Provisional translation

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Expert Committee on Food Additives

Food Safety Commission of Japan

Guidelines for the Risk Assessment of Food Additives (Revised Guideline for Assessment of the Effect of Food on Human Health Regarding Food Additives)

Chapter 1. General Provisions

Article 1. Background

The Food Safety Commission of Japan (FSCJ) (hereinafter referred to as "the Commission") has established guidelines for assessment of the effect of various foods and related subjects on human health, based on the "Basic Matters" prescribed by Article 21, paragraph 1 of the Food Safety Basic Act (the Cabinet Decision on June 29, 2012)[1]. The said assessment represents "the Assessment of Effect of Food on Human Health" prescribed by Article 11, paragraph 1 of the Food Safety Basic Act (Act No.48, 2003) (the same hereinafter), and the Commission took into account the point of view that the guidelines shall ensure fairness and transparency of assessments.

In May 2010, the FSCJ created "Guideline for Assessment of the Effect of Food on Human Health Regarding Food Additives" (Decision of the Commission on May 27, 2010, hereinafter referred to as "Guideline 2010"), based on the results of the previous assessments of the effect of food on health as well as stance on safety assessments developed by the Japanese and foreign governments. As a consequence, the Commission decided that "Guideline 2010" should be followed whenever assessments are conducted going forward.

Afterwards, the FSCJ established "Guidelines for the Assessment of Flavoring Substances in Foods on Health" (Decision of the Commission on May 17, 2016), "Guidelines for the Risk Assessment of Additives (Enzymes) in Foods" (Decision of the Commission on July 18, 2017), and "Guidelines for the Risk Assessment of Food Additives for Fortification" (Decision of the Commission on July 18, 2017).

[1] The Cabinet decision Item1-3(1)-3 prescribed that the Food Safety Commission of Japan (FSCJ) is to endeavor to establish guidelines for the assessment of food-related hazards on human health (hereinafter referred to as "the risk assessment"), and review the guidelines as necessary.

Consequently, the Commission decided to apply “Guideline 2010” for later risk assessments of additives other than flavoring substances, enzymes and additives for fortification.

In addition, the Commission amended “Guideline 2010” in July 2017 in association with establishment of “Stance for the Risk Assessment of Processing Aids (Food Disinfectants and Extractants)”.

The FSCJ’s Expert Committee on Additives recently summarized the stance on risk assessment of additives in foods used as breastmilk substitutes for infants under 4 months old, and amended this Guideline. Moreover, the Expert Committee examined and amended the provisions in the Guideline considering new scientific findings and trends in international standards for assessments both in and outside Japan, since “Guideline 2010” was established more than 10 years ago. From now on, the present guidelines shall be applied for the risk assessments whenever conducted.

Article 2. Purpose

The purpose of this guideline is to establish the guiding principle of risk assessment on additives and to define the scope of the required documents. The risk assessment shall be conducted for the cases where the Minister of Health, Labour and Welfare (MHLW) designates additives having no risk to human health as provided in Article 12 of the Food Sanitation Act (Act No. 233 of 1947), or where MHLW intends to establish standards or specifications in accordance with the provisions of Article 13, paragraph 1 of the Act.

Article 3. Definition

1. Food additives

   Food additives are defined in Article 4, paragraph 2 of the Food Sanitation Act as substances which are used by being added, mixed or infiltrated into food or by other methods in the food producing process or for the purpose of food processing or preserving.

2. Internationally commonly used food additives

   Internationally commonly used food additives are food additives selected, from among those that meet both of following requirements, as the additives to start reviewing toward this designation without waiting for requests to be made by private corporations and other organizations[2].

   (1) An international safety assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has been completed, and the safety has been confirmed.

   (2) The use has been widely permitted in the U.S. and EU member states and there is a global consensus on the necessity of use.

Article 4. Approach for the Risk Assessment of Food Additives

A. Safety factors will be applied to the risk assessment of food additives after the Commission summarizes the approach for it. For the time being, the Expert Committee shall have the

[2] In accordance with the agreement reached by the Food Sanitation Subcouncil of the Pharmaceutical Affairs and Food Sanitation Council on July 26, 2002, the MHLW was supposed to start reviewing relevant substances for this designation without waiting for requests to be made by private corporations and other organizations.

responsibility of deciding how to apply the safety factors based on the provision No.6-1(3)-b.

B. For "Internationally commonly used food additives", the risk assessment shall be conducted based on assessment reports generated by the JECFA, the U.S. and European countries ("report-based assessments") in principle, after the latest scientific findings are examined.

C. Although the existence of a threshold for genotoxic carcinogens[3] has been a topic of international discussion for some time, no consensus has yet been reached. Therefore, an assessment shall be conducted in principle on the assumption that no such threshold exists. A substance must be classified into a genotoxic carcinogen carefully based on the MOA (Mode of Action) and WOE (Weight of Evidence).

D. If a food additive is evaluated to be genotoxic carcinogen, the relevant substance should not be approved in principle at this point in accordance with the previous paragraph. If a exogenous (including naturally occurring matter; the same hereinafter), a byproduct and/or a degradation product that is unavoidably contained during the manufacturing process of the food additive is a genotoxic carcinogen, a comprehensive assessment shall be conducted based on the concept of virtually safe dose (VSD), while the content should be reduced to the level as low as technologically possible.

E. Effects for a particular cohort of people such as pregnant women, fetuses, infants, children and elderly people shall be assessed as necessary. If findings of adverse effects for each particular cohort are available, such findings should be taken into consideration in the abovementioned assessment. For a substance that falls under another provision in this guideline, assessment shall be conducted based on the said provision.

F. If an *in vitro* study that is commonly implemented in another field such as drug development is recommended also for safety assessment of additives, application of such a study shall be desirably considered as necessary. Such a study, for example, is a case where results of an *in vitro* study with cultured human cells or with human metabolic enzymes is extrapolated to human when adverse effects are concerned from animal studies.

G. If a finding on the interaction of an assessed additive with a medicinal product is available, such a finding shall be examined as necessary.

H. The necessity for assessment should be examined also for decomposition products, mixed exogenous, and metabolites that characteristically generated in humans. The stability of the additives and the stability in foods should be also examined. If it is found to be unstable, the main types of decomposition products and the levels at which they are generated should also be examined.

