THEORETICAL AND EXPERIMENTAL MEDICINE

Kolesnyk S.D

RISK ASSESSMENT OF CHEMICALS IN FOOD AND IN SILICO TOXICOLOGY (SHORT OVERVIEW)

L. I. Medved Research Center of Preventive Toxicology, Food and Chemical Safety of Ministry of Health of Ukraine, Kyiv, Ukraine

Abstract: In the article current internationally accepted approaches to risk assessment of chemicals in food are described and relevant in silico (computational) methods that may be employed at different steps of risk assessment process for different types of chemicals in food are considered.

KeyWords: In silico Toxicology, Food safety, QSAR, Risk Assessment

INTRODUCTION

Food is composed of thousands of chemicals naturally occurring in particular food item as well as added by man along food chain or introduced unintentionally due to contamination from environment. Intentionally added chemicals are regulated with legal requirements for most of them regarding their toxicological assessment before adding into the food chain. Other ones, unintentionally introduced to food from the environment, naturally occurring or man-made, raise concerns for public health and are also extensively studied. Finally, the most numerous group of food chemicals are those which toxicological/biological properties are not fully understood or not understood at all. This article deals with consideration of internationally accepted approaches to risk assessment of chemicals in food and the role of the so-called “in silico” methods and future perspectives for their use.

Corresponding Author:
Serhii Kolesnyk, MD, head of sector, L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety, Ministry of Health, Ukraine, e-mail: skolesnick@gmail.com

2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of this study was to describe current internationally accepted approaches to risk assessment of chemicals in food and determine relevant in silico methods that may be employed at different steps of risk assessment process for different types of chemicals in food.

Object of the study is in silico methodology and its application in risk assessment process of chemicals in food

2.2 Subjects & Methods

The study involved a review of regulatory governing acts with risk assessment of food safety issues and recent scientific literature on application of in silico methods for chemical hazard identification and characterization.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Risk assessment of chemicals in food. Definition, requirements, main steps and international guidelines

On the one hand, modern society substantially benefits from chemicals in everyday life, but on the other hand it faces a challenge of not introducing dangerous ones into

the environment or diet. For example, nearly 100,000 commercial chemicals have been inventoried in the USA, including 8,600 food additives, 3,400 cosmetic ingredients, 1,800 pharmaceuticals, and 1,000 active pesticide ingredients. [1]. Each year, estimated 2,000 new ones are introduced for use in such everyday items as foods, personal care products, prescription drugs, household cleaners, and lawn care products. We do not know the effects of many of these chemicals on our health, yet we may be exposed to them while manufacturing, distributing, using, and disposing them or when they become pollutants in our air, water, or soil. [2] To date, FAO-WHO Joint Expert Committee on Food Additives has evaluated more than 2600 food additives, approximately 50 contaminants and naturally occurring toxicants, and residues of approximately 75 veterinary drugs. [3]

Figure 1 presents a scheme classifying the types of food chemicals.

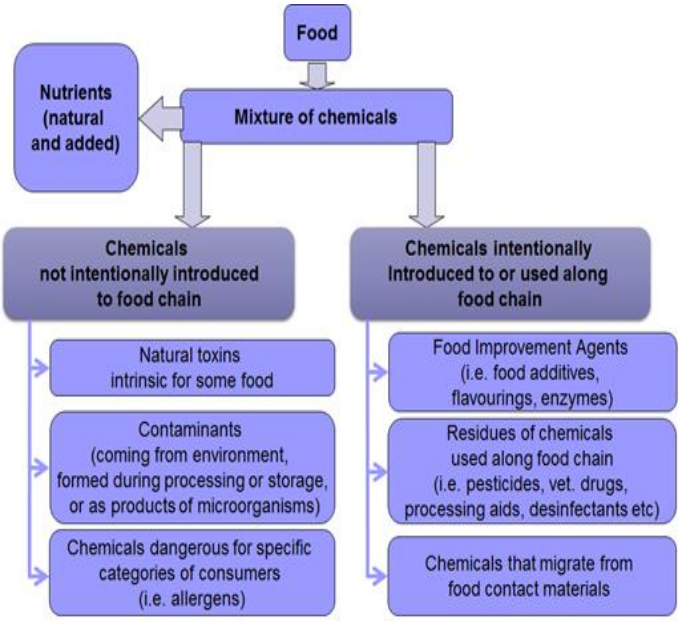

Figure 1. Food as a mixture of chemicals

Since food is a subject of international trade, its safety is regulated by multilateral agreements within World Trade Organization, namely WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). According to SPS Agreement, implementation of any requirements on food safety and "measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations" [4].

