Bioenergetics: Open Access

ISSN: 2167-7662

Computers are Good Enough for Prediction of Toxicity by Chemicals?

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Introduction

I have been personally involved in various toxicological studies of industrial chemicals, pesticides and pharmaceuticals in a chemical company for so many years. My professional interests include metabolism, carcinogenicity, mode of toxic action, endocrine disruptors and Omics technology. I strongly believe that the recent advances in IT and Omics technology and the availability of huge toxicological database with high quality will shape the future strategy for how to conduct safety assessment of a large number of chemicals having their impact to human safety and to the environment. In this respect, one major question I want to address is whether computational technology today can provide us with reliable prediction of the chemical hazard potential.

It is well known that regulatory agencies worldwide require extensive mammalian and/or environmental toxicological data for the registration of pesticides and pharmaceuticals. On the other hand, a more relaxed approach generally appears to be taken in the registration of industrial chemicals when compared with pesticides and pharmaceuticals. This may be due, in part, to the fact that pesticides and pharmaceuticals are biologically active compounds, whereas industrial chemicals are generally being considered as biologically inactive. Production volume is being considered as important criteria for determination of the data requirement for industrial chemicals. An almost complete toxicological data package is requested for high production volume chemicals according to the current REACH registration in EU. The number of industrial chemicals in commerce is large and in addition, new chemicals and/new uses will be marketed year after year. In order to protect consumers and the environment, how can industries and/or governments conduct environmental and human safety assessment of these chemicals with limited resources? We need to establish scientifically valid and cost effective approaches to determine the physical chemical properties/reactivity, environmental persistence/transport potential and acute/chronic/cumulative/aggregate risks to ecological organisms and humans. More importantly, we need a mechanism to prioritize hazard potential [persistence (P), bioaccumulative (B) and toxicity (T)] of a vast number of chemicals for testing and regulation. Efficient and high-throughput systems are desired for this hazard potential evaluation. Other than time and resource limitations, our consideration to reduce animal testing and enhance animal welfare is also important. To meet these demands, computational approaches (*in silico* prediction of toxicity) are being considered by both the US Environmental Protection Agency (EPA) and EU (REACH) as alternative (or as the initial screening) for chemical hazard potential. One such approach is the Computational Toxicology Initiative (ToxCast) by the US EPA and Technical Guidance Documents for read-across and chemical category are available for prediction of toxicity for REACH registration.

As for how to optimize the discovery pipeline, it is very important for chemical industries to make a decision on "go or no-go" in the early discovery stage. In addition to efficiency and production cost, one of the criteria is the environmental and human hazard potentials. Early risk assessment is now a part of discovery phase in the product life cycle. Chemical industries are working on the development of simple or alternative testing strategy to assist with this product development plan.

Approaches in computational (*in silico*) toxicology are read across, category approach, SAR (Structure Activity Relationships) or QSAR(Quantitative Structure Activity Relationships). The principle of *in silico* toxicology is simple: similar chemical structure or substructure generally promote similar toxicological outcome. In the past several years, *in silico* methods have become more promising and advantageous, because many toxicological database with high quality have been available commercially or freely. The higher the quality of the database is, the more reliable the *in silico* prediction is. Such high quality database includes ACToR (EPA) (http://actor.epa.gov/actor/faces/ACToRHome.jsp) and eChemPortal (OECD)

(http://www.echemportal.org/echemportal/page.action?pageID=0. Moreover, newly available toxicological database are Global Product Strategy (ICCA) (http://www.icca-chem.org/en/Home/ICCA-initiatives/global-product-strategy/) or summary of REACH registration (http://echa.europa.eu/information-on-chemicals/ registered-substances;jsessionid=8FEE1721002C9FD2F395255A218CE227.live1). I suppose that additional toxicological information will be freely available in the future.

In addition to database, open source computational tools are available for properties prediction. For example, such free software include the OECD Application Tool Box Ver 2.3 (http://www.oecd.org/document/54/0,3746,en_2649_34379_42923638_1_1_1_1,00.html) or other several ones (i.e., ToxPredict: http://apps.ideaconsult.net:8080/ToxPredict, ECOSAR: http://www.epa.gov/oppt/newchems /tools/21ecosar.htm) and commercial software (Derek: https://www.lhasalimited.org/derek_nexus/ Topkit: http://accelrys.com/mini/toxicology /predictive-functionality. html) are also available. The software allow us to predict the chemical, environmental and toxicological properties, based on chemical structure features. Nevertheless, aside from the availability of the software, expert judgments are still necessary. One of the challenges we face is how to make prediction process of these software more transparent.

In silico methods are very promising as mentioned above. However, there is actually the lack of biological confirmation. I recommend that biological confirmation methods (such as high through-put *in vitro* assay) be applied to validate the *in silico* predicted toxicity.

To deal with this problem, I would like to propose a combination of *in silico* methods and Omics technology using several cell lines,

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especially for mammalian toxicity. Omics technology provides comprehensive data of gene expression, proteins and metabolites, and has currently at least two major fields: toxicogenomics and metabolomics. Toxicogenomics enables us to understand the first response of cells to chemicals in terms of gene expression. From my experiences, there are so many genes whose expressions are found to be perturbed by exposure to chemicals. In addition, it is sometimes difficult to know which change of gene expression is relevant to physiological changes. In toxicogenomics experiments, it is of a great importance to determine when the gene expression is measured, because gene expression greatly depends on sampling times. With respect to metabolomics, metabolites are comprehensively examined and the data from this method appear to be related to physiological changes more closely than those from toxicogenomics. The integration of both toxicogenomics and metabolomics is very promising for elucidation of mode of toxic action and demonstration of biological equivalency of chemicals.

In order to improve the quality of toxicity prediction in mammals and environmental species, *in silico* technology and Omics technology (toxicogenomics and metabolomics) should be applied together. This combination enables us to predict toxicological effects by chemicals more precisely than solely *in silico* methods do. In addition, *in silico* prediction should be done on parent compounds as well as their metabolites or degradates in the future. However, it will need much more efforts to predict metabolites or degradates in mammals or environmental species. When the precise prediction of metabolites or degradates become possible, *in silico* methods will be more indispensable for regulation and development of new chemicals.