I. No method has been established internationally to evaluate the harmful effects of simultaneous intake of different food additives at present, although studies to establish such methods are in

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[3] A genotoxic carcinogen is a substance that induces gene mutation or chromosomal aberration by affecting DNA directly either by itself or through its metabolites, and whose genotoxic reaction is considered to be a part of the carcinogenic mechanism. Desirably, its genotoxicity shall be confirmed *in vivo* (in the carcinogenic target organ, if possible).

progress. However, securing safety of intake of multiple food additives is considered to be feasible through complete assessment of each food additive based on the reports contained in the "Collection of Information and Survey on Effects of Intake of Multiple Food Additives"[4]. If findings are available with respect to the risk of taking multiple food additives including the assessed additive, the assessment should be carried out based on the latest scientific findings.

J. If a test is scarcely used by JECFA and other organizations at present, and is generally unused in assessments by the Commission, such a test requires careful handling.

K. Food additives manufactured based on new technologies such as nanomaterials may have different toxicological characteristics from additives manufactured based on conventional technologies. When assessment of these substances becomes necessary, each case shall be examined appropriately.

L. In repeated dose toxicity studies, the toxicity shall be assessed in consideration of the followings.

   a. In the case where the repeated dose increases frequency and degree of spontaneous lesions which are observed also in control groups, the observed changes are basically evaluated as the effects of the repeated dose if the changes show the toxicological implication such as a dose-response relationship regardless of whether the changes are within the range of background data or not.

   b. Regarding how to extrapolate the toxicity findings into human, it is necessary to evaluate with care examining the endpoints after classify them into functional changes, non-neoplastic morphological changes, neoplastic changes, changes in reproductive activity, and others.

M. In carcinogenicity studies, the toxicity shall be assessed in consideration of the followings.

   a. For additives with positive carcinogenicity, fundamentally an ADI cannot be specified if the additive is determined to be a genotoxic carcinogen because of its genotoxicity. However, if an additive is determined to be apparently a nongenotoxic carcinogen because of negative genotoxicity, an ADI can be specified. In addition, if suspiciously genotoxic impurities or side-products are inevitably produced or remain in the assessed additives, the ADI may be specified for such additives in some cases after making necessary examinations.

   b. If the incidence rate of lesion is relatively low, carcinogenicity may be evaluated by implementing significance test on the total incidence of benign neoplastic lesions and malignant neoplastic lesions.

   c. Even if tumor incidence increases at non-predominant site or if incidence of rare tumor increased, it is desirable to assess carcinogenicity including carcinogenic mechanism.

   d. Carcinogenicity shall be assessed in consideration of factors such as suppressed body weight or decreased survival rate that modify tumor incidence.

   e. It should be considered in the assessment whether mechanism of observed tumor induction is species specific or not.

N. When a name of food additive is removed from the list of Existing Food Additives specified in the Supplementary Provisions (Article 2-2, paragraph 1) to the Law Concerning Amendments to the Food Sanitation Law and Nutrition Improvement Law, (No. 101, 1995), the risk assessment shall be conducted in accordance with this guideline.

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[4] Compiled in the 2006 General Survey to Ensure Food Safety conducted by the FSCJ.

Article 5. Approach for the Documents required for the Risk Assessment

A. The scope and notes on the documents required for the risk assessment are basically shown in Chapter II and Appendix, and additional information is given below.

a. If the target substance concerns with one of following items (1) to (5) under normal usage condition, a part of regular evaluation of toxicity is sometimes unnecessary. Therefore, it shall be determined whether some of tests can be omitted or not after considering about each of the items (1) to (5).

(1) A part of the tests can be omitted if the target substance is easily degraded in foods or in digestive tract into a same substance as a food component.

(2) A part of the tests can be omitted if the target substance is easily degraded in foods or in digestive tract into a same substance as a food component.

(3) A part of the tests can be omitted if a food component originated from the target substance is absorbed as effectively as that of relevant food component, and does not inhibit the absorption of other ingredients.

(4) A part of the tests can be omitted if a large amount of the undegraded or partially degraded component of the target substance is not excreted in stool and does not accumulate in the body after ingestion.

(5) A part of the tests can be omitted if an excess ingestion of food component derived from the target substance does not occur by a consumption of foods produced with the target substance.

b. If the target substance is an internationally commonly used food additive, the risk assessment shall be implemented taking into consideration the long eating experience in humans (See Chapter I, Article 4, paragraph B.

c. When there is a scientifically rational reason for doing so regarding the target substance, a part of evaluation tests can be omitted clarifying the relevant reason. Such reason includes the facts that the target substance and a previously designated additive have the same chemical structure except the basic moiety, or the target substance is an isomer of a previously designated additive.

B. Revision of the standards for use or compositional standards should be conducted in accordance with the following points of concern.

a. Revision of the standards for use shall be handled as follows.

(a) If the risk assessment of the target substance has been completed by the Commission, the Commission requests the risk management organizations for submission of materials based on which the daily intake was estimated. The materials are such as the data about addition of the foods for which the additive is to be used or change of the usage dose. If there is a new toxicological finding, the Commission also requests for submission of the data on that finding.

(b) When the risk assessment of the target substance by substance the Commission has not been implemented, submission of materials required for the risk assessment for the designation of

the additive is requested by the Commission to the risk management organizations in principle.

b. For the revision of compositional standards, the validity and safety of the revised compositional standards should be demonstrated.

C. Points to be concerned in the risk assessment are as follows.

a. The applicant is responsible for submitting the materials required for the risk assessment and must ensure the reliability of the content of the materials. As the materials required for the risk assessment, the applicant must submit in principle: (1) results from tests conducted at a facility under an appropriate management (i.e., a GLP facility) and by a method with ensured reliability, (2) assessment reports complied by international organizations, and (3) reports with scientific reliability. If materials concern safety issues of the food additive, such materials must be submitted for examination regardless of their reliability.

b. Autopsy and histopathological tests should be conducted by specialists with ample experience.

c. The applicant must hold raw data and samples from animal tests conducted for the application until the assessment is completed so that the data or samples can be submitted whenever necessary.

D. In principle, the risk assessments should be conducted based on the materials submitted by the applicant. If the submitted materials are considered insufficient, the applicant shall be asked to submit additional materials.

Article 6. The Risk Assessment (The assessment of food-related human health hazard)

1. Toxicological Assessment

(1) Interpretation of the data on Toxicokinetics and Toxicity

Aim of toxicokinetics study is estimation of the fate of additives after ingestion in the human body in terms of absorption, distribution, metabolism, and excretion (ADME). Therefore not only summarizing the results of animal studies, estimation of ADME in the human body and the possible adverse effects should be discussed in these studies.

