Title of Research:

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

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Summary of Research:

Repeated-dose toxicity (RDT) tests are essential for assessing the safety of chemical substances. However, due to the complexity of RDT, developing alternative methods to animal testing remains challenging. In this study, we aimed to develop an objective read-across method utilizing information on chemical structures and toxicity-related in vitro tests. First, we prepared subgroups of chemical substances based on their partial structures and performed predictions for liver and blood toxicity using the results of in vitro tests. We found that toxicity could be accurately predicted in some subgroups (e.g., aromatic amines) with in vitro tests. Next, using model substances containing aniline- and phenol-like structures, we explored a method for grouping based on toxicity profiles across multiple toxicity endpoints. We found that predicted biological activity values are useful for grouping substances with similar toxicity. Additionally, using three or four molecular descriptors, we identified several subgroups of chemicals that contained only negative or positive substances for specific liver or blood toxicity endpoints. Finally, we found that for certain groups of chemicals, cytochrome P450 inhibition assay data are valuable for quantitatively predicting LOEL values for hepatotoxicity. In conclusion, our present results may assist in establishing a methodology for predicting the RDT of chemical substances through read-across, taking into account multiple toxicity endpoints and utilizing molecular descriptors and in vitro test data.

Timeline:

March 1, 2024 - February 28, 2025

Topics:

None

Publications:

1. J Takeshita, Y Goto, S Yamamoto, T Sasaki, K Yoshinari. Comprehensive analysis of the toxicity-related findings from repeated-dose subacute toxicity studies of industrial chemicals in male rats. *Crit Rev Toxicol,* 54:996-1010, 2024.
2. N Uchida, Y Harakawa, T Hosaka, R Shizu, J Takeshita, K Yoshinari: Quantitative correlation analysis between the liver toxicity LOEL and P450 inhibitory activity, 51st Annual Meeting of the Japanese Society of Toxicology (July 3-5, 2024, Fukuoka)
3. N Uchida, M Shibata, Y Harakawa, A Ooka, T Hosaka, R Shizu, J Takeshita, K Yoshinari: Development of a toxicity evaluation method for structurally similar compounds using RNA sequence data, 7th Symposium on Drug Toxicity Mechanisms (January 8-9, 2025, Shizuoka)
4. Y Harakawa, J Takeshita, A Ooka, T Hosaka, R Shizu, K Yoshinari: Development of a read-across method for repeated dose toxicity evaluation: Evaluation of the usefulness of in vitro test data related to toxicity mechanisms, Ibid.