The Procedure for Preparing Application Documents for Designation of Food Additives and Revision of Use Standards for Food Additives

Standards and Evaluation Division

Department of Food Safety

Pharmaceutical and Food Safety Bureau

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This document is the English translation of "*食品添加物の指定及び使用基準改正の要請資料作成に関する手引き*." The Ministry of Health, Labour and Welfare offers this translation as a service to a broad international audience/readers. While the ministry has attempted to obtain translation that is as faithful as possible to the Japanese version, we recognize that the translated version may not be as precise, clear, or complete as the original version. The official version of this document is the Japanese version.

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A. Application documentation

Anyone may submit an application for designation, or revision of the existing specifications and standards, of a food additive using the Form of Appendix 1 or 2. The application should be accompanied by documentation on an overview of the food additive that is the subject of the application (subject food additive) and the effectiveness and safety of the food additive (hereinafter "Overview Documentation"), and materials quoted in Overview Documentation (hereinafter "References").

The Overview Documentation should be in Japanese. The References do not need to be in Japanese and the References in English are also acceptable. The Overview Documentation should be preferably prepared using the Model of Appendix 3 and the checklist of Appendix 4 with reference to "B. Explanations and notes for the preparing Overview Documentation" in this procedure.

B. Explanations and notes for preparing Overview Documentation

I. Information of the subject food additive

1. Name and uses

1.1. Explanations

(1) Name

Enter the general name (Japanese name, and English name), and the chemical name (conforming to IUPAC (International Union of Pure and Applied Chemistry) Name).

(2) Registry number

Enter the CAS registry number, INS (International Numbering system) number, or the like.

(3) Uses

Denote the use status in Japan and other countries, and intended uses/purposes specified by Codex Alimentarius Commission (Codex).

1.2. How to confirm the relevant information

The uses and INS number specified by Codex and use status in Japan can be confirmed at the following websites.

(1) Codex

The specified uses of food additives are published in Section 3 and Section 4 of the Class Names and the International Numbering System for Food Additives (CAC/GL 36-1989). The GSFA online also provides brief information.

Some listed food additives in GSFA online do not undergo safety evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

(2) Japan

In Japan, there are few food additives whose use is restricted by use category. Some examples of uses are published at the MHLW website.

2. Origin or details of development

Describe an outline leading up to the request for designation, such as when and in what country the target substance was developed, and subsequently in which countries it became used as a food additive.

If the substance naturally occurs in food products, provide information on a history of human consumption as food as reference.

3. Use status in other countries

3.1 Explanations and notes

Provide use standards specified by the Codex, and foreign countries' authorization status and use standards.

Notes

· The minimum entry should provide use standards established by the Codex Commission, and authorization status and use standards in the European Union (EU), the United States, Australia, and New Zealand. (When the authorization status and the use standards are not established, the statement should be provided.)

· When the maximum use concentration is established per food product as the use standards, the maximum use concentration of not only each target product but also of each non-target food product should be provided.

·For the basis of the authorizations and use standards, copies of regulatory documents or the like should be attached.

3.2. How to confirm the relevant information

Use standards specified by Codex, and authorization status and use standards in the EU, the United States, Australia, and New Zealand can be confirmed at the following websites. In some cases, for example, when the definition of the food additive is different between Japan and other countries, websites other than the following should be also consulted for additional information.

(1) Codex

Food additives

Maximum use concentrations and other necessary matters are specified for each food product category in Tables 1 and 2 of the General Standard for Food Additives (CODEX STAN 192-1995), (GSFA). Food

additives with no maximum use concentrations are listed in Table 3. Brief information is also provided at the GSFA online.

Processing aids, vitamins, or minerals

The Codex does not treat processing aids, vitamins, and minerals as food additives; therefore, use standards for these categories are not specified in the GSFA. Instead, they may be established in "the Codex commodity standards."

(2) EU

Food additives

Maximum use concentrations are provided for each food product in Attached Table II of Regulation (EC) No 1333/2008. Attached Table II is periodically updated, and the latest use standards can be confirmed at the Food Additives Database.

Processing aids, vitamins, or minerals

The EU does not treat processing aids, vitamins, or minerals as food additives; therefore, Regulation (EC) No 1333/2008 does not establish use standards for them.

(3) The United States

Food additives (including processing aids)

The Code of Federal Regulations Title 21 (21CFR) sets forth the maximum use concentrations for each food product. In addition, the GRAS (Generally Recognized as Safe) Notice Inventory publishes those permitted for use in food as GRAS substances.

Vitamins or minerals

As a general rule, these are controlled under DSHEA (Dietary Supplement Health Education Act).

(4) Australia and New Zealand

Food additives

Schedules 1 to 5 of Standards 1.3.1 of the Food Standards Code set forth the maximum use concentrations for each food product.

For food additives except colors, Schedule 1 sets forth the maximum use concentrations for each food product. Schedule 2 lists the food additives whose maximum use concentrations are not established. For colors, Schedule 3 lists those whose maximum use concentrations are not established, and Schedule 4 sets forth the maximum use concentrations for each food product.

Processing aids

Standard 1.3.3 of the Food Standards Code sets forth the maximum use concentrations for each intended purpose.

Vitamins or minerals

Standard 1.3.2 of the Food Standards Code sets forth the maximum use concentrations for each food product.

4. Assessments by national and international organizations

4.1. Explanations and notes

An overview of the results of safety evaluations by international organizations, like JECFA, and foreign countries should be provided.

Notes

· Not simply stating the evaluation result like "Considered to have no safety issues," the grounds for setting ADI and an overview of the evaluation should be briefly noted. Details on individual safety studies should be provided under the heading of "III. Findings regarding safety."

· Evaluation documents cited in the safety evaluation must be attached.

4.2. How to confirm the relevant information

Results of safety evaluations by JECFA, the European Food Safety Authority (EFSA), the Scientific Committee on Food (SCF), the Food and Drug Administration (FDA), the Food Standards Australia New Zealand (FSANZ), and the Food Safety Commission of Japan（FSCJ）can be confirmed at the websites given in each section below.

