（別紙）研究成果の概要（英文）

Title of research project	Research on application condition of the benchmark dose methods for health risk assessment
Research project number	1804
Research period	FY 2018 – 2019
Name of principal research investigator (PI)	Akihiko Hirose

Abstract/Summary

Benchmark dose (BMD) method has been increasingly used for risk assessment practice, including the determination of the point of departure (POD) for toxicological assessment of chemical substances. Besides, model selection criteria for the BMD method have been highly variable by existing guidelines of different organizations. Also, inconsistent applications of pathological data to the BMD method are conducted in different organizations. As for application of BMD method to epidemiological data, some pitfalls exist. Therefore, it is necessary to establish guidance for application of BMD approach to the regulatory risk assessment.

In this study, we performed literature survey, conducting systematic review analysis to understand technical issues surrounding the application of BMD method, and evaluated model selection criteria by using simulation-based approach.

The mathematical exercise revealed that the similarity between the two are supported by limited sample size during animal experiments, coincidentally meeting the necessity of $BMDL_{10}$ due to sampling error. Model selection criteria were evaluated, restricting our analysis to the application of BMD method to quantal response data using simulation-based approach. Candidate criteria included the use of 1) smallest $BMDL_{10}$, 2) smallest BMD_{10}, 3) smallest AIC, and 4) an option to take model averaging values. The model averaging with 3 models with the lowest AIC values (MA-3) returned reasonable results overall, while it did not always yield the best performance. We gathered the information of simulation-based performance by applying Kolmogorov-Smirnov test p-value and the ratios of BMD/BMDL, and BMDU/BMDL. No exclusion criteria we considered in the present study greatly improved the performance of evaluation, i.e. reliability and validity, in none of dose-response patterns. To assess the added values of parameter restriction or imposing statistical constraints for parameters, we have discussed its details proposed by literature, and concluded that they do not have to be applied.

Consideration on the application of BMD method to pathological data, we summarized issues and points of note for applying the BMD method to histopathological findings. Based on some case studies using published toxicity data, setting of clear criteria for grading in the histopathological analysis was needed to consider application of the BMD methods. To combine incidence data derived from different toxicity studies or findings, biological equivalence of the background or mechanism of the corresponding histopathological findings should be clarified. Quantitative data by image analysis revealed that the imaging data could be used as markers related to the toxicologically significant findings.

As for application of BMD method to epidemiological data, we have enumerated and compared technical characteristics of epidemiological data against those of animal experiment data. Epidemiological data tend to involve evaluation of continuous response data, and the incidence data can be usable for the analysis of BMD method. We noted that the representativeness, i.e. if the quantified outcome is applicable to the entire population, confounders, cut-off value, and quantiles are often problems, whenever the application of BMD method to epidemiological data is considered.

If a technical guidance of the BMD methodology with a single recommended criterion for applying animal experimental data is required, we considered that one may recommend

MA-3 method as the method to calculate $BMDL_{10}$ as a POD to the reference dose. When the pathological data or related imaging data are used for the BMD method, we should verify whether the quantitative data is appropriate for explaining toxicologically significant dose-responses. We found the possible points to be considered below at the application of BMD method to epidemiological data: *The infinite number of confounders may be related since the epidemiological is usually based on observational researches (i.e. nothing such as randomization). *Studies sometimes includes the smaller number of high-dose data. *Quantiles of observed continuous data are sometimes unknown. The development of BMD methods (e.g. model averaging, hybrid model, and Bayesian-based BMD method) possibly changes the methods of risk assessment.

1. List of papers published on the basis of this research

None

2. List of presentations based on this research

Yoshii1 K, Nishiura1 H, Inoue K, and Hirose A. Simulation-Based Assessment of Model Selection Criteria during the Application of Benchmark Dose Method to Quantal Response Data. Society of Toxicology (SOT) 58th Annual Meeting (SOT2019), (2019.3.10-14), Baltimore, USA. (The abstract is available from Toxicologist. (Toxicological Sciences. 173 (1), Suppl. 426, 20219))

Keita Yoshii, Hiroshi Nishiura1, Kaoru Inoue, Akihiko Hirose. Assessing model selection criteria during the application of benchmark dose method to quantal response data: Japanese perspectives. 15th International Congress of Toxicology (Hawaii, USA), 2019.7.15-18.

Yoshii K., Nishiura H., Inoue K., Hirose A. Evaluation of Model Selection Criteria Including Model Averaging during the Application of Benchmark Dose Method to Quantal Response Data (PS2253). Society of Toxicology (SOT) 59th Annual Meeting (SOT2020), (2020.3.14-18), Anaheim, USA (The meeting was cancelled by COVID-19 epidemic, but the abstract is available from *Toxicologist*. (*Toxicological Sciences. 174 (1), Suppl. 299*, *2020*).)

Hirose A, Yoshii K, Inoue K, Shigeta Y, Matsumoto M, Kawamura T, Yamaguchi T, Nishiura H. Performance Comparison of BMDL Calculation by the Model Averaging Methods for Quantal Dataset (PS1573). Society of Toxicology (SOT) 59th Annual Meeting (SOT2020), (2020.3.14-18), Anaheim, USA (The meeting was cancelled by COVID-19 epidemic, but the abstract is available from *Toxicologist*. (*Toxicological Sciences. 174(1), Suppl. 131*, *2020*.)

3. The number and summary of patents and patent applications

None

4. Others (awards, press releases, software and database construction)

None