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Title of research project	Research on application of the benchmark dose approach in the dose response assessment
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【Abstract】

The Benchmark dose (BMD) approach has gained more acceptances for dose response assessment, because the dose response and the statistical uncertainty were reflected more than the NOAEL approach. Recently, the lower confidence limit of BMD (BMDL) has also been used as the point of departure for the genotoxic cancer risk assessment as well as for threshold effects instead of the NOAEL. The guidance for the BMD approach has been published from the international organizations such as IPCS and EFSA and U.S. EPA. However, there are some inconsistencies of the application methods between EFSA and EPA approaches, and no guidance is provided in Japan. Therefore, we have developed more realistic guidance of the BMD application for general toxicity data, by analyzing the dose-response data assessed by some international/domestic assessment bodies, such as WHO, U.S. EPA (IRIS database) and Japanese existing chemical evaluation program. As the criteria for the BMDL calculation, we proposed 10% as the BMR for dichotomous data and one SD (standard deviation) as the BMR for continuous data. As for the model selection, we proposed the rules in which the BMD/BMDL ratio should be less than 10 and the lowest dose/BMDL ratio should be less than 100. For the epidemiological data, the hybrid approaches are more appropriate for the BMD calculation because cutoff point can be set more easily and the confounding factors can be managed.

In order to ensure the applicability of BMD approach to the experiment with multiple dose and combined exposure, we have also conducted the experimental rat studies including combined exposure with DEHP and DHP. We found some qualitative merits for using the BMD approach in the analysis of combined exposure effects, but more novel approaches would be necessary for quantitative analysis. However, the combined exposure study with DEHP and DHP is considered to be useful for research of mixture effects of multiple chemicals, because synergic effects, additive effects and antagonistic action are included in one system.

Finally, we could post the proposed guidance for BMD approach with the BMDS (developed by U.S.EPA), the PROAST (developed by RIVM) and SPBS program (developed by Dr. K Murata, Akita Univ.) (http://dra4.nihs.go.jp/bmd) and BMD calculation results for many dose-response data on our public website.