(1) JECFA

JECFA evaluates internationally the safety of food additives. The WHO releases the results for each evaluation year as the WHO Food Additives Series (FAS) and the WHO Technical Report Series (TRS) at the WHO website. When (year) JECFA evaluated the safety of respective food additives can be searched at the INCHEM database of the International Programme on Chemical Safety (IPCS).

(2) EFSA and SCF

Under the EU system, EFSA is responsible for safety evaluations for food additives. The results are released at the EFSA website as Scientific Opinion. Prior to foundation of EFSA, SCF conducted safety evaluations. If EFSA did not conduct any safety evaluation of a substance, confirm whether SCF conducted any safety evaluation of the substance at the SCF website.

(3) FDA

In the United States, the FDA evaluates the safety of food additives. Until about the 1970s, the safety of GRAS substances had been evaluated by the FDA. The GRAS substances already evaluated are released in the SCOGS (Select Committee on GRAS Substances) list. The evaluation results are available from the National Technical Information Service (NTIS) website using NTIS Accession Number (pay services).

GRAS documents submitted since 1997 are published as the GRAS Notice Inventory.

Although the safety evaluation results for GRAS substances not referred to this section and other food additives are not released on FDA's websites, anyone can make a request to the FDA for application materials based on the Freedom of Information Act.

(4) FSANZ

In Australia and New Zealand, FSANZ evaluates the safety of food additives. The results are released as Approval Reports at the FSANZ website.

(5) FSCJ

Results of evaluations of food effects on human health by the FSCJ are released as evaluation documents at the FSCJ website.

4.3 Example of description

· Evaluation by JECFA

At its 10th Assembly (1966), JECFA established the conditional ADI for the additive polyvinylpyrrolidone at 0 to 1 mg/kg body wt./day. At the 17th Assembly (1973), however, this conditional ADI was rescinded over concerns of potential internal accumulation of the substance through intake by reticuloendothelial system (RES) cells of the mesenteric lymph nodes or others. Review of accumulated research data at the subsequent 25th Assembly (1981) led to restoration of the provisional ADI (0 to 1 mg/kg body wt./day).

At the 27th Assembly (1983), a re-examination of toxicity data associated with the additive polyvinyl-pyrrolidone found no harmful effects in a long-term toxicity test. Thus, the provisional ADI was modified to 0 to 25 mg/kg body wt./day.

Research of the immune function in dogs repeatedly administered with PVP was reviewed at the 29th Assembly (1985). It was determined that harmful effects were not evoked despite accumulation in RES cells. At this assembly, furthermore, the carcinogenicity of hydrazine, admixed in PVP in extremely trace amounts, was presented as an issue. A two-year administration test in rats of PVP added to feed at a concentration of 100 g/kg feed, however, did not induce tumors. Consequently, no concerns for inducing cancer in humans were deemed to exist under ordinary use conditions as a food additive, and the provisional ADI of 0 to 25 mg/kg body wt./day was retained.

Based on data showing current admixed concentrations of hydrazine in the additive polyvinylpyrrolidone to be no greater than 1 mg/kg, the ADI for additive polyvinylpyrrolidone was established at 0 to 50 mg/kg body wt./day at the 30th Assembly (1986).

5. Physicochemical properties

The structural formula, manufacturing method, specifications*[1], stability, and analytical methods of the subject food additive in food products should be provided.

5.1. Structural formula

· Structural or rational formula

In the case of an organic compound, the *Japan's Specifications and Standards for Food Additives* should be referred to.

*1 "Specifications" includes (1) draft specifications, (2) comparison table of draft and existing specifications (specifications established by international organizations and foreign countries and pharmaceutical specifications), (3) grounds for establishing the draft specifications, and (4) verification data of test methods and test results.

· Molecular formula and molecular weight

Describe the molecular formula and molecular weight for an organic compound, or the compositional formula and formula weight for an inorganic compound, in conformance to the rules of *the Japan's Specifications and Standards for Food Additives*. For a mixture, describe the molecular formulas and molecular weights of all the ingredients contained in it.

5.2. Manufacturing methods

The manufacturing process should be briefly described, for example, in a flow chart.

The removal process of harmful factors should also be noted.

5.3. Specifications

5.3.1. Explanations and notes

Requirements to ensure a constant level of quality for the safety and effectiveness of the subject food additive should be established.

(1) Draft specifications

In the specifications, the name, content (purity), chemical and physical properties (identification, specific properties), limits of impurities, and purity test of the additive should be presented.

For specific explanations of each item, refer to IV. Guidelines for drafting specifications.

Notes

· Specifications should be preferably tabulated.

· The JECFA Combined Compendium of Food Additive Specifications, US Food Chemical Codex (FCC), and EU regulations should be cited in a proper manner.

· If the Japanese Pharmacopoeia establishes specifications of the substance (the subject food additive), they should be cited as necessary.

· If no specifications exist for the subject food additive, specifications should be newly established for the substance.

· Any laws referenced should be indicated by the reference specification number (Ref. Spec.) in tabular form. The relevant parts should be attached as Reference.

· As a general rule, test methods established as GENERAL TESTS in *Japan's Specifications and Standards for Food Additives* should be used.

(2) Comparison table of draft and existing specifications

A table comparing the draft specifications with the existing specifications established by international organizations and foreign countries and pharmaceutical specifications, etc. should be attached.

(3) Grounds for establishing the draft specifications

The grounds (reason for setting the item, source, reaction principle, etc.) and an overview of the review of testing method in sequence of the item numbers in the draft specifications should be shown.

Notes

· For any items established in the international or foreign countries' specifications but not selected in the draft specifications, the reasons for non-selection should be described.

· When using newly developed testing methods or modified methods of any standard testing methods, the reasons for inapplicability of the general testing methods provided in *the Japan's Specifications and Standards for Food Additives* should be described and the testing methods in detail should be shown.

