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| Title of research project | A study on the risk assessment method of genotoxic carcinogens |
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**【Abstract】**

To develop and propose the guidelines for quantitative assessment of genotoxic carcinogens in food which unified used for the risk assessment of food related chemicals in the Food Safety Commission of Japan, two themes of researches were conducted, i.e. (1) The use of mutagenicity data for the definition of mutagenic carcinogens and cancer risk assessment, and (2) Development of the principle guideline for risk assessment of genotoxic carcinogens.

We conducted TG assays in the MutaMouse liver using four hepatocarcinogens; 2-acetylaminoflioren (2-AAF), 2,4-diaminotoluen (2,4-DAT), dimethylnitrosamine (DMN), and diethylnitrosamine (DEN) based on OECD TG488 guideline. We calculated a BMDL10 of the TG assay (TGBMDL10) for each carcinogen using the Benchmark Dose Software (US-EPA), and compared it with the BMDL10 of liver carcinogenicity (CARCBMDL10). We newly defined “mutagenic carcinogens” as (1) chemicals inducing mutagenicity and carcinogenicity in a same organ, (2) the minimum dose inducing mutagenicity must be lower than that inducing carcinogenicity. According to this definition, the 4 chemicals used in this study were identified as “mutagenic carcinogens.” However, the treatment duration does not mean the time required to induce mutagenicity and carcinogenicity. The combination assay with carcinogenicity and mutagenicity in same animals is ideal to demonstrate “mutagenic carcinogens”. The result of the dose-relationship between TGBMDLs10 and CARCBMDLs10 was well corresponding, indicating that TGBMDL10s from TG assays may be used for cancer risk assessment if there is no carcinogenicity data. However, further studies on the dose relationship between mutagenicity and carcinogenicity of chemicals with different modes of action are necessary to actually use TG assay for a risk assessment.

We collected information on guidelines and cases of risk assessment in Europe and the United States, and discussed potential methods which are applicable and suitable for a quantitative risk assessment of genotoxic carcinogens in the FSCJ, in expert meetings on the relevant subject. Consequently, we proposed “The guideline for quantitative assessment of human carcinogenic risks from oral ingestion of genotoxic carcinogens in food” based on the discussion in the expert meetings. The proposed guideline consists of two parts. The first part is for a genotoxicity evaluation which determines whether carcinogenic threshold exists or not based on the results from genotoxicity tests, the second part is indicating the overall framework and concept of the most appropriate methods for quantitative evaluations of the carcinogenic risk to humans from the oral ingestion of genotoxic carcinogens which reflect the genotoxicity evaluation results. The guideline we proposed in this study may be yet inapplicable to an actual risk assessment, because detailed mechanisms of genotoxicity have not been verified for all genotoxic chemicals. Thus, the actual risk assessment will be conducted based on the

weight of evidence. Although the proposed guideline is based on the current scientific knowledge and agreement of many experts, mechanisms of genotoxicity and carcinogenicity, and issues of their thresholds are still not completely clear and many researches have been conducted. Thus, in the future when new knowledge is obtained, it is necessary to discuss it again.