When interpret the data, it should be discussed from the scientific point of view that the observed toxicity and residual level in the body is a characteristics of the additive itself and not an incidental effect of other factors such as the nutritional condition of the subject. When evaluate the endpoints, statistical significance or dose-response relationship in the findings regarding each of general conditions, body weight, food intake, hematological tests, blood biochemical tests, urine tests, pathological tests and other tests must be interpreted rationally and scientifically.

In these cases, the toxicological mechanism should be determined as clearly as possible.

(2) Determination of NOAEL

In order to determine the NOAEL in a test, an appropriate dose setting should be ensured. In a toxicity test, the maximum dose should be set at the level at which a toxic effect is detected, and the minimum dose should be set at the level at which no toxic effect is detected. Also, different dose levels should be set appropriately so that the dose-response relationship can be observed. In the case

of a feeding study, however, care should be taken to prevent nutritional disturbance. So in general, studies with the feed added with the substance to the level exceeding 5% (W/W) is unnecessary. In the case of a gavage study, if no toxic effect is observed at the maximum does that is technically feasible or at 1,000 mg/kg bw, the toxicity study with a higher dose is not required.

(3) Approach for setting ADI

ADI shall be set in accordance with the following approaches.

a. When more than one NOAEL are indicated as a base for an ADI after comprehensive evaluation of toxicity studies, the lowest NOAEL of those indicated by the studies in each animal species and toxicity study should be used as the base for the ADI. However, when a certain study is obviously more appropriate than others in terms of its design or results and the test periods were different among all, a study with a longer period and more appropriate design should be put more weight in specifying the NOAEL used to determine the ADI. If metabolic data or pharmacokinetic data are applicable, the NOAEL for specifying the ADI may be determined based on the toxicity study in the animal species that is closest to humans. In addition, BMDL (Benchmark Dose Lower Confidence Limit)[5] obtained by Benchmark Dose Method (BMD) can be used.

b. A safety factor of 100 is used in consideration of species differences and individual differences. It should be noted, however, that the safety factor of 100 is not an invariant value but rather should be set individually in each case based on the toxicity and test data.

(a) When the human data are used, species differences need not to be considered. Based on individual differences, a safety factor of 1 to 10 should be used, depending on the number of surveyed cohorts.

(b) When sufficient information is not available and if the target substance shows serious toxicity[6], the additional factor of 1 to 10 should be applied for each factor.

(c) When the ADI is set based on the LOAEL, the additional factor of 1 to 10 should be applied.

c. When a group of substances that have a structure-activity correlation or that have a similar level of toxicities which generate additive physiological/toxicological effects without a structure-activity correlation is used as additives, the ADI should be set for the substances as a group in order to manage the cumulative intake. When establishing a group ADI, the lowest NOAEL of those for all the substances in the group should be used, in principle. The relative quality of the test data and the test period should be taken into consideration when establishing the NOAEL. If a particular NOAEL is significantly higher or lower than the other NOAEL of the substances in the group, that substance should be excluded from the

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[5] Guidance on the Use of the BMD Approach in Risk Assessment by the FSCJ (October 2019, the FSCJ)

[6] The Principles for the Safety Assessment of Food Additives and Contaminants (IPCS, EHC70) lists the following two items as examples:
a) Irreversible reaction seen in a prenatal developmental toxicity test
b) Finding of carcinogenicity

group.

d. In the case of the additive that was determined as a genotoxic carcinogen, it should be concluded that the ADI cannot be specified.

e. The ADI may not be specified if the additive falls under the following cases.

(a) The toxicity of the additive is determined to be extremely low.

(b) The EDI (Estimate Daily Intake) of the additive is determined to be sufficiently low comparing to the NOAEL etc.

(c) The additive does not fit with the concept of ADI because of the standards for use or its characteristics (e.g. the additive is eliminated from the final products).

2. Exposure Assessment

In the Exposure Assessment, the daily intake should be estimated taking care to avoid underestimation. In principle, the estimation is made by multiplying the daily intake of the food for which the additive is used by the amount of the additive used. Regarding additives used for particular foods of which consumption by specific population is suggested by the standards for use, the estimated daily intake in the relevant specific population shall be considered if more appropriate estimation is possible.

The daily intake of relevant food should be properly estimated based on the food group intakes given in the National Health and Nutrition Survey or other materials. Estimations based on data obtained by other reliable methods, such as market basket surveys and production analysis, can also be used. The daily intake should be estimated for the mean body weight based on the latest decision of the Commission.

3. Risk Characterization

Risk from an additive shall be characterized based on the characteristics of the additive, standards for use, toxicological assessment, exposure assessment and so on. The results of the risk assessment shall be described by the following phrases.

(a) “The Acceptable Daily Intake (ADI) is specified to be XX.”
The phrase is used when specification of the ADI is considered to be appropriate as the results of the risk characterization based on the characteristics of the additive, standards for use, toxicological assessment, exposure assessment and so on.

(b) “It is unnecessary to specify the ADI, since the assessed item is considered to have no safety concern as long as it is used appropriately as an additive.” The phrase is for the case where the ADI is not specified despite that it can be specified, in accordance with the conclusion that the toxicity of the assessed additive is considerably low or the EDI is sufficiently low compared to the NOAEL.

(c) “The assessed item is of no concern for food safety as long as used appropriately as a food additive.” The phrase is for the case where the Margin of Exposure (MOE) is assessed for the additive that does not fit with the concept of ADI.

(d) “The ADI cannot be specified”

The phrase is for the case where the ADI cannot be specified for the additive and other substance that are evaluated as a genotoxic carcinogen.

Article 7. Revision of the Risk Assessment

The risk assessment of additives should be conducted or revised appropriately in the following cases. Such as: When new data to suggest serious safety concern are obtained, and when different conclusions of the previous assessment is found to require re-evaluation based on new scientific findings and/or global trends in the standards for assessment.

Article 8. Revision of this Guideline

This guidelines should be reviewed when it is found to be necessary because of global trends of the standards for assessment and scientific findings inside and outside Japan.

Article 9. The risk Assessment of Flavoring Substances

Regarding additives used for the purpose of flavoring (flavoring substances), the risk assessment shall be conducted in accordance with “Guidelines for the Assessment of Flavoring Substances in Foods on Health” (Decision of the Commission on May 17, 2016).

Article 10. The Risk Assessment of Enzymes

Regarding enzymes used as additives, the risk assessment shall be conducted in accordance with “Guidelines for the Risk Assessment of Additives (Enzymes) in Foods” (Decision of the Commission on July 18, 2017).

Article 11. The Risk Assessment of Additives for Fortification

Regarding food additives used for the purpose of fortification such as vitamins and minerals, the risk assessment shall be conducted in accordance with “Guidelines for the Risk Assessment of Food Additives for Fortification” (Decision of the Commission on July 18, 2017).