(4) Validation data of test methods and test results

The validation data of test methods and test results should be shown. Conformity to specification values established in the draft specifications with respect to the content (purity), chemical and physical properties (identification, specific properties), limits of impurities, etc. should also be explained.

Notes

· To show appropriateness for test methods established, verification data of testing methods (e.g., recovery tests) should be provided.

· To show that the subject food additive conforms to the specifications established in the draft specifications, analytical results of an appropriate number of lots (e.g., 3 lots per product, 3 measurements per lot) should be provided.

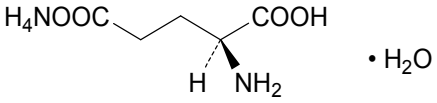
5.3.2. How to confirm the relevant information

Specifications of JECFA, the United States and the EU are available at the websites of JECFA, European Commission (EC) and U.S. Pharmacopeial Convention (USPC), respectively.

5.3.3. Examples of description

(1) Draft specifications

Table X Draft specifications

Item[a)]		Draft Specifications	Ref. Spec.
(a) Japanese Name		Lーグルタミン酸アンモニウム	
(b) English Name		Monoammonium L-Glutamate	1
(c)	Alternative Japanese Name	--	―
	Alternative English Name	--	―
(d) Structural or Rational Formula			1, 2
(e) Molecular or Compositional Formula		$C_5H_{12}N_2O_4 \cdot H_2O$	1
Molecular or Formula Weight		182.18	1
(f) Chemical Name		Monoammonium monohydrogen (2*S*) - 2 -aminopentanedioate monohydrate	3
(g) CAS Registry Number		[139883 - 82 - 2]	3
(h) Definition[b)]		--	
(i) Assay(Content)[c)]		Contains not less than 99.0% of monoammonium L-glutamate monohydrate ($C_5H_{12}N_2O_4 \cdot H_2O$) on the dried basis.	1
(j) Description		Monoammonium L-Glutamate occurs as colorless to white crystals or white crystalline powder.	1
(k) Identification		(1) Use an aqueous solution (1 in 200) of Monoammonium L-Glutamate as the test solution and a solution (1 in 200) of monosodium L-glutamate monohydrate as the control solution. …	1
		(2) Monoammonium L-Glutamate responds to the test for the ammonium salt.	1, 2
(l) Specific Rotation[c)]		$[\alpha]^{20}_D$ = +25.4 to +26.4° (10 g, hydrochloric acid (1 in 6), 100 mL, on the dried basis)	1
pH		6.0 to 7.0 (1.0 g, water 20 mL)	1

(m) Purity	(1)	Lead: Not more than 1 μg/g as Pb (4.0 g, Method 1, Control solution Lead Standard Solution 4.0 mL, frame method)	1, 2
	(2)	Arsenic: Not more than 3 μg/g as As (0.50 g, Method 1, Standard color Arsenic Standard Solution 3.0 mL, Apparatus B)	2
	(3)	Pyrrolidone carboxylic acid: Weigh 0.50 g of Monoammonium L-Glutamate and dissolve in water to prepare 100 mL of test solution. Separately, weigh 0.50 g of monosodium L-glutamate monohydrate and 2.5 mg of DL-2-pyrrolidone-5-carboxylic acid, and dissolve them in water to make exactly 100 mL of control solution. Measure 2 μL each of the test solution and the control solution, …a 2:1:1 mixture of 1-butanol/water/acetic acid …	1, 2, 4
(n) Loss on Drying[c)]		Not more than 0.5% (50°C, 4 hours)	1, 2
(o) Residue on Ignition[c)]		Not more than 0.1% (800°C, 15 minutes	1, 2
(p) Microbial Limit		--	—
(q) Method of Assay[c)]		Weigh accurately about 0.15 g of Monoammonium L-Glutamate, add 3 mL of formic acid to dissolve, and then add 50 mL of acetic acid. Titrate the resulting solution with 0.1 mol/L perchloric acid. Confirm the endpoint …	1, 2
(r) Storage Standards		--	—

Reference specifications

1: JECFA Combined Compendium of Food Additive Specifications (Ref. X)

2: *Japan's Specifications and Standards for Food Additives, 8th Edition* (Ref. X)

3: Food Chemical Codex Ninth Edition (Ref. X)

4: Japanese Standards of Quasi-Drug Ingredients 2006 (Ref. X)

[a)] For the items given in (a) to (r), requirements to assure a certain level of quality concerning safety and effectiveness of the subject food additive should be established (see IV. Guidelines for the preparation of draft specifications).

[b)] If the subject food additive originates from animals, plants or minerals, or the extract of microorganisms, the definition should include information on the origin, preparation method, nature, and impurities.

Example of (h) Definition: Dunaliella Carotene is obtained from the entire part of the alga *Dunaliella bardawil* or *Dunaliella salina* and consists mainly of β-carotene. It may contain edible fats or oils. Reference specification: JECFA monograph Carotenes (Algae). Grounds for scientific names: NCBI Taxonomy.

[c)] The items to be set in (i), (m), (n), (o), and (q) should be entered.