Being a member of WTO and in path to the European Union (EU), Ukraine has obligation to follow the rules of the SPS agreement. Accordingly, basic principles of the EU legislation on food safety include risk analysis as the cornerstone of food safety policy. [5] In Ukraine, Article 15 of the Law of Ukraine [6] provides that all food safety requirements should be based on scientific principles and current scientific justification and should be developed according to the results of risk assessment employing the methods of risk assessment elaborated by relevant international organizations. The Procedural Manual of the FAO/WHO Codex Alimentarius Commission provides internationally accepted definition of the relevant terms concerning risk analysis related to food safety [7].

It defines Risk Assessment as a scientifically based process comprising the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Figure 2 provides schematic representation of the whole process of risk analysis in food safety, as adapted from [8].

In silico methods used in risk assessment of food chemicals. Definition and types

According to the definition of the Royal Society of Chemists (2012), Predictive toxicology is concerned with the

Figure 2. Risk Analysis framework for food safety (adapted from [8])

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 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 identification of significant perturbations of biological pathways at a molecular level to a cellular or organ level to predict outcomes [9].

Predictive toxicology is described as follows: “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)” [10].

Tools of predictive toxicology include computational (in silico) modelling of biological activity (including toxicological endpoints), in vitro methods, OMICS technologies etc. The term “in silico” is used as an analogy to a generally used phrases in vivo and in vitro to describe any process performed on a computer or via computer simulation [11]. The United States Environmental Protection Agency (USEPA) defines in silico toxicology as the integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals. Broader understanding of in silico methodologies may be envisaged as anything we can do with a computer in toxicology. [12] Thus, the following types of in silico tools in toxicology may be distinguished:

1. Planning of experiments and power analysis
2. Data analysis procedures
3. Data mining and data-rich methods (e.g. data analysis procedures for omic and image analysis technologies)
4. Prediction models
5. Expert systems
6. (Quantitative) structure activity relationship (QSAR)
7. Modelling tools
8. Models of kinetics of substances (e.g. physiologically based toxicokinetic models)

Schematic representation of tools, steps to generate prediction models, and categories of prediction models adapted from [13] is given in Figure 3.

Speaking about hazard identification and characterization steps of risk assessment, Table 1 illustrates some of the currently available software and range of endpoints relevant to dietary risk assessment, as presented in [14].

European Food Safety Authority (EFSA - risk assessment agency in the field of food safety for EU) has thoroughly assessed applicability of in silico methods (namely QSAR, read across combined with threshold of toxicological concern (TTC) approach) for Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment [15].

For this purpose genotoxicity and carcinogenicity of such metabolites is a very important endpoint. Thus, application of integrated computational approaches including combined (Q)SAR models and read-across should be explored in future studies for the evaluation of genotoxicity alerts [16].

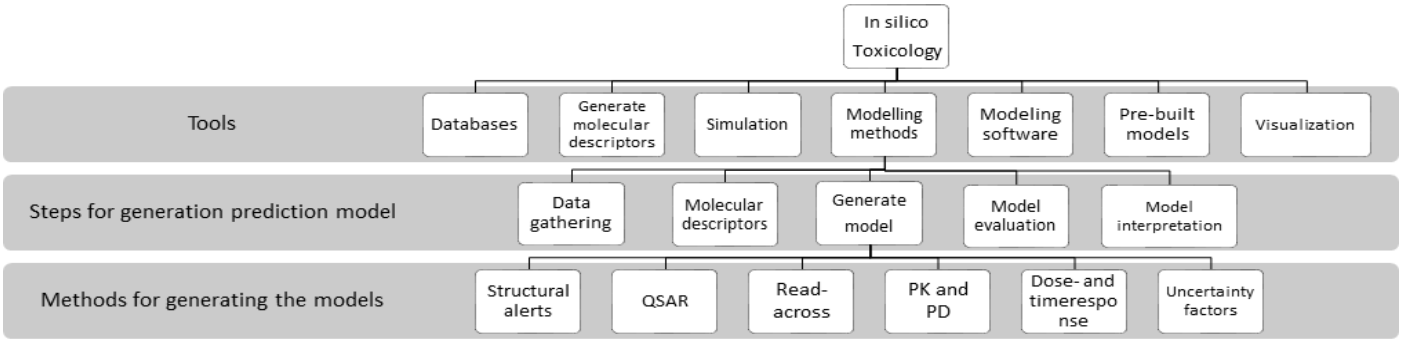

Figure 3. In silico toxicology tools, steps to generate prediction models, and categories of prediction models [13]

Table 1.