Chapter 2. Detailed Exposition

The materials required for the risk assessment are listed in Appendix, and are as follows. Note that the stance on the risk assessment of the processing aids and of the additive used in substitutes for breast milk mainly for infants up to 4 months old, Chapter 3 and Chapter 4 are referred respectively.

Article 1. Outline of the additives to be assessed

1. Name and usage
2. Origin or process of discovery
3. Usage in other countries
4. Assessments by international organizations and other organizations
5. Physiochemical properties

Chemical name, (generic names in Japanese and English, CAS number), molecular structure, molecular weight, structural formula, manufacturing method, chemical nature, stability (including stability in food), draft of compositional standards, etc.

6. Draft Usage Standards

(a) When the usage standards is considered necessary for regulation of the foods for which the additive is used and the amount of additive to be used, based on a comprehensive examination of the safety and efficacy of the food additive, the reasons for establishing such usage standards must be clearly explained. When establishing the standards, the estimated daily intake obtained by the described estimation (See Article 3) and the ADI obtained from toxicity tests should be taken into consideration.

(b) When the usage standards is considered unnecessary to be established, the reasons of the decision should be clearly indicated.

7. Others (Information useful for the risk assessment)

Article 2. Findings regarding the Safety

In each test on the safety, following maters need to be considered. In principle, the tests should be implemented complying with internationally approved test guidelines such as the Guideline published by the Organisation for Economic Co-operation and Development (OECD). (See Example of the test method).

1. Toxicokinetics study
   a. The food additive or the substance labeled with a radioisotope should be used as the test substance. When a radioisotope-labeled substance is used, the species of the radioisotope and the labeling site should be clearly indicated.
   b. It is desirable to conduct tests with two species consisting of one rodent [generally rats] and one non-rodent [generally dogs]. In this regard, animal should be chosen appropriately in light of the toxicity study.
   c. In principle, the test substance should be administered orally. Absorption, distribution, metabolism, and excretion (ADME) should be estimated using single-dose and repeated-dose. Additional tests with intravenous administration and other tests may be carried out when necessary in order to calculate accurate ratio of absorption or for other purposes.
   d. When setting the dose, the maximum dose used in the repeated dose toxicity study or NOAEL shall be referred. The low level dose shall be set, if possible, considering the dose of which intake through foods is presumable.
   e. The following data of tests on the assessed substance are required for examination of each process of absorption, distribution, metabolism, and excretion (ADME); Blood concentration, urinary and fecal excretion, change over time in the concentration in each organ; *in vivo* metabolites, and factors that influence on each process.
   f. Potential target organs for toxicity tests should be presumed based on the data of the abovementioned studies on ADME (e.g., highest plasma concentration, change over time in concentration in each organ, and elimination half-life). In such cases, the feasibility of extrapolating

the results into humans must be concerned considering the species difference of animals and the species specificity.

g. When the test substance is a racemic body, it is desirable to examine toxicokinetics of each optical isomer if it is necessary in relation to the toxicity.

h. In principle, the existence of human-specific metabolites must be examined and toxicity of such metabolites must be studied as necessary.

[Example of the test method]

・OECD Test Guideline. Test No. 417: Toxicokinetics

2. Toxicity test

(1) Genotoxicity test

Genotoxicity shall be assessed based on the results of studies on genotoxicity in general, but not restrictedly on "Mutagenicity" in the narrow sense. Among standard battery for genotoxicity testing (the bacterial reverse mutation test, the chromosomal aberration tests in cultured mammalian cells, and the micronucleus tests in rodent), the chromosomal aberration tests in cultured mammalian cells may be replaced with the mouse lymphoma TK test (MLA) or with the *in vitro* micronucleus test. In addition, the following tests for examples are applicable to the additional experiments for supplementing to the results of the tests in the standard battery.

[Examples of genotoxicity test which uses gene mutation as an index]

・Gene mutation tests in cultured mammalian cells

・Gene mutation tests in rodents

・*In vivo* mutation tests in transgenic animals

[Examples of genotoxicity test which uses chromosomal aberration as an index]

・Chromosomal aberration tests in bone marrow cells of rodents

・Chromosomal aberration tests in germ cells of rodents

・*In vivo* dominant lethal test in rodents

・Sister-chromatid exchange (SCE) tests in mammalian cells

[Examples of genotoxicity test which uses DNA damage as an index]

・Unscheduled DNA synthesis (UDS) test in mammalian cells

・Single cell gel electrophoresis test (Comet assay)

Provided that one of tests composing the standard battery cannot be implemented because of the technical constraint, relevant test shall be replaced with another test of which validation test is completed and reliability has been approved, after the reason is explained based on the scientific evidences.

The test results are interpreted and concluded as follows.

a. If "the bacterial reverse mutation test" shows positive results, the results shall be comprehensively

concluded in fully consideration of the results of *in vivo* tests (Comet assay, *In vivo* mutation tests in transgenic animals and others) that use gene mutation or DNA damage as an index.

b. If "the chromosomal aberration tests in cultured mammalian cells" shows positive results and relevant effect is confirmed by "the micronucleus tests in rodents", the examined substance is determined to be genotoxic.

c. Even if "the chromosomal aberration tests in cultured mammalian cells" shows positive results, the genotoxicity of relevant substance can be judged to be negative if the negative results are obtained in "the micronucleus tests in rodents" implemented appropriately up to the high dose (it is desirable that exposure of the target organ is improved).

(2) Repeated dose toxicity study

a. The tests shall be implemented in one rodent species (generally rats are used) and one non-rodent species (generally dogs are used), or in two rodent species (generally rats, mice or guinea pigs are used). Basically, the same number of male and female animals shall be used.

b. In principle, subacute toxicity test (subchronic toxicity test) and chronic toxicity test shall be implemented.

c. Basically, duration of administration for subacute toxicity test (subchronic toxicity test) and chronic toxicity study shall be 90 days and 12 months and more, respectively.
However, if results of the tests for 90 days are not available, it should be determined whether the other results are reliable as necessary documents for the assessment or not, based on the results of the studies for 28 days and the other studies.

d. In principle, the test substance should be administered 7 days a week by dietary administration or through drinking water, but it can be also administered by gavage if oral administration is difficult.

e. At least three groups receiving the administration with different doses should be established in addition to the control group. The reasons for setting each dose should be clearly indicated. Common ratios should be appropriate for specifying NOAEL

f. Care should be taken to prevent nutritional disturbance among test animals when feeding them the substance. Usually, the amount of the substance as a proportion of the feed does not have to exceed 5% (W/W). When the substance is given by gavage administration, the general maximum dose needed is the technically possible maximum dose or 1,000 mg/kg bw. If no effect is observed at that dose, the administration of a higher dose is not required.

g. When neurotoxicity or immunotoxicity is suspected, necessity of additional tests complying with the OECD test guideline or WHO/IPCS guidance should be examined as necessary.

h. Regardless of "the description a", one rodent species for a chronic toxicity test may be replaced with one rodent species for a combined chronic toxicity/carcinogenicity study.

i. Addition of an *in-utero* exposure phase should be considered as necessary.