(2) Comparison table of draft and existing specifications

Table X Comparison table of draft and existing specifications

	Draft Specifications	JECFA	FCC	EU
Assay (Content)	Not less than 99.0% (dried basis)	Not less than 99.0% (dried basis)	98.5%–101.5% (dried basis)	99.0%–101.0% (anhydrous basis)
Description	Colorless to white crystals or white crystalline powder	White, practically odorless crystals or crystalline powder	White, free flowing crystalline powder	White, almost odorless crystals or crystalline powder
Identification tests				
Test for ・・・	Positive (TLC: ninhydrin coloration)	Positive (TLC: ninhydrin coloration)	--	Positive (TLC)
Test for ・・・	Positive	Positive	--	Positive
Solubility	Not established	Freely soluble in water	--	--
Infrared Spectrum	Not established	--	Matches reference spectra	--
(Specific properties)				
Specific Rotation $[\alpha]^{20}_{D}$ (dried basis)	+25.4 to +26.4° (10% w/v, hydrochloric acid (1 in 6))	+25.4 to +26.4° (10% w/v, 2N HCl)	+25.4 to +26.4° (10% w/v, 2N HCl)	+25.4 to +26.4° (10% soln., 2N HCl) (Identification)
pH	pH 6.0–7.0 (1.0 g, water 20 mL)	pH 6.0–7.0 (1 in 20)	pH 6.0–7.0 (1:20) (Description)	pH 6.0–7.0 (5% solution) (Identification)
Purity tests				
Lead (Pb)	Not more than 2 μg/g	Not more than 1 mg/kg	Not more than 5 mg/kg	Not more than 2 mg/kg
Arsenic (As)	Not more than 3 μg/g	--	--	--
____ acid	Negative (TLC)	Negative (TLC)	--	Not more than 0.2%
Loss on Drying	Not more than 0.5% (50°C, 4 hours)	Not more than 0.5% (50°C, 4 hours)	Not more than 0.5% (50°C, 4 hours)	Not more than 0.5% (50°C, 4 hours)
Residue on Ignition	Not more than 0.1% (800°C, 15 minutes)	Not more than 0.1% (800°C, 15 inutes)	Not more than 0.1% (800°C, 15 inutes)	Not more than 0.1%
Method of Assay	Non-aqueous titration, sample mass 0.15 g, 0.1 mol/L perchloric acid	Non-aqueous titration, sample mass 200 mg, 0.1N perchloric acid	Non-aqueous titration, sample mass 250 mg, 0.1N perchloric acid	No procedure listed

5.4 Stability

Review the stability of the food additive including a search for decomposition products.

5.5 Analytical methods of the subject food additive in food products

Basically, analytical methods should be established for foods in which the food additive is likely to be used at high possibility. They should be methods to identify the addition of the food additive quantitatively and qualitatively by chemically analyzing target foods. If the use standard does not need to be established, or if the food additive does not remain in food, the assay may be omitted from the analytical methods of the food additive in food products.

Notes

· In case the use standards are established, analytical methods must be denoted as a general rule.

· A quantitative assay to separate the subject additive from other food additives with the same purpose should be considered.

6. Draft use standards

Study the needs for establishing use standards upon comprehensive review of the safety, effectiveness, and estimated intake of the subject food additive, and the Codex standards and other countries' use standards for that substance.

Notes

· If codex standards or other countries' standards are proposed as the draft standards, use standards for other food additives must be taken into consideration.

· The use standards should be preferably tabulated as needed.

· Any revisions to use standards should be marked by underscoring and crossing out.

6.1. Drafting use standards

Comprehensively review the safety and effectiveness of the food additive. If the establishment of use standards is determined necessary, describe appropriate use standards.

Notes

The draft of use standards must be prepared with reference to use standards for other food additives already established.

6.2. Grounds for establishing use standards

Provide the grounds for establishing the use standards based on use status in foreign countries and materials related to effectiveness and safety. Attach the materials quoted as the grounds for establishment as "References."

Notes

· Even if codex standards or standards of other countries are proposed as the use standards, applicants should discuss whether there are any issues of safety with reference to safety studies and intake estimates.

7. Other

Describe any other necessary matters.

II. Findings regarding effectiveness

1. Explanations and notes

The following are noted in the guideline published by the Ministry of Health and Welfare in 1996.

2. Effectiveness

It should be proven or confirmed that the use of the food additive comes under one or more of the purpose set out in (1) to (4) below. However, where the manufacturing or processing method for a target food can be improved or modified at comparatively low cost, and the improved or modified method does not require the food additive for the manufacture or processing of the food, the use of the food additive is not justified.

(1) To preserve the nutritional quality of the food.
An intentional reduction in the nutritional quality of a food would be justified in the circumstances dealt with in section (2) below and also in other circumstances where the food does not constitute a significant item in a normal diet.

(2) To provide necessary ingredients or constitutions for food manufactured for consumers who have special dietary need, provided that the food additive is not intended to provide medical effects, such as prevention or treatments of certain disease.

(3) To enhance the keeping quality or stability of a food or to improve its organoleptic properties, provided that this does not so change the nature, substance, or quality of the food as to deceive the consumer.

(4) To provide aids in the manufacture, processing, preparation, treatment, packing, transport, or storage of food, provided that the food additive is not used to disguise the effects of the use of faulty raw materials or of undesirable (including unhygienic) practices or techniques during the course of any of these activities.

Documents on effectiveness

(i) Studies concerning effectiveness should be conducted to establish that the food additive has expected effects, according to its purposes. For example, the studies to clarify the correlation between the effect of the antioxidant for the target foods and the added amount, and/or the time-course after the addition of the antioxidant. For preservative, the studies to clarify the improved effect of shelf life time induced by the preservative property should be conducted.

(ii) Comparisons in effects with a widely used food additive, which has already been approved for the same use, are desirable.

(iii) Studies on the stability of the food additive in foods should be conducted. For unstable food additives, breakdown products should be examined on their kinds and extent.

(iv) Effects of the food additive on main nutrients in foods should be also examined.

The points of analytical methods to generate effectiveness data and of its submission

- The applicant is required to submit evidence from well-designed study to demonstrate that the food additive indeed has the intended effect and to clarify the purpose of the use of the food additive.
- Where possible, these studies should be conducted using graded levels of the additive in the food and the effects should be noted. The effects should be compared with controls using no additive.
- Test results should be proven effect by statistically treating them, including the application of the test of significance. These data should be used not only to demonstrate the effectiveness, but also to establish the minimum effective use level.
- Presentation of the results in tabular and graphical form is desirable to help to facilitate the interpretation of the results. For example, a graphical representation of effects of a food additive at various use levels allows quick visualization of the minimum levels of efficacious use of the food additive.
- Where possible, the data demonstrating the effectiveness should be those that have been published in scientific journals and evaluated objectively.

