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Title of research project	Study on the procedure for the risk assessment of flavorings in Japan
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【Abstract】

After the risk assessments of the internationally widely used 54 flavorings are completed, risk assessments of new flavorings are necessary for designation of flavoring in Japan. The aim of this study is to make a draft of a new procedure for the risk assessment of the flavorings for new designation.

Risk assessments of flavorings (synthetic flavoring compounds) as food additives for new designation are conducted by FSCJ according to "The procedure for the risk assessment of flavorings used internationally widely" (hereinafter, "the evaluation method in 2003"). The features of "the evaluation method in 2003" are (1) to determine the NOAEL based on repeated dose toxicity test data, (2) to compare the NOAEL with the estimated intake of the flavoring, and (3) to determine whether adequate safety margin exists. On the other hand, the features of the risk assessment methods of JECFA and EFSA are as follows: (1) to classify the flavoring into three Cramer structural classes on the basis of the structures and putative metabolic pathways and (2) to compare the estimated intake of the flavoring with the respective Cramer class threshold (the permissible exposure threshold for each structural class), that is the TTC (Threshold of Toxicological Concern) techniques.

Ten years has passed since "the flavorings used internationally widely" was issued, and new "flavorings used internationally widely" have appeared. Risk assessments of these flavorings are expected to be performed for new designation in Japan. Consequently, we thought it necessary to review the risk assessment methods for flavorings in Japan, taking into account how overseas risk assessment methods are reviewed.

In this study, we conducted the followings.

1. Collecting the documents on overseas risk assessment for flavorings and interviews with industry.
2. Comparison of risk assessment methods for flavorings in Japan and overseas.
   Genotoxicity evaluation, general toxicity and pathological evaluation, and intake estimation method.
3. Study on the group evaluation of structural analogs.
4. Study on the usage of human metabolite prediction software.
5. Making a draft of a new risk assessment method for flavoring in Japan and validating.

We made a draft of a new risk assessment method for flavoring based the following general principle.

1. The new method was made with reference to the risk assessment method by EFSA. At first genotoxic evaluation, then general toxicity evaluation based on TTC technique are to be conducted.
2. In the genotoxic evaluation procedure, it is allowed to evaluate the flavoring with reference to the genotoxicity test results of structural analogs, based on the structural analog group adopted for the flavoring group evaluation (FGE) conducted by EFSA.

3. It is recommended to use QSAR system to verify the structural alert with reference to the ICH M7 guideline, if no or little genotoxicity test data are available.
4. In general toxicity evaluation procedure, it is adopted basically the evaluation technique by the decision tree of JECFA, except the followings. Step 33 in Cramer classification procedure and Step B5 (Is the intake greater than 1.5μg / day?) in the decision tree are not adopted. The exceptions are the same as in "the evaluation method in 2003".
5. The prediction of metabolites is basically based on experiment data with the experimental animals. It is appropriate to use human metabolites prediction software to help expert judgment.
6. Intake estimation is basically based on MSDI method. It is suitable to use SPET method in which the Japanese dietary habit is reflected (Japanese version SPET method), in conjunction with MSDI method.

We hope that the results of this study are helpful for enactment of a new risk assessment method for flavorings in FSCJ.