[Example of the test method]

・OECD Test Guideline. Test No. 408: 90-day repeated dose toxicity study in rodents.
・OECD Test Guideline. Test No. 409: 90-day repeated dose toxicity study in non-rodents.
・OECD Test Guideline. Test No.452: Chronic toxicity test.
・OECD Test Guideline. Test No.453: Combined chronic toxicity/carcinogenicity test.

(3) Carcinogenicity tests

a. The tests shall be implemented in two rodent species (generally rats, mice or guinea pigs are used). Basically, the same number of male and female animals shall be used.
b. In principle, the test substance should be administered 7 days a week by dietary administration or through drinking water with the duration of 24 months to 30 months for rats and of 18 months to 24 months for mice. The test substance can be also administered by gavage if oral administration is difficult.
c. At least three groups receiving the administration with different doses should be established in addition to the control group. The reasons for setting each dose should be clearly indicated. Common ratios should be appropriate for specifying NOAEL.
d. Care should be taken to prevent nutritional disturbance among test animals when feeding them the substance. Usually, the amount of the substance as a proportion of the feed does not have to exceed 5% (W/W). When the substance is given by gavage administration, the general maximum dose needed is the technically possible maximum dose or 1,000 mg/kg bw. If no effect is observed at that dose, the administration of a higher dose is not required.
e. Regardless of “the description a”, one rodent species for a carcinogenicity test may be replaced with one rodent species for a combined chronic toxicity/carcinogenicity study.
f. Addition of an *in-utero* exposure phase should be considered as necessary.

[Example of the test method]
・OECD Test Guideline. Test No. 451: Carcinogenicity test

(4) Reproductive toxicity tests

a. The tests shall be implemented in one rodent species (generally rats are used). Basically, the same number of male and female animals shall be used.
b. In principle, the test substance should be administered 7 days a week by dietary administration or through drinking water. The test substance can be also administered by gavage if oral administration is difficult.
c. At least three groups receiving the administration with different doses should be established in addition to the control group. The reasons for setting each dose should be clearly indicated. Common ratios should be appropriate for specifying NOAEL.
d. Care should be taken to prevent nutritional disturbance among test animals when feeding them the substance. Usually, the concentration of the substance in the feed does not have to exceed 5%

(W/W). When the substance is given by gavage administration, the general maximum dose needed is the technically possible maximum dose or 1,000 mg/kg bw. If no effect is observed at that dose, the administration of a higher dose is not required.

e. When neurotoxicity or immunotoxicity is suspected from the tests in offspring, necessity of additional tests complying with the OECD test guideline or WHO/IPCS guidance should be examined as necessary.

[Example of the test method]

・OECD Test Guideline. Test No. 416: Two generation reproductive toxicity tests

(5) Developmental toxicity tests

a. The tests shall be implemented in one rodent species (generally rats are used) and one non-rodent species (generally rabbits are used), total in two species.

b. The test substance should be administered into pregnant animals every day, at least for the duration including the time from implantation to organogenesis period of main organs.

c. The substance is principally given by gavage administration. The dose should be calculated from the latest body weight so that an immediate reaction to the sudden change in the body weight during pregnancy becomes possible. If no effect is observed at the technically possible maximum dose or 1,000 mg/kg bw, the administration of a higher dose is not required. Care should be taken to prevent nutritional disturbance among test animals when feeding them the substance. Usually, the concentration of the substance in the feed does not have to exceed 5% (W/W).

d. At least three groups receiving the administration with different doses should be established in addition to the control group. The reasons for setting each dose should be clearly indicated. Common ratios should be appropriate for specifying NOAEL.

[Example of the test method]

・OECD Test Guideline. Test No. 414: Developmental toxicity tests

(6) Allergenicity tests

Few methods for predicting the allergenicity of orally ingested chemical substances have been established, particularly no method for predicting the immediate type of allergenicity is available. Nonetheless, if allergenicity is suspected in consideration of the findings on the additives and the usage, the potential allergenicity shall be examined with adequate sensitization and induction methods. For the time being, skin sensitization test in guinea pigs or Local Lymph Node Assay (LLNA) in mice may be used for allergenicity studies using delayed allergy as an indicator. In addition, if allergenicity of the analogous substance or reaction originated from the allergenicity is already known, it is desirable to study allergenicity of target substance using similar methods to that used for said analogous in addition.

The OECD test guideline has been established for Adverse Outcome Pathway (AOP)-based chemical

safety assessment which is alternative to conventional study methods using animals. Although it is difficult to predict allergenicity by a single alternative method upon assessment, those alternative methods shall be useful if assessment is conducted with defined approach[7] by Integrated Approaches to Testing and Assessment (IATA) based on AOP.

[Example of the test method]

- OECD Test Guideline. Test No. 406: The guinea pig maximization test (GPMT)
- OECD Test Guideline. Test No. 429: The local lymph node assay (LLNA) in mice
- OECD Test Guideline. Test No. 442C: The direct peptide reactivity assay (DPRA)
- OECD Test Guideline. Test No. 442D: The ARE-Nrf2 luciferase test method
- OECD Test Guideline. Test No. 442E: The human cell line activation test (h-CLAT)

As was designated in Chapter 2, Article 2-3-(3) of Guidelines for the Risk Assessment of Additives (Enzymes) in Foods, potential concern of allergenicity of enzymes shall be comprehensively evaluated. Accordingly, allergenicity of additives which contain proteins (excluding enzymes) as the major ingredient should be assessed according to said guidelines.

(7) Other tests

When neurotoxicity of the target substance is suspected following the subchronic toxicity test and other test, additional tests should be conducted as necessary in compliance with the OECD test guideline and other materials.

When immunotoxicity is suspected following a subchronic toxicity test and other tests, proper immunofunctional tests should be added as necessary in accordance with the WHO/IPCS guidance and other materials. Immunofunctional tests should be also carried out as necessary when immunotoxicity in humans is suspected based on existing findings.

If data on the general pharmacological properties of target substance are available, relevant data should be presented as necessary.