Notes

- There is often the case that attached effective data is only for some target foods intended to use without providing any explanation for reason of abbreviation of effective data on other target foods. Explanation of the adequacy should be described if the applicant presents effective data only for some target foods.
- The attachment of minimum and basic safety data demonstrating the effectiveness is desirable, not just making a statement to the effect that the subject additive is widely used overseas.
- Description of difference (advantage) compared with other food additives that is already approved and distributed for the same intended use is desirable.
- Concrete explanation of the use with functional mechanism, reaction mechanism, data or the like is desirable.

2. Examples of actual cases

Documents for food additives already assessed in Japan are released to the public in "新規指定の可否に関する薬事・食品衛生審議会食品衛生分科会添加物部会報告書"—the Reports on Approval of New Designations by the Committee of Food Additives of the Food Sanitation Council under the Pharmaceutical Affairs and Food Sanitation Council on the website of MHLW. Documents on actual cases in Australia and New Zealand are released as "Approval Report" in the website of FSANZ. Documents submitted in EU are also released as "Scientific Opinion on safety evaluation of food additives" in the website of EFSA.

Four examples from information released to the public in Japan, EU, Australia and New Zealand are shown at V. Examples of findings regarding effectiveness.

III. Findings regarding safety

1. Disposition studies

1.1 Explanations and notes

Disposition studies are intended to obtain information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of a test substance after its administration in animals in order to estimate the pharmacokinetics and development of adverse effects in humans. Discussions that contribute to the evaluation of toxicity studies or their results should also be included whenever possible.

The following are noted in the assessment guideline by the FSCJ.

1. Deposition studies

Studies to examine the disposition within the body should comply with the disposition study guideline published by the Ministry of Health and Welfare in 1996. They also should follow the notes below.

(1) The food additive or substance labeled by an isotope should be used as the test substance. When an isotope-labeled substance is used, the species and location of the isotope should be clearly indicated.

(2) It is preferable to conduct tests on more than two species (more than one rodent species [typically rats] and more than one non-rodent species [typically dogs]).

(3) In principle, the test substance should be administered orally. Absorption, distribution, metabolism, and excretion should be estimated after single-dose administration and repeated-dose administration. 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.

(4) Each process of absorption, distribution, metabolism, and excretion must be examined and values recorded, such as concentration of the active ingredient in the blood; amount of the substance in urine, feces and other excretory matter; and successive changes in the concentration in each organ; metabolites found in organisms, as well as factors that are influential in each step.

(5) The results regarding absorption, distribution metabolism and excretion (e.g., highest concentration in blood plasma, successive change in concentration in each organ, and elimination half-life) should be used to determine the organ(s) that can be a target of toxicological tests. In such cases, the feasibility of extrapolating the results to obtain the effects on the human body must be examined with regard to differences among animal species and species specificity.

(6) For tests using a racemic body, it is preferable to examine the disposition of each optical isomer within the body if it is necessary to understand the association with toxicity.

(7) In principle, the existence of human-specific metabolites must be examined and toxicological tests of such metabolites must be carried out as necessary.

This study will include tests conducted in accordance with the guideline published by the Ministry of Health and Welfare in 1996. However, other appropriate methods may be considered depending on the nature of the test substance, and tests based on the OECD test guidelines or ICH (International Conference

on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines, for example, may be selected or other tests may be substituted as befits the purpose of the study. Appropriate data on the pharmacokinetics of the test substance that has been obtained from toxicity studies may also be used.

(1) Absorption

Blood concentration-time profile

Information such as the maximum concentration in blood (Cmax) after dosing, the time to reach the maximum concentration (Tmax), and the area under the blood concentration-time curve (AUC) should be noted for each test animal to show the extent and rate of test substance absorption.

It is also useful to discuss comparisons of these parameters with the same parameters after intravenous administrations or other standard administration methods.

Absorption rate

The level of urinary, fecal, biliary, and respiratory excretion, for example, after administration of the test substance as well as the absorption rate in the body calculated on the basis of the above total excretion level should be described.

(2) Distribution

The organ and tissue distribution, as well as the changes and accumulation over time after single and repeated doses of the test substance, should be described for each test animal. The results of measurements at several time points should preferably be described in order to accurately reflect the pharmacokinetics.

Organs and tissues characterized by high concentrations of distribution or accumulation and by adverse reactions as a result of repeated doses should preferably be discussed, as should their form.

(3) Metabolism

To provide information on the metabolic pathway and the extent and rate of metabolism, quantitative values for unchanged compound and metabolites in biological samples, such as blood, urine, bile, and feces, after single and repeated doses should be described for each test animal.

In vitro tests of samples of the organs involved in metabolism, such as slices, homogenates, cell suspensions, and cell fractions, may also be described.

(4) Excretion

The levels of urinary, fecal, respiratory, biliary, lactic or other excretion over time after single and repeated doses should be described for each test animal to provide information on the excretory pathway of the test substance and principal metabolites, as well as the extent and rate of their excretion.

Notes

・When existing evaluation reports are cited, the study source should be identified.

・The species, strains, gender, and number of test animals, as well as the method of administration, vehicle, dose, and method of labeling should be clearly indicated.

・Results should be tabulated for ease of comprehension, but information that is not amenable to tabulation should be described in detail in some paragraphs.

・When residue levels are evaluated from the test that uses radioisotope, it is preferable to be described as residual radiation level (%TRR or %TAR) or residual concentration (mg/kg or μg/kg).

・Assessments such as of pharmacokinetics and the development of adverse effects in humans should also be discussed whenever possible.

* When the food additive is scientifically known to be a common component of food or to be broken down in food or in the digestive tract into a common component of food, test results showing the validity of the following based on items in Table 2 of the guideline published by the Ministry of Health and Welfare in 1996 should be noted.

When it is not validated to be or to be broken down into a common component of food, test results for the following should be noted for each animal species.