Software capable of predicting toxicological endpoints relevant to dietary risk assessment [14]

SOFTWARE	Acute oral toxicity	Repeat dose (chronic) oral toxicity	Genotoxicity (including mutagenicity)	Carcinogenicity	Reproductive (including developmental) toxicity	Endocrine activity / disruptiopn	Hepatotoxicity	Nephrotoxicity (+ urinary tract toxicity)	Neurotoxicity	Cytotoxicity	Immunotoxicity
ACD/Tox Suite (ToxBoxes)	*		*			*					
ADMET Predictor (Simulations Plus Inc.)		*	*	*		*	*				
BioEpisteme				*			*	*			
Caesar project models (Mario Negri Institute)			*	*	*						
Derek (Lhasa Ltd)			*	*	*	*	*	*	*		*
HazardExpert (CompuDrug)			*	*							
Lazar (In Silico Toxicology; Freiburg university)			*	*			*				
Leadscope (Leadscope)			*	*			*	*	*		
MCASE/MC4PC (MultiCASE)	*			*			*	*		*	
MDL QSAR (MDL)	*			*			*	*			
OASIS-TIMES (Laboratory of Mathematical Chemistry, Bourgas University)			*			*					
OncoLogic (US EPA)				*							
Pallas Suite including ToxAlert, Cytotoxicity (CompuDrug)			*	*					*	*	
TerraQSAR (TerraBase)	*					*					
TOPKAT (Accelrys)	*	*	*	*	*						
Toxtree (JRC)		*	*	*							
Molcode Toolbox (Molcode Ltd)		*	*	*		*				*	

US Food and Drug Administration (FDA) currently uses QSAR as a decision support tool in the safety evaluations of food-contact substances. This is a premarket evaluation in which the QSAR predictions are used in conjunction with literature search results and submitted toxicity tests. Occasionally, an impurity in a FCS with low dietary exposure may have only one genetic toxicity test submitted. In this case, QSAR results along with the genetic toxicity test and SAR analyses can be used to make a safety determination on the compound or provide sufficient support for recommending additional toxicity testing. [17]

Exposure assessment step of risk assessment also employs a number of in silico tools. One of them is MCRA (Monte Carlo Risk Assessment), which is a web-based system for probabilistic exposure and risk assessment of chemicals in the diet. Examples of this model and software validation for acute and chronic exposure assessment of pesticide residues in food are given in [18; 19]

Given that chemicals in food are regulated by different legislative acts, it is worth to mention that any method used for regulatory purposes should be validated and accepted. Rules for validation of QSAR methods are 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" [20].

Furthermore, for a QSAR prediction to be adequate, it should be not only reliable (i.e. derived from a valid (Q)SAR model and within its applicability domain), but also relevant for regulatory decision. [21]

Figure 4 provides graphical representation of the criteria for identifying an adequate (Q)SAR model.

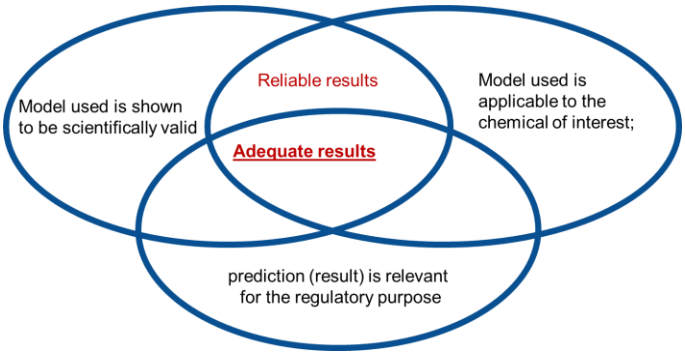

Figure 4 The overlapping considerations of validity, applicability and relevance needed to demonstrate (Q)SAR adequacy

4 CONCLUSIONS

Scientifically based risk assessment is required by legislation when new chemical food safety parameters are introduced. Huge number of chemicals to be assessed needs prioritization. Furthermore, toxicological testing of chemicals needs to be data driven. Both this tasks could be achieved and/or assisted by appropriately validated and adequate in silico tools. In fact, at each step of risk assessment process one or another computational tool has its role to play.

REFERENCES

1. Egeghy, P. P., Vallero, D. A., & Cohen Hubal, E. A. (2011). Exposure-based prioritization of chemicals for risk assessment. Environmental Science and Policy, 14(8), 950-964. https://doi.org/10.1016/j.envsci.2011.07.010

2. National Institute of Environmental Health Sciences, & National Institutes of Health. (2017). About NTP. Retrieved February 4, 2017, from https://ntp.niehs.nih.gov/about/index.html

3. ECFA. (2016). Joint FAO/WHO Expert Committee on Food Additives Fact Sheet. Retrieved from http://www.who.int/foodsafety/chem/jecfa/publications%3E.