3. Findings in human

When available, appropriate clinical tests, epidemiological data and other information regarding humans must be actively used. When allergenicity is suspected, findings in human should be especially valued because it is often infeasible to extrapolate the results of animal tests to human.

Article 3. Estimation and consideration of the Daily Intake

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[7] OECD (2016), OECD Guidance document on the reporting of defined approaches and individual information sources to be used within integrated approaches to testing and assessment (IATA) for skin sensitization. Paris, France: Organisation for Economic Cooperation and Development.

a. The items in this article follow Chapter 1, Article 6-2.
b. The estimated daily intake should be compared with the ADI obtained from toxicological tests, and consideration of the results of such comparison should be described. In the consideration, safety of concomitant intake with same kind of additives should be evaluated by comparing the sum of estimated daily intake to the group ADI, or by any other method as necessary.
c. Where considered necessary based on food consumption habits in Japan, the overconsumption of nutritional elements and effects on electrolyte balance should also be examined along with other relevant effects.

Chapter 3. Approach for the Risk Assessment of Processing Aids

Regarding the additives used as processing aids[8] such as food disinfectants and extractants, the Commission amended "Guideline 2010" in July 2017 in association with establishment of "Stance for the Risk Assessment of Processing Aids (Food Disinfectants and Extractants)".
Afterward, the risk assessment of the processing aids has been implemented in accordance with the amended "Guideline 2010".

After the results of "Study on risk assessment for food additives focusing on transferring to the body"[9] which was conducted under the FSCJ Research Program for Risk Assessment Study on Food Safety in 2019, the Commission on the Additives decides that the risk assessments of toxicity, exposure assessments and risk characterization of processing aids shall be implemented as follows from now on. Note that the provisions in Chapter 1 and 2 shall be applied to the items which are not prescribed in this chapter.

Article 1. Scope of application

The provisions in this article are principally applied to the risk assessments of processing aids, including impurities, side products and degradants, of which daily intake can be estimated.

Article 2. Risk assessment procedure

The risk assessments described in this chapter are implemented by stepwise approach where results of various toxicity tests necessary for assessments are utilized depending on the estimated daily intake of the target substance. The actual steps are as follows.

1. Estimated intake of the target substance is classified based on the daily intake estimated from the results of residue test (Refer to Article 3 for details).

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[8] "Processing aids" in this Supplement designates the substance that meets one of the following two conditions, among food additives used in food processing.
(1) An additive that is removed from the food before final packaging.
(2) An additive that is converted to a naturally contained component in food, and the amount of the component does not significantly increase the amount of the natural component.
(3) An additive that is found only in trace amounts in the final food product and has no effect on the food.

[9] T. Umemura *et al*., Study on risk assessment for food additives focusing on transferring to the body (No. 1901), the FSCJ Research Program for Risk Assessment Study on Food Safety 2019 (Researches on risk assessment methodology).

2. Toxicity of the target substance shall be evaluated based on the results of various toxicity tests that are required by each class of the estimated daily intake (Refer to Article 4 and 6 for details).
3. Risk from intake of the target substance shall be evaluated based on the results of toxicological assessment and exposure assessment of the target substance (Refer to Article 5 for details).

Article 3. Classification criteria for the Estimated Daily Intake

1. Outline

Daily intake shall be estimated in principle multiplying the daily intake of target substance by the maximum residue in the final food added with the substance from the results of residue testing, replacing the provision of Chapter 1, Article 6-2 of this guideline. Daily intake of the degradants expected to be produced during the use of the target substance shall be estimated similarly.

When the residue determined by the residue testing is below the lower detection limit and below the lower limit of quantitation, principally the lower detection limit and the lower limit of quantitation shall be used as the maximum residue, respectively.

In case where appropriate residue testing is unfeasible by scientific reasons, daily intake of relevant substance may be estimated by multiplying the maximum usage or theoretical maximum residue by daily intake of the target food.

The daily intake of relevant food should be properly estimated based on the food group intakes given in the National Health and Nutrition Survey or other materials. The daily intake should be estimated for the mean body weight based on the latest decision of the Commission.

Classification of estimated daily intake of the substance to be assessed shall be done by applying the estimated daily intake to the classification of estimated daily intake range described in Table 1, in principle. In case if a daily intake becomes overestimated because of the estimation method, however, estimation may be done with comprehensive consideration.

Table 1. Classification of estimated intake

Class	Estimated Intake Range
Class a	90 μg/person per day or less
Class b	More than 90 μg/person per day 2,000 μg/person per day or less
Class c	More than 2,000 μg/person per day

[Reference] Description of Class of the Estimated Intake

[Class a]

Estimated intake of this class equivalents to or less than threshold of toxicological concern (TTC) of Cramer Structural classes III by Munro (1996)[10]. When the assessed substance is considered to be of no

[10] Munro IC, Ford RA, Kennepohl E and Sprenger JG: Correlation of a structural class with No Observed-Effect-Levels:a proposal for establishing a threshold of concern. Food Chem. Toxicol., 1996; 34: 829-867.

genotoxic concern relevant to human health, non-carcinogenic toxicity and non-genotoxic carcinogenicity are generally assumed to be of low-concern.

[Class b] and [Class c]

Low-concern for non-carcinogenic toxicity and non-genotoxic carcinogenicity of the substance in this class are generally unpredictable. From the viewpoint of the exposure levels, [Class b] is assumed to have concern for these toxicity lower than that of [Class b].

2. Basic requirement for residue testing and analysis

Basically, assessment shall be conducted using the results of residue testing and of analysis that fulfill both of the following requirements.

(1) Results from tests and analysis conducted at an experimental facility whose operational management is recognized as appropriate (i.e., a GLP facility).

(2) Results obtained by a method whose reliability or good quality is ensured.

Article 4. Toxicological assessment

1. Outline

In principle, toxicity of the substance to be assessed shall be evaluated based on the results from various toxicity tests that are required for each class of estimated intake described in Table 2. When the target substance or toxicity to be evaluated corresponds to the item 1 and 2 of Article 6, results from tests described in said item 1 and 2 are also demanded.

In addition, if necessary for evaluation, results from additional toxicity tests may be demanded.