Table 2. Items to be studied to determine whether the food additive is broken down in food or in the digestive tract into a common component of food

1. Under conditions in which food additives are commonly used, the substance must be readily broken down in food or in the digestive tract into a substance that is identical with a common component of food.
2. Major factors involved in the breakdown of the substance in food or in the digestive tract (such as pH or enzymes) must be ascertained.
3. When the proper amount is used under conditions in which food additives are commonly used, the food additive must be absorbed in the body to the same extent as food components and must not interfere with the absorption of other nutritional components.
4. Non-hydrolysates or partial hydrolysates of the ingested food additive cannot be excreted in large amounts in feces. Non-hydrolysates or partial hydrolysates also cannot accumulate in biological tissue.
5. Ingestion of food in which the food additive is used cannot result in excessive ingestion of the primary component of the food.

1.2. Examples of description

When writing up the descriptions, existing evaluation reports at the FSCJ website can be used as reference. The following are typical examples.

(1) Absorption

Absorption in rats

a. Blood concentration profile

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted to analyze blood concentration profiles after the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [time per period] in XX-old XX [animal species] (X males and females each per group [group establishment]). As shown in Table 1, the results showed that the blood concentrations of XX [test substance] in the XX dose group(s) peaked (XX to XX mg/L) at X hours post-dose, and was XX at X hours post-dose and XX at X hours post-dose, with a $T_{1/2}$ of X hours and an AUC of X μg•hr/g (Ref. X).

Table X: Pharmacokinetics parameters in blood

Gender	Dose (mg/kg body weight)	Tmax (hr)	Cmax (μg/g)	$T_{1/2}$ (hr)	AUC (μg・hr/g)

b. Absorption rate

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted to analyze the *in vivo* absorption rate after the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [time per period] in XX-old XX [animal species] (X males and females each per group [group establishment]). Based on the radioactive concentration in test samples [such as urine, cage wash, feces, and bile], the *in vivo* absorption rate in the X-dose group(s) was estimated to be at least X% (Ref. X).

(2) Distribution

Distribution in rats

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted to analyze *in vivo* distribution after the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [time per period] in XX-old XX [animal species] (X males and females each per group [group establishment]). As shown in Table X, the results revealed that

XX [test substance] was distributed in high concentrations in XX and XX at X hours post-dose, but that the distribution peaked in XX at X hours post-dose and was XX at X hours post-dose (Ref. X).

Table X: Total radioactivity level in tissues after XX administration of X-labeled XX in rats (%TRR, etc.)

Tissue	Time after dose (hours)			
Liver				
Kidney				
Large intestine				
Muscle				
Plasma				
Whole blood				
Milk				

(3) Metabolism

Metabolism in rats

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted to identify metabolites in XX and XX after the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [time per period] in XX-old XX [animal species] (X males and females each per group [group establishment]). As shown in Table 3, XX and XX were found as the unchanged compound and metabolite of XX [test substance] (Ref. X).

Table X: Radioactivity level of XX and metabolites after XX administration of X-labeled XX in rats (%TRR, etc.)

Number of doses	Dose (mg/kg body weight)	Gender	Samples	Unchanged compound	Metabolites (%TRR)
Single dose			Blood		A ( ), B ( ), C ( ), D ( ), and sulfate conjugate of D ( )
			Urine		
			Bile		
			Feces		

Repeated doses					

(4) Excretion

Excretion in rats

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted to analyze over time the excretion rate in urine and feces after the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [time per period] in XX-old XX [animal species] (X males and females each per group [group establishment]). As shown in Table 4, the results showed that X% of XX [test substance] was excreted in XX at X hours post-dose, and X% was excreted in XX at X hours post-dose. The principal excretory pathway was XX (Ref. X).

Table X: Percent excreted (%TRR) in urine and feces at X and X hours-post dosing

Number of doses	Dose (mg/kg body weight)	Gender	Samples	X hours post-dosing	X hours post-dosing	Total
			Urine			
			Feces			

2. Toxicological studies

2.1 Explanations and notes

Toxicological studies are intended to obtain information on the effects of the administration of a test substance in animals in order to deduce, for example, the ways in which adverse effects develop in humans and the doses at which they occur.

The following are noted in the assessment guideline by the FSCJ.

2. Toxicological studies

(1) Subchronic toxicity studies and chronic toxicity studies

(a) Tests should be conducted on one rodent species (generally rats) and one non-rodent species (generally dogs). In principle, the same number of male and female animals should be used.

(b) The administration period should be 28 days or 90 days for subchronic toxicology tests and more than 12 months for chronic toxicology tests. The 28-day test can be omitted when a test with a 90-day administration period is carried out.

(c) In principle, the test substance should be orally administered 7 days a week. The substance should be administered in animal feed or water, but it can be also administered by gavage.

(d) At least three groups receiving different levels of the administration dose should be established in addition to the control group. The reasons for choosing each dose level should be clearly indicated. Proper ratios should be chosen so that an appropriate NOAEL can be obtained.

(e) 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.

(f) When the frequency or severity level of a naturally occurring pathological change that is also observed within the control groups increases due to the administration of the substance, even within the context of the background data it should, in principle, be taken as an effect caused by the administration of the substance if biological some significance, such as a relationship between the dose and the frequency or severity level, is recognized.

(g) When neurotoxicity or immunotoxicity is suspected, the need for additional tests as described in the OECD test guideline or ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline should be examined.

(h) The procedure to extrapolate the findings of toxicological tests to humans should be examined carefully by analyzing the endpoints separately and for different factors, such as functional changes, non-oncological morphological changes, oncological morphological changes, and changes to reproductive functions.

(i) When a combination test for chronic toxicity and carcinogenicity is carried out using one rodent species, a chronic toxicity test and carcinogenicity test on another rodent species can be omitted.

(j) The need to add an *in utero* exposure phase should be examined where necessary.

(2) Carcinogenicity studies

(a) Tests should be conducted on more than two rodent species (rats, mice or hamsters are used generally). In principle, the same number of male and female animals should be used.