4. WTO. Agreement on the Application of Sanitary and Phytosanitary Measures (1995). https://doi.org/doi:10.1163/ej.9789004145641.i-565.41

5. European Parliament and Council. (2002). Regulation (EC) No 178/2002 of 28 January 2002 laying down the general principles and requirements of food law,

establishing the European Food Safety Authority and laying down procedures in matters of food safety. Official Journal of the European Communities, L31, 1–24. https://doi.org/2004R0726 - v.7 of 05.06.2013

6. erkhovna Rada Ukrayiny. Zakon Ukrayiny “Pro osnovni pryntsypy ta vymohy do bezpechnosti ta yakosti kharchovykh produktiv.” Ukrayina: (Vidomosti Verkhovnoyi Rady Ukrayiny (VVR), 1998, # 19, st. 98) [Verkhovna Rada of Ukraine. The Law of Ukraine "On basic principles and requirements for safety and quality of food." Ukraine: (Journal of Verkhovna Rada of Ukraine (VVR), 1998, № 19, p. 98).] Retrieved from http://zakon1.rada.gov.ua/laws/show/771/97-вр/ed20160101

7. Joint FAO/WHO Food Standards Programme. (2016). Codex Alimentarius Commission procedural manual (25th ed.). Rome. Retrieved from ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_25e.pdf

8. AO/WHO. (2009). Environmental Health Criteria 240: principles and methods for the risk assessment of chemicals in food. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. WHO, Geneva. Retrieved from http://www.who.int/foodsafety/publications/chemical-food/en/

9. Royal Society of Chemistry. (2012). Royal Society of Chemistry View on Predictive Toxicology. Retrieved from http://www.rsc.org/images/Predictive-Toxicology-Position-Consultation_tcm18-223078.pdf

10. Helma, C. (2005). A Brief Introduction to Predictive Toxicology. In Predictive Toxicology (pp. 1–9). CRC Press. https://doi.org/doi:10.1201/9780849350351.ch1

11. Raunio, H. (2011). In silico toxicology non-testing methods. Frontiers in Pharmacology, JUN(June), 1–8. https://doi.org/10.3389/fphar.2011.00033

12. Hartung, T., & Hoffmann, S. (2009). Food for thought... on in silico methods in toxicology. Altex, 26(3), 155–166.

13. Raies, A. B., & Bajic, V. B. (2016). In silico toxicology: computational methods for the prediction of chemical toxicity. Wiley Interdisciplinary Reviews. Computational Molecular Science, 6(2), 147–172. https://doi.org/10.1002/wcms.1240

14. EC Joint Research Center. (2010). Applicability of QSAR analysis to the evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances for dietary risk assessment.

15. Worth, A., Lapenna, S., Lo Piparo, E., Mostrag-Szlinchtyng, A., Serafimova, R., & Institute for Health and Consumer Protection. (2010). The applicability of software tools for genotoxicity and carcinogenicity prediction : case studies relevant to the assement of pesticides. https://doi.org/10.2788/61485

16. EFSA. (2012). Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment 1. EFSA Journal, 10(7), 2799. https://doi.org/10.2903/j.efsa.2012.2799.

17. Arvidson, K. B., Chanderbhan, R., Muldoon-Jacobs, K., Mayer, J., & Ogungbesan, A. (2010). Regulatory use of computational toxicology tools and databases at the United States Food and Drug Administration’s Office of Food Additive Safety. Expert Opinion on Drug Metabolism & Toxicology, 6(7), 793–6. https://doi.org/10.1517/17425255.2010.493555

18. van der Voet, H., de Boer, W. J., Kruisselbrink, J. W., Goedhart, P. W., van der Heijden, G. W. A. M., Kennedy, M. C., … van Klaveren, J. D. (2015). The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides. Food and Chemical Toxicology, 79, 5–12. https://doi.org/10.1016/j.fct.2014.10.014

19. Yang, C., Valerio, L. G., & Arvidson, K. B. (2009). Computational Toxicology Approaches at the US Food and Drug Administration a, 523–531.

20. OECD. (2007). Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)Sar] Models. Transport, 2(February), 1–154. https://doi.org/10.1787/9789264085442-en

21. ECHA. (2016). Practical Guide 5 - How to use and report (Q)SARs. Retrieved from http://echa.europa.eu/view-article/-/journal_content/title/further-advice-on-how-to-use-qsars-for-reach-registration.

Received: 13-Jan. – 2016
Accepted: 28-Mar. - 2016