Dr Masamitsu Honma, National Institute of Health Science, gave this presentation at the "Streamlining Drug Discovery" symposium held in Tokyo, Japan on 5 June 2018.

Abstract

Currently, more than 130 million chemical substances have been registered in the CAS registry, and this number is increasing at a rate of 4,000/day. Among these chemicals, approximately 120,000 are industrially produced and exist in our environment. To cover the huge number of chemical substances that affect human health, effective screening tools are required. *In silico* and quantitative structure–activity relationship (QSAR) models defining toxicological endpoints are desirable for regulatory authorities to identify chemicals causing adverse effects without conducting actual toxicological studies.

There has been considerable effort in the development of QSAR models to predict mutagenicity among many toxicological endpoints because mutagenic chemicals pose the highest concern for human health. The recently developed ICH-M7 guideline (Assessment and control of DNA-reactive impurities in pharmaceuticals to limit potential carcinogenic risk) allows the use of the *in silico* approach to predict Ames mutagenicity for initially assessing impurities in pharmaceuticals. This is the first international guideline addressing the use of QSAR models *in lieu* of an actual toxicological study for human health assessment. QSAR models for the Ames assay now require higher prediction power to definitely capture mutagenic chemicals. To increase the prediction power, experimental data sets required to build the models are important. A large number of highly reliable data sets are essential to allow the development and improvement of QSAR models. DGM/NIHS in Japan has the largest Ames mutagenicity database, containing approximately 12,000 new chemicals that have not been previously used for developing QSAR models. We provided the Ames data to vendors to improve their QSAR models. The Ames/QSAR international collaborative project, together with 12 QSAR vendors, started in 2014 and has recently been completed. All QSAR models have considerably improved. Some QSAR models showed nearly 90% prediction power, which is the same level as that of the inter-laboratory correspondence of the Ames assay. Using the *in cerebro* (expert judgement) approach, we can further predict the relevance of mutagenicity data in humans. We are approaching a new era wherein “*in silico/in cerebro*” will replace “*in vitro/in vivo*” in genetic toxicology.

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