(b) In principle, administration should be carried out orally 7 days a week. For rats, the period should be between 24 months or longer and 30 months or shorter. For mice, the period should be between 18 months or longer and 24 months or shorter. The test substance should be orally administered in animal feed or with water, but it can be also administered by gavage if oral administration is difficult.

(c) At least three groups receiving different levels of the administration dose should be established in addition to the control group. The reasons for choosing each dose level should be clearly indicated. Proper ratios should be chosen so that an appropriate NOAEL can be obtained.

(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) If the test for carcinogenicity is positive, the ADI cannot be established in principle if genotoxicity is positive and the substance is determined to be a genotoxic carcinogen. If the test for carcinogenicity is negative, the ADI can be established if genotoxicity is negative and the substance is determined not to be a genotoxic carcinogen. Even if the food additive being assessed unavoidably generates/contains a byproduct/residue that is suspected of being genotoxic, the ADI may be established in some cases after a required examination.

(f) If the incidence rate of lesions is relatively low, carcinogenicity may be determined during the assessment by conducting a significance test using either: (1) the sum of benign tumor-like lesions and malignant tumor-like lesions; or (2) the sum of precancerous lesions, benign tumor-like lesions and malignant tumor-like lesions. Assessment of carcinogenicity, including precancerous lesions, is especially preferable where there is an increase in endocrine system tumors, a type of lesion that frequently occurs with rodent species.

(g) If an increase in tumors in a region where tumor incidence is not normally high or when an increase in rare tumors is recognized it is preferable to include the carcinogenic mechanism in the assessment.

(h) Factors that modify the development of cancer (suppression of weight increase or decrease of survival rate) should be taken into consideration for the assessment.

(i) Special attention should be paid to species-specific toxicological findings (e.g., hypertrophy, hyperplasia and tumor of thyroid follicle epithelium [specific to rodents] and renal disorder and tumor [specific to male rats]).

(j) When a combination test for chronic toxicity and carcinogenicity is carried out using one rodent species, a chronic toxicity test and carcinogenicity test on another rodent species can be omitted.

(k) The need to add an *in utero* exposure phase should be examined where necessary.

(3) Toxicity/carcinogenicity combination studies with one-year repeated-dose administration

Notes in (1) and (2) should be followed.

(4) Reproductive toxicity studies

Studies to examine reproductive toxicity should comply with the reproductive toxicity study guideline published by the Ministry of Health and Welfare in 1996. They also should follow the notes below.

(a) Tests should be conducted on more than one rodent species (rats are used generally). In principle, the same number of male and female animals should be used.

(b) In principle, administration should be carried out orally 7 days a week. The test substance should be orally administered in animal feed or with water, but it can be also administered by gavage if oral administration is difficult.

(c) At least three groups receiving different levels of the administration dose should be established in addition to the control group. The reasons for choosing each dose level should be clearly indicated. Proper ratios should be chosen so that an appropriate NOAEL can be obtained.

(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) When neurotoxicity or immunotoxicity is suspected, the need for additional tests as described in the OECD test guideline or ICH guideline should be examined.

(5) Prenatal developmental toxicity studies

Studies to examine prenatal developmental toxicity should comply with the teratogenetic study guideline published by the Ministry of Health and Welfare in 1996 and the notes below. The minimum period of administration should be from the date of implantation to the estimated delivery date, and the substance should be administered daily to the pregnant animals.

(a) Tests should be conducted on more than two species (more than one rodent species [typically rats] and more than one non-rodent species [typically rabbits]).

(b) The test substance should be orally administered by gavage.

(c) At least three groups receiving different levels of the administration dose should be established in addition to the control group. The reasons for choosing each dose level should be clearly indicated. Proper ratios should be chosen so that an appropriate NOAEL can be obtained.

(6) Genotoxicity studies

Studies to examine genotoxicity should comply with the mutagenicity test guideline published by the Ministry of Health and Welfare in 1996. But the examination should not be limited to the narrow definition of "mutagenicity" and the assessment should be carried out based on the test results regarding genotoxicity in general. Among the tests included in the standard combination (i.e., combination of bacterial reverse mutation tests, chromosome aberration tests using cultured cells of mammals, and micronucleus tests on rodents), the chromosome aberration tests using mammalian cultured cells can be replaced with a mouse lymphoma TK assay (MLA) or *in vitro* micronucleus test. In order to supplement the results from the standard test combination, single cell gel electrophoresis ("Comet Assay") and *in vivo* transgenic animal mutation assay can be used, in addition to those described in the Ministry of Health and Welfare guideline of 1996.

If one of the tests in the standard combination cannot be conducted due to technical constraints, the reason should be explained backed up by scientific evidence. One of the internationally validated tests can be used as a replacement.

The test results should be judged in accordance with the following procedure.

(a) If the results of the bacterial reverse mutation tests are positive, a comprehensive judgment should be made by fully considering the results of *in vivo* tests that use genetic mutation or DNA damage (Comet Assay, *in vivo* transgenic animal mutation assay) as an indicator.

(b) If the results of the chromosome aberration tests using mammalian cultured cells are positive and the effect is also confirmed with rodent micronucleus tests, the substance can be determined as positive for genotoxicity.

(c) Even if the results of the chromosome aberration tests using mammalian cultured cells are positive, if the results of the rodent micronucleus tests (preferably with evidence to show exposure of the target organ) are negative, the substance can be determined as negative for genotoxicity.

(7) Allergenic potential studies

Studies to examine the allergenicity of food additives should follow the antigenicity tests guideline published by the Ministry of Health and Welfare in 1996. There is no well-established method for predicting the allergenicity of chemical substances when orally ingested, particularly for predicting the immediate type of allergenicity. Therefore, studies should be carried out with sensitization and induction methods approved by specialists. For the time being, allergenicity studies using delayed allergy as an indicator should at least be carried out. Examples of tests for such studies include skin sensitization tests

on guinea pigs (e.g., guinea pig maximization test [GPMT] in the OECD test guideline 406) and lymph node reaction tests on mice (e.g., the local lymph node assay [LLNA] in the OECD test guideline 429).