Details of each test item shall follow the provision in Chapter 2, Article 2. However in case of disinfectants, assessment of decomposition products that may be produced during use may be necessary. (Refer to Chapter 1, Article 4-H of this Guideline)

Estimated Intake Range		Testing
Class a	90 μg/person per day or less	Genotoxicity test
Class b	More than 90 μg/person per day 2,000 μg/person per day or less	Genotoxicity test Subacute (Subchronic[11]) toxicity test
Class c	More than 2,000 μg/person per day	Toxicokinetics test Genotoxicity test Repeated dose toxicity test Carcinogenicity test Reproductive toxicity test Developmental toxicity test Allergenicity test

Table 2. Testing required by each class of Estimated Intake Range

Note: In addition to the testing items in Table 2, available information of the target substance regardless of class of Estimated Intake Range (particularly results of toxicity tests other than the tests required for each class) is demanded to be collected and provided.

Article 5. Risk Characterization

1. Outline

The Risk Characterization shall be conducted as follows replacing the provision described in Chapter 1, Article 6-3.

If the estimated intake of target substance is classified to [class a], risk from relevant substance shall be characterized based on the results from genotoxicity test.

If the estimated intake of target substance is classified to [class b] or [class c], compare the estimated intake of the target substance with NOAEL of relevant substance and thereby evaluate the risk for health in the target population from intake of relevant substance.

As for additives that have been used in the world since before, usage experience of the substance and others shall be also considered.

[11] Basically, the testing shall be “90-day repeated dose test”.

2. Principle approach for risk characterization

(1) When the estimated intake class meets [class a]

i. Management of the target substance judged to be genotoxic.

If a food additive is evaluated to be genotoxic carcinogen, the relevant substance should not be approved in principle at this point. If a exogenous (including naturally occurring matter; the same hereinafter), a byproduct and/or a degradation product that is unavoidably contained during the manufacturing process of the food additive is a genotoxic carcinogen, a comprehensive assessment shall be conducted based on the concept of virtually safe dose (VSD), while the content should be reduced to the level as low as technologically possible (Refer to Chapter 1, Article 4-D).

ii. Management of the target substance not judged to be genotoxic.

If the estimated intake class of the assessed substance meets [class a], non-carcinogenic toxicity and non-genotoxic carcinogenicity are generally assumed to be of low-concern. Accordingly, human health risk from the assessed substance is expected to be sufficiently low.

(2) When the estimated intake class meets [class b] or [class c]

i. Management of the target substance judged to be genotoxic.

The target substance shall be evaluated in a way similar to that described in (1)-i.

ii. Management of the target substance not judged to be genotoxic.

Principally, MOE shall be evaluated as follows.

a. When multiple NOAELs are obtained as the result from comprehensive evaluation of toxicity tests, the risk shall be characterized using the lowest NOAEL comparing the values in each animal species and toxicity test.

b. MOE shall be evaluated based on the comparison of the estimated daily intake with NOAEL and others. Note that daily intake occasionally overestimated if the target substance is removed or degraded through the food production. In such a case, risk should be characterized after comprehensive evaluation.

Article 6. Substances and toxic effects requiring special consideration

1. Substances requiring special consideration

With regard relevant substances, such as substances with high reactivity like disinfectants, metals, inorganic substances and proteins, testing results required for [class b] are demanded even if the estimated intake class is [class a].

2. Toxic effects requiring special consideration

(1) Neurotoxicity

No toxicity test specialized for neurotoxicity is essential regardless of estimated intake class of the target substance. However, if neurotoxicity is suspected from available information, testing results that provide findings regarding such toxicity may be required regardless of estimated intake class of the target substance.

(2) Immunotoxicity

No toxicity test specialized for immunotoxicity is essential regardless of estimated intake class of the target substance. However, if immunotoxicity is suspected from available information, testing results that provide findings regarding such toxicity may be required regardless of estimated intake class of the target substance.

(3) Endocrine disrupting effects

No testing specialized for endocrine disrupting effects is essential regardless of estimated intake class of the target substance. However, if endocrine disrupting effects are suspected from available information, testing[12] results that provide findings regarding such effects may be required regardless of estimated intake class of the target substance.

Chapter 4. Approach for the risk assessment of additives in foods used as breast milk substitutes for infants under 4 months old

The FSCJ has been conducting the risk assessment of additives in foods used as breastmilk substitutes[13] for infants under 4 months old[14], based on "Guideline 2010". Breast milk or infant formula is the sole nutrient for infants under 4 months old, and ADME (absorption, distribution, metabolism and excretion) mechanism and *susceptibility to* exogenous chemical substances in these infants are different from adults. Because of the characteristics, methods for the risk assessment of food additives particularly targeted at infants have been demanded.

Recently, the FSCJ decided that toxicological assessments, exposure assessment and risk characterization of additives used in breast milk substitutes targeted at infants up to 4 months should be implemented as follows, based on the results from "Study on methods for safety assessments of food additives - Proposal for methods for safety assessments in infant formula and guidelines of toxicological studies based on international trends" (Research project No. 1805)[15]. Note that matters not provided in this chapter shall be pursuant to provisions in Chapter 1 and Chapter 2.

Article 1. Scope of application

This chapter shall be applied to the risk assessment of additives in foods used as breastmilk substitutes[16]

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[12] Necessary measure shall be taken in consideration of estimated intake and predicted toxicity of the target substance, also considering OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters.

[13] In the Ministerial Ordinance on Milk and Milk Products Concerning Compositional Standards, Partial amendment of Specification and Standards for Foods, Food Additives, etc. (Notice of Deputy Director-General for Environmental Health and Food Safety, Minister's secretariat, No. 0808-1, 8, Aug. 2018), it has been written that "Breastmilk substitute is defined as powdered formula, prepared liquid milk and other powdered milk for childcare".

[14] Matters to be taken into consideration upon the assessments of additives for infants up to 12-week old has been described by JECFA, while the guidance for the risk assessment mainly targeting to additives used for infant formula for use in infants up to 16-weeks old has been provided by EFSA.

[15] Takashi Umemura *et al*., "Study on methods for safety assessments of food additives - Proposal for methods for safety assessments in infant formula and guidelines of toxicological studies based on international trends". (Research project. No.1805)

[16] In the Ministerial Ordinance on Milk and Milk Products Concerning Compositional Standards, Partial amendment of Specification and Standards for Foods, Food Additives, etc. (Notice of Deputy Director-General for

for infants under 4 months old[17].

Article 2. Toxicological assessment

Toxicological assessment of the target substances shall be conducted by comprehensively examining biological effects of relevant additives in accordance with provision in Chapter 2, Article 2, and shall be discussed basically along with the following items in addition to the documents designated in Chapter 1, Article 5. Note that the documents can be substituted for other documents clarifying a rational reason if available.

1. Toxicokinetics

   Since physiological characteristics of infants is different from that of adults, toxicokinetics or mechanism of toxicity caused in infants by intake of the targeted substances should be studied considering the physiological difference between adults and infants[18]. When necessary, toxicokinetics of the targeted substances in infants shall be studied additionally using data from juvenile animal studies and/or *in vitro* studies.

