thresholds. Since the uncertainty of the prediction can be calculated, it is shown for each new molecule on a graph, for a worst case analysis. In Figure 3 we see that for this molecule, even in case the result underestimates the real toxicity, the assignment to a class can be safely done.

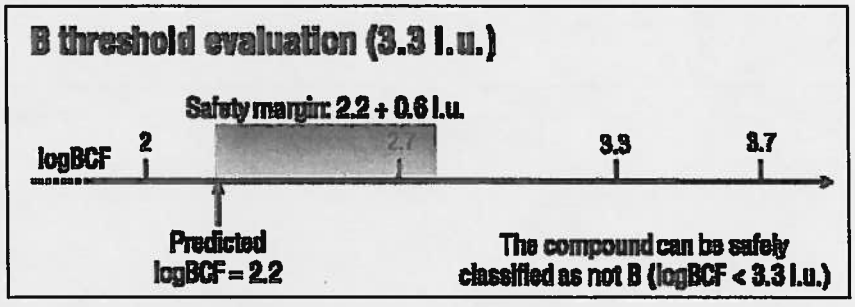

Figure 3. The final indication from the BCF model, indicating the proposed classification in the risk classes as defined in REACH.

3. EVALUATING THE INTERACTION COMPUTER-USER

We clearly identified the dialogue between the developers of the computer software and the users as a need. This is quite different from the past approach, with developers trying to capture the opportunity to introduce in the market the result of their study, which was typically based on premises not overlapping the users need.

On a technical point of view modern *in silico* models offer ways to critically evaluate the reliability of their results. Recently, an exercise with tens of experts demonstrated that human experts identified reasons of possible concern evaluating the results of some *in silico* models (Benfenati et al. 2013). Comparing VEGA with other platforms, the users appreciated the details provided by the VEGA platform, which uses language and figures more understandable, and with more details on the chemical and biological point of view.

Indeed, modern *in silico* models provide a complex evaluation of the target compounds, and not simply the predicted value. On the basis of the results of the comparison of a series of *in silico* models, we identified the strengths and weaknesses of the individual models, associated to the evaluation of the individual chemical classes and mode of actions. Nowadays, the *in silico* model can analyze the quality and uncertainty of the experimental data, produce an understandable description of the implicit knowledge at the basis of the toxicity phenomena, identify rules associated to the toxic effect, measure the reliability of the predictions, show similar chemicals and their experimental properties, assess the accuracy of the prediction on the basis of the results of the most similar compounds.

Further evaluation involves the analysis of the experimental values of large databases, in order to assess the toxic effect to the chemical classes. Finally, the uncertainty of the experimental values relative to the individual chemical classes has been investigated, and is shown.

In this way, the user sees the molecules of the similar compounds, and can compare the experimental values of these similar compounds with the effect which is predicted, pinpoint possible errors in prediction, identify relationships between certain physico-chemical properties and the biological effects, recognize the occurrence of chemical fragments associated to toxicity. All these elements are provided by the VEGA platform, which also measures the reliability of the prediction, and lists reasons of concern. In this way, the platform is a complete tool which assists the user, providing the prediction, and in addition elements to support the assessment, or conversely motifs of concern and uncertainty. Thus, VEGA does not simply provide a value, the predicted one, but provides the basis for that value, and supports that value with case studies on chemicals similar to the target compound. This is done using different, independent programs (from molecular similarity, to clustering, to classifiers), which increase the confidence on the overall evaluation, or identify reasons of concern, and show the uncertainty in the prediction. The user is the subject untitled to take the final decision, on the basis of the information provided.

A final consideration about the addition of the downloadable version containing all the models of VEGA. In the web application all the complexity is on the web side. The advantage is that it can be used also by occasional users, and that they can easily train on the different models. However regulators do not accept using web services; they need to be independent from communication or server stops, they do not want to be online, they do not want that the server can see confidential data. For this reason VEGA can be downloaded as a PC application.

4. CONCLUSION

In the development of the VEGA platform we analyzed the needs of the users, and the barriers to the use of computers. The result has been a platform offering as much as possible not only the predicted toxicity value, but also the reasoning about the likely effect. This is done using a language and schemes familiar to the user, in order to improve understanding and acceptance of a technology, the computer program, which is not common in the field. Thus, VEGA provides to the human experts a sound, transparent, understandable basis allowing an improved basis the final evaluation which is operated by the toxicologist. Stakeholders are continuously involved, and their feed-back used to improve the platform.

The VEGA platform can be found at http://www.vega-qsar.eu; it contains the web application and the downloadable software.

ACKNOWLEDGEMENT

We acknowledge the EU LIFE project CALEIDOS for partial financial support.

REFERENCES

Benfenati E., Crètien J.R., Gini G., Piclin N., Pintore M., Roncaglioni A. (2007) Validation of the models. In Quantitative Structure-Activity Relationships (QSAR) for Pesticide Quantitative Structure-Activity Relationships (QSAR) for Pesticides Regulatory Purposes, Elsevier, p 185-200.

Benfenati E., Gini G., S Hoffmann S., Luttik R. (2010) Comparing in vivo, in vitro, in silico methods and integrated strategies for chemical assessment: problems and prospects. *ATLA* 38 (2), 153.

Benfenati E., Gonella Diaza R., Cassano A., Pardoe S., Gini G., Mays C., Knauf R., Benighaus L. (2011) The acceptance of in silico models for REACH: Requirements, barriers, and perspectives, *Chemistry Central Journal,* Vol 5, pp 58. http://journal.chemistrycentral.com/content/5/1/58.

Benfenati E. et al. (2013) Using toxicological evidence from QSAR models in practice. *Altex*, Vol. 30, p 19-40.

ECHA (2008). Guidance on information requirements and chemical safety assessment: Chapter R.6: QSARs and grouping of chemicals (p.10). http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirementsand-chemical-safety-assessment.

Ferrari T., Gini G., Golbamaki Bakhtyari N., Benfenati E. (2011) Mining structural alerts from SMILES: a new way to derive structure-activity relationships, Proc. IEEE SSCI 2011, Paris, April 2011, p. 120-127.

Ferrari T., Gini G. (2010) A new multistep model to predict mutagenicity from statistic analysis and relevant structural alerts, *Chemistry Central journal*, 2010, 4(Suppl 1):S2 http://www.journal.chemistrycentral.com/

Gini G, Katritzky A (Eds.) (1999) Predictive Toxicology of Chemicals: Experiences and Impact of Artificial Intelligence Tools. Proc. AAAI Spring Symposium on Predictive Toxicology, AAAI Press, Menlo Park, California.

Lombardo A., Roncaglioni A., Boriani E, Milan C., Benfenati E. (2010) Assessment and validation of the CAESAR predictive model for bioconcentration factor (BCF) in fish. *Chem Cent J.* 2010 Jul 29;4 Suppl 1:S1. doi: 10.1186/1752-153X-4-S1-S1.

OECD Toolbox: http://www.qsartoolbox.org/doc/tb_3_0_getting_started_en.pdf (accessed March 2013)

Raskin, J. (2000) The Humane Interface: New Directions for Designing Interactive System. Addison Wesley.

Toxtree (2012) software download: http://sourceforge.net/projects/toxtree/

Weininger D (1988) Smiles a chemical language and information system. 1. Introduction to methodology and encoding rules. *J. Chem. Inf. Comput. Sci.* 28, 31--36.