CURRENT ADVANCES OF IN SILICO METHODS FOR IDENTIFICATION OF GENOTOXIC AND CARCINOGENIC CHEMICALS IN FOOD SAFETY RISK ASSESSMENT

Serhii KOLESNYK,
Sector of scientific basis of international food and chemical safety regulations, L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safetyб
Kyiv, Ukraine

Summary

The aim of this article is to consider current possibilities of use of in silico tools, namely QSAR software, for use in risk assessment of chemicals in food. Existing QSAR software for genotoxicity and carcinogenicity is considered and briefly characterized. Conclusions are made concerning possible use of such software for risk assessment of chemicals in food.

Keywords*: in silico, QSAR, food safety risk assessment, genotoxicity, carcinogenesis*

Резюме

Текущие возможности in silico инструментов для оценки риска химических веществ в пищевых продуктах

Цель статьи – рассмотреть текущие возможности использования in silico инструментов, а именно программного обеспечения QSAR при оценке риска химических веществ в пищевых продуктах. Рассматривается и кратко охарактеризованы существующие QSAR программы для генотоксичности и канцерогенности. Сделаны выводы о возможности использования программного обеспечения для оценки риска химических веществ в продуктах питания.

Ключевые слова*: in silico, QSAR, оценка риска безопасности пищевых продуктов, генотоксичность, канцерогенез*

Introduction

The aim of this article is to consider current possibilities and future perspectives of use of *in silico* tools, namely QSAR software, as element of predictive toxicology for use in risk assessment of chemicals in food.

Predictive toxicology has no clear and agreed definition and in accordance with name itself is aimed at forecasting/prediction of toxicological properties of chemicals by using a set of tools, techniques and approaches. Based on this existing definition rather suggest the aims and describe methods that can be combined in term "predictive toxicology".

By definition of the Royal Society of Chemists, 2012, Predictive toxicology is concerned with the development of new non-animal tests that do not simply duplicate existing animal tests but which provide a new scientific basis for safety testing. It reflects a paradigm shift away from adverse effects observed in experimental animals, sometimes at high doses, to analyzing the effects of chronic exposures to low concentrations on cells and organ systems. It involves identifying significant perturbations of biological pathways at a molecular level through to the cellular or organ level to predict outcomes (Royal Society of Chemistry, 2012).

The book *Predictive toxicology* (Helma, 2005) predictive toxicology is described as following: «In predictive toxicology, we try to develop procedures (algorithms in computer science terms) that are capable to predict toxic effects (the output) from chemical and biological information (the input).

Tools of predictive toxicology include computational (*in silico*) modeling of biological activity, including toxicological endpoints, in vitro methods, OMICS technologies etc.

Current advances of *in silico* methods for risk assessment of chemicals in food and identification of carcinogens

One of the types of in silico methods are (Quantitative) Structure Activity Relationship (QSAR) models. Simply, idea of QSAR model can be described by the following formula: [Toxicity] = *f* (Structure), which is to say that toxicity of chemical for certain organism can be predicted from its structure. One of the option to predict toxicological properties, namely genotoxicity and carcinogenicity, even without of computer modeling is based on the use of structural alerts (SA). One of the first lists of SA for mutagenicity was proposed by Ashby, which later was extended it with additional SAs and some detoxifying functionalities. (Ashby, 1985; Ashby and Tennant, 1988).

Currently available QSAR for prediction of genotoxicity and carcinogenesis are mostly developed as software products, both on-line and standalone. In the *table 1* below (Serafimova, Gatnik, and Worth 2010).

Table 1

QSAR and exbert system software for genotoxicity and carcinogenicity modeling/prediction (Serafimova, Gatnik, and Worth, 2010)

Software	*Comments (endpoints predicted, applicability and performance)*
CAESAR http://www.caesar-project.eu/	Mutagenicity, carcinogenicity
DfW (Lhasa Ltd.) http://www.lhasalimited.org	Mutagenicity, chromosome damage, genotoxicity, carcinogenicity, peroxisome proliferation
GAP – Genetic Activity Profile Database developed by US EPA	Data on 299 chemicals compiled by IARC and US EPA. Data are available on 299 compounds selected from volumes 1-50 of the IARC Monographs and on 115 compounds identified as Superfund Priority Substances.

Hazard Expert http://www.compudrug.com	Mutagenicity, oncogenicity
Lazar http://lazar.in-silico.de	Ames mutagenicity, carcinogenicity
MDL-QSAR http://www.symyx.com/	Carcinogenicity
Mol Code Toolbox http://molcode.com/	Ames mutagenicity, carcinogenicity
Multicase (MCASE/MC4PC) MultiCASE Inc http://www.multicase.com	Research tool - applies a statistical approach that automatically identifies molecular substructures that have a high probability of being relevant to the observed biological activity. Requires a learning set comprised of a mix of active and inactive molecules of diverse composition.
OASIS – TIMES http://www.oasis-lmc.org	Ames mutagenicity, chromosomal aberrations
OECD Toolbox http://toolbox.oasis-lmc.org	Includes two so-called "profilers" associated with genotoxicity and carcinogenicity, as well as three databases with experimental data that can be used to support grouping and read-across
OncoLogic™ http://www.epa.gov/oppt/newchems/tools/oncologic.htm	Carcinogenicity
PASS Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow http://ibmc.p450.ru/PASS//	Classification models giving probability of mutagenic effects. There are two models, one for Ames mutagenicity, and another covered multiple in vitro and in vivo mutagenicity endpoints in mammals.
TOPKAT (Accelrys) http://www.accelrys.com	Ames mutagenicity, carcinogenicity
Toxtree http://ecb.jrc.ec.europa.eu/qsar/	Includes modules for mutagenicity, carcinogenicity, and the *in vivo* micronucleus assay

Positive and negative predictivities of some mentioned above software for genotoxicity and carcinogenicity for DSSTox dataset substances are given in the *table 2*.

Table 2

Positive and negative predictivities for genotoxicity and carcinogenicity

Software	*Genotoxicity*		*Carcinogenicity*	
	Positive predictivity	*Negative predictivity*	*Positive predictivity*	*Negative predictivity*
CAESAR	0.79	0.84	0.74	0.64
Derek	0.81	0.83	0.71	0.63
HazardExpert	0.69	0.73	0.66	0.59
Lazar (Kazius/Bursi)	0.77	0.70	0.80	0.53
Lazar (Tox-benchmark)	0.79	0.71		
TOPKAT	0.84	0.84	0.67	0.57
ToxBoxes	0.93	0.93	N/A	N/A
Toxtree	0.73	0.82	0.71	0.64

Given the fact, that chemicals in food are regulated by different legislative acts, it's worth to mention that any method used for regulatory purposes should be validated and accepted. Riles for validation of QSAR methods are already developed by Organization of Economic Cooperation and Development (OECD). The agreed OECD principles are as follows: "To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1) a defined endpoint;

2) an unambiguous algorithm;

3) a defined domain of applicability;

4) appropriate measures of goodness-of-fit, robustness and predictivity;

5) a mechanistic interpretation, if possible." (OECD 2007).

Conclusions

Given the number of substances to be considered in chemical food safety risk assessment, including regulated chemicals, their metabolites and impurities, as well as possible natural constituents of foods, predictive toxicology tools, particularly QSAR software, is promising approach for prioritization and classification of such substances for further detailed toxicological assessment, especially for endpoints demanding long and expensive tests for their assessment, such as carcinogenesis.

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