2. Toxicity study

   Toxicity shall be studied using toxicity studies on the exposure in an infant using juvenile animals. Animal species for use should be selected considering extrapolation of data to humans[19], and describe the rationale for choosing it.

3. Findings in human

   If there is an appropriate test (such as clinical studies or post-marketing surveillance) targeting infants regarding targeted substances or relevant substances, such a test should be applied.

Environmental Health and Food Safety, Minister's secretariat, No. 0808-1, 8, Aug. 2018), it has been written that "Breastmilk substitute is defined as powdered formula, prepared liquid milk and other powdered milk for childcare."

[17] Matters to be taken into consideration upon the assessments of additives for infants up to 12-week old has been described by JECFA, while the guidance for the risk assessment mainly targeting to additives used for infant formula for use in infants up to 16-week old has been provided by EFSA.

[18] Study on methods for safety assessment in infants has described as follows. "Newborns and infants are known to be particularly susceptible to adverse effects of forcompounds. It is specifically because of; immature enzymatic detoxication mechanism, functionary incomplete excretory organs, different intestinal bacterial flora, different body water content, incomplete formation of physiological barrier such as intestinal barrier and blood brain barrier, low level of serum proteins that bind to harmful substances, in comparison with adults.

[19] Regarding direct oral administration tests in newborn animals, JECFA has recommended to use pigs under one month old as a model of infants of 0 - 12 weeks old, since direct oral administration tests in newborns are essential to assess safety of additives for infants, and since breastmilk is the sole nutrient for pig infants under the age of one month after birth in animal studies. While, a repeated dose study with direct oral administration into newborn animal (such as newborn pig model) has been described to be necessary when adverse effects were not observed by toxicity studies in adult animals and toxicokinetics study showed that the tested substance was not absorbed at a level to be examined.

Article 3. Exposure Assessment

Intake of the additive derived from foods to be added (targeted food) shall be estimated in principle multiplying the maximum amount which is approved to add to the targeted food by the daily intake[20] of the targeted food, replacing the provision of Chapter 1, Article 6-2 of this guideline. Note that the basis on which the values are specified for use in estimating the intake should be described considering significant changes in body weight[21] during exposure duration, although the duration of exposure to the additive derived from the targeted food is limited.

Article 4. Risk Characterization

Replacing the provision of Chapter 1, Article 6-3, safety risk of an additive for which ADI is considered not necessary to specify principally shall be evaluated by evaluating MOE as follows based on the results from tests on juvenile animals. As for additives for which ADI has been specified, the risk assessment shall be conducted separately.

a. When more than one NOAEL are indicated as a base for an ADI after comprehensive evaluation of toxicity studies (including studies in juvenile animal), the lowest NOAEL of those indicated by the studies in each animal species and toxicity study should be used as the base for the ADI.
b. MOE evaluation should be made by comparing estimated daily intake and NOAEL or others.
c. MOE should be comprehensively evaluated in consideration of toxicokinetics of the targeted substance in infants, mechanism of toxicity, design of animal study which was critical for setting NOAEL (such as; selected animal species, duration of administration, dose, and others), toxicity detected by studies in juvenile animal, overall profile of toxicity, results from studies targeted infants, and others.

Appendix: Documents that are required to the risk assessment of additives for designation request

Item		Designation[22]	Amendment of Standard
Summary of Additive to be assessed			
1	Name and Use	○	○
2	Origin or History of Discovery	○	△
3	Usage in other countries	○	○
4	Evaluation in International Organizationns	○	△
5	Physicochemical charecteristics	○	△

[20] Dietary Reference Intakes for Japanese (MHLW) provides a regression equation for artificially fed infants to estimate total energy consumption in estimated energy requirement (a sum of total energy consumption and energy storage) in infants.

[21] Data from National growth survey on preschool children (MHLW) showed the mean body weight of preschool children. Standard weight to be used for evaluating physique of Japanese preschool children has been indicated by the Joint committee of The Japanese Society for Pediatric Endocrinology/The Japanese Association for Human Auxology for standard value.

[22] Documents that are required to the risk assessment of additives for designation request

6	Draft Usage Standard	○	○
7	Others	△	△
Findings on Safety			
1	Toxicokinetics test	○	△
2	Toxicity test		
	(1) Genotoxicity test	○	△
	(2) Repeated dose toxicity test	○	△
	(3) Carcinogenicity test	○	△
	(4) Reproductive toxicity test	○	△
	(5) Developmental toxicity test	○	△
	(6) Allergenicity test	○	△
	(7) Other tests	△	△
3	Findings in human	○	△
4	Estimation of Daily Intake, and others	○	○

Note 1) ○: Documents must be provided, △: Documents to be provided when necessary, such as when useful findings or new findings are available.

Note 2) Request for an additive of which the risk assessment by the Commission is not completed should be accompanied with Documents required for designation. For requesting amendment of standard of an additive of which the risk assessment by the Commission is completed, documents for amendment of standard should be provided.

Note 3) Regarding an additive falls under Chapter 1, Article 5, A (a)-(c), documents concerning the relevance should be provided.

Note 4) Regarding an additive falls under the scope of application of Chapter 3 or Chapter 4, documents should be provided in accordance with relevant chapter. In a request for Amendment of standards, the necessary documents should be provided after confirming that the contents of amendment falls under the scope of application of relevant chapter.

Reference

Article 1. A glossary of terminology

Terms and their definitions of general terminology used in this guideline are referenced in the latest "Glossary of terminology regarding food safety" edited by the Commission. Definition of term not described in said glossary is as follows.

1. Evaluation with WOE (weight of evidence)
   Evaluation based on the importance of evidentiary information.

Article 2. Related documents

1. Glossary of terminology regarding food safety. http://www.fsc.go.jp/yougoshu.html

2. Research Program for Risk Assessment Study on Food Safety completed in FY 2015. Draft guidelines on safety assessments of nutrients and processing aids. Research Program Report.
3. Research Program for Risk Assessment Study on Food Safety completed in FY 2015. Research survey on methods for risk assessment of food additives in foreign countries.
4. Research Program for Risk Assessment Study on Food Safety completed in FY 2018. Study on methods for safety assessments of food additives - Proposal for methods for safety assessments in infant formula and guidelines of toxicological studies based on international trends. Research Program Report.
5. Research Program for Risk Assessment Study on Food Safety completed in FY 2019. Study on risk assessment for food additives focusing on transferring to the body. Research Program Report.