**An *in silico* approach to cytotoxicity of pharmaceuticals and personal care products on the rainbow trout liver cell line RTL-W1.**

MELEK TÜRKER SAÇAN1, SERLİ ÖNLÜ1, MÜGE KÜÇÜKALİ1,

1Boğaziçi University, Institute of Environmental Sciences, Istanbul, Turkey,

msacan@boun.edu.tr

Pharmaceuticals and personal care products (PPCPs) are a diverse group of many hundreds of chemicals widely used in human health and cosmetic care as well as agricultural and veterinary reasons. They include over-the-counter and prescription therapeutics, veterinary drugs, cosmetic products and fragrances. Synthetic musks are commonly used fragrance materials in almost all scented personal care products (PCPs) such as perfumes, skin and hair care products. The potential acute and chronic toxicity of PPCPs to non target organisms are not known adequately yet. In addition, short- and long-term ecotoxicological information on fish is required for substances produced in or imported into the EU under REACH Regulation. *In vitro* assays using fish cells have a great concern with the advantage of minimising animal use, allowing the testing of a wide range of chemicals and concentrations. These *in vitro* assays also provide a quick and cost-effective option that has high positive correlations with *in vivo* results and could be suited for the first screening of acute toxicity of environmentally significant chemicals on non target organisms. Furthermore, the replacement of bioassays with alternative methods has gained great attention recently. The toxicity data predicted from validated Quantitative Structure−Activity/(Toxicity) Relationship (QSAR/(QSTR)) models are accepted instead of new experimental studies (1).

In this study, seventeen structurally diverse and widely used cytotoxic pharmaceuticals, synthetic musks and an industrial chemical on the rainbow trout (*Oncorhynchus mykiss*) liver cell line RTL-W1 have been subjected to QSAR studies. Data were taken from literature (2) including eleven pharmaceuticals from different therapeutic classes, as well as five synthetic musks from the two major groups, nitromusks (musk ketone, musk xylene) and polycyclic musks (galoxolide, tonalide, celestolide) and one industrial chemical (pentachlorophenol). The endpoints from two cytotoxicty assays namely the Alamar Blue (AB) for changes in energy metabolism and 5-carboxyfluorescein diacetate acetoxymethylester (CFDA-AM) assay for evaluating membrane integrity were used in searching the relationship between cytotoxicty and descriptors obtained from chemical structure. In the data set, the LogKow and cytotoxicity of the chemicals had no relationship. Therefore, it is useful to search for descriptors which can be used to relate cytotoxicity obtained from the two *in vitro* bioassays. The Multiple Linear Regression analysis which is an unambiguous algorithm in accordance with the OECD requirements was adopted in this study for cytotoxicity modelling. Calculated SPARTAN 10 and DRAGON 6 descriptors were selected using all subset in QSARINS ((version 2.2.1.) (3, 4)). In both endpoints, the molecules in the data set were encoded best with the CATS 2D atom-pair descriptors. Five chemicals were used to test the predictivity of the generated models. Unknown cytotoxicity values of ten pharmaceuticals which fell in the applicability domain of the generated models were predicted from the developed models.

**Aknowledgments:** The support of this study by Boğaziçi University Research Fund (no: 8502) is acknowledged. Authors also would like to thank Prof. P. Gramatica for providing QSARINS program.

**References:**

1) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Official Journal of the European Union, L 396, 1−849.

2) Schnell S., Bols N.C., Barata C., Porte C. Single and combined toxicity of pharmaceuticlas and personal care products (PPCPs) on the rainbow trout liver cell line RTL-W1, Aquatic Toxicology, 93, 244-252.

3) P. Gramatica, N. Chirico, E. Papa, S. Cassani, , S. Kovarich, J. Comp. Chem., 34 (2013), 2121-2132.

4) P. Gramatica, S. Cassani, N. Chirico, J. Comp. Chem. 35 (2014) 1036–1044. <http://www.qsar.it>