Title of Research:

22-6-02

Development of an objective read-across method based on statistical and mathematical sciences for evaluation of repeated-dose toxicity

Principal Investigator:

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Summary of Research:

Repeated-dose toxicity (RDT) test is important for chemical safety evaluation. Currently, it is highly recommended to develop alternatives to rat RDT tests, but it remains very difficult to develop such a method largely due to the diversity and complexity of the toxicity. The aim of this project is to develop an objective read-across method, in which the toxicity of an untested substance is predicted from the toxicity information of similar substances (called "source substances"), using chemical information and in vitro assays as an alternative to rat RDT tests. In this year, we selected test substances from HESS and REACH databases and set 8 group endpoints (6 hepatotoxicity- and 2 hematotoxicity-related) as targets. Studies were conducted on criteria for judging the presence or absence of toxicity of test substances from source substances, molecular descriptors to be used for similarity assessment, and methods for selecting source substances. Results obtained indicate that the criteria for judging the toxicity of test substances should be adjusted based on the positive rate of the group endpoints, source substances differ depending on the type of inter-substance distances used, the descriptors should be selected by an appropriate method, and the accuracy of toxicity prediction is improved by appropriately selecting descriptors.

Timeline:

March 1, 2022 - February 28, 2023

Topics:

Publication #1 (Yu Harakawa) received Presentation Award for Students at the 35th annual meeting of the Japanese Society for Alternatives to Animal Experiments.

Publications:

1. Y Harakawa, N Omura, J Takeshita, R Shizu, T Hosaka, Y Kanno, K Yoshinari. Development of a read-across method for evaluating repeated-dose toxicity using molecular descriptors: Examination of methods of selecting molecular descriptors for better prediction. The 35th annual meeting of the Japanese Society for Alternatives to Animal Experiments. Shizuoka, Japan, 2022.11.18-20.
2. K Yoshinari. Evaluation of developmental neurotoxicity of chemical substances by a read-across method using chemical structure information. The 35th annual meeting of the Japanese Society for Alternatives to Animal Experiments. Shizuoka, Japan, 2022.11.18-20.
3. K Yoshinari. Safety assessment of chemical compounds by in vitro and in silico methods: challenges and future prospects. ILSI Japan symposium: Alternatives to animal experiments in the food science area -current situation, trends and initiatives for the future. Online, 2023.2.3.
4. Y Harakawa, N Omura, R Shizu, T Hosaka, J Takeshita, K. Yoshinari. Examination of the selection method of molecular descriptors for the evaluation of repeated-dose toxicity using a read-across approach. The Society of Toxicology 62nd Annual Meeting and ToxExpo. Nashville, TN, USA. 2023.3.19-23.