Allergenicity assessment of food additives containing protein should follow the "Standards for the Safety Assessment of Genetically Modified Foods (Microorganisms)" (FSCJ decision, June 26, 2008).

(8) General pharmacological studies

Studies to examine general pharmacological properties of food additives should follow the general pharmacological test guideline published by the Ministry of Health and Welfare in 1996.

(9) Other studies

When neurotoxicity is suspected following a subchronic toxicity test and other tests, 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 ICH guideline and other materials. Immunofunctional tests should be also carried out as necessary when immunotoxicity in humans is suspected based on existing findings.

This study will include tests conducted in accordance with the guideline published by the Ministry of Health and Welfare in 1996. However, other appropriate methods may be considered depending on the nature of the test substance, and tests based on the OECD guidelines or the ICH guidelines, for example, may be selected or other tests may be substituted as befits the purpose of the study.

Acute toxicity study information may be included in application documentation.

If a 90-day repeated-dose toxicity study is conducted, there will be no need to conduct a separate 28-day repeated-dose toxicity study in the same species.

If one-year repeated-dose toxicity and carcinogenicity studies are conducted in the required species, there will be no need to conduct a combined one-year repeated-dose toxicity/carcinogenicity study. Conversely, if a combined one-year repeated-dose toxicity/carcinogenicity study is conducted in a rodent species, there will be no need to conduct separate one-year repeated-dose toxicity and carcinogenicity studies in a rodent species.

* When the food additive is scientifically known to be a common component of food or to be broken down in food or in the digestive tract to become a common component of food, there will be no need to attach toxicity-related data, as per the guideline published by the Ministry of Health and Welfare in 1996, but materials on 28-day repeated-dose toxicity studies in rodents and genotoxicity studies should preferably be attached.

* Regarding assessment methods for enzymes, FSCJ says "safety assessments of enzymes are, in principle,

carried out based on the data in Appendix 1 and other information. When the safety of a production strain is not known for enzymes obtained from microorganisms, appropriate tests must be conducted to assess the safety of the original microorganism. Pathogenic or toxin-producing production bacteria should not in principle be used for the production of enzymes. When it is scientifically proven that the enzyme is broken down in the digestive tract to become a common component of food (such judgment should be made by considering the items in Table 2 in the guideline published by the Ministry of Health and Welfare in 1996), the materials regarding toxicity listed in Appendix 1 can be omitted. The materials regarding toxicity listed in Appendix 2[*1] should be submitted."

(1) Acute toxicity studies

· The results of acute toxicity studies should preferably be expressed as the LD_{50} (median lethal dose), for example.

(2) Subchronic toxicity studies

· The results of repeated-dose toxicity studies (28-day and 90-day repeated-dose toxicity studies) should be described in this section.
· Information on toxicity findings and the doses at which they occurred (with statistical analysis) should be described.
· Information on the NOAEL or LOAEL should be described.

(3) Chronic toxicity studies and carcinogenicity studies

· The results of life-long, chronic repeated-dose toxicity studies (one-year repeated-dose toxicity studies and carcinogenicity studies, and combined one-year repeated-dose toxicity/carcinogenicity studies) should be described in this section.
· The main point of carcinogenicity studies is whether or not the additive is carcinogenic.

(4) Reproductive toxicity studies

· Information on the reproductive functions of males and females, estrus cycle, mating behavior, conception, delivery, lactation, and development and behavior of offspring in reproductive testing (multigeneration reproductive toxicity studies) should be noted.
· Information related to the effects on fetal development in teratogenicity studies (prenatal development toxicity studies) should be noted.

[*1] Materials listed in Appendix 2: materials on (1) 90-day repeat-dose toxicity studies in rodents, (2) genotoxicity studies and (3) allergenicity studies

* Observation and test parameters in reproductive testing: general condition, body weight, food consumption, water consumption, parameters related to pregnancy and delivery (such as copulation rate, pregnancy rate, and birth rate), neonatal parameters (such as number of pups, number of dead pups, number of live pups, external anomalies, and results of necropsy), results of necropsy, and histopathology etc.
* Observation and test parameters in teratogenicity studies: general condition, body weight, food consumption, water consumption, and necropsy results for dams and fetuses etc.

(5) Genotoxicity studies (mutagenicity test)

- The technical product and, if necessary, metabolites should be described under the separate categories of *in vitro* tests (such as microbial reverse mutation assay and chromosomal aberration assay in cultured mammalian cells) and *in vivo* tests (rodent micronucleus assay).
- It should be clearly indicated whether any metabolic activator was added or not.

(6) Other studies

- Special studies such as allergenic potential studies, general pharmacology studies, neurotoxicity studies, and immune function studies should be described as needed.

Notes

- Even when existing evaluation reports are cited, the study source should be identified.
- In principle, tests involving oral administration should be described.
- Results should preferably be tabulated, but if it is difficult to put together into tables, detailed information should be described in writing in individual paragraphs.
- The bacterial strains, types of cells, the animal species, strains, gender, and number of test animals, the method of administration, vehicle, and dose should be clearly indicated.
- Food additive degradation products and contaminants should also be studied as needed.
- The doses should preferably be indicated in units of "mg/kg body weight per day."
- Suitability of the tests for the GLP should preferably be indicated.

2.2. Examples of description

When writing up the descriptions, existing evaluation reports at the FSCJ website can be used as reference. The following are typical examples.

The results of multiple acute toxicity and genotoxicity studies should preferably be tabulated collectively. Also, the results of repeated-dose toxicity studies should preferably be tabulated for each study. Information that is not amenable to tabulation may be described in writing.

(1) Acute toxicity studies

The results of acute toxicity studies on XX [test substance] and its metabolites in rats and mice are presented in Table X (Ref. X).

Table X: Summary of acute toxicity study results

Test substance	Route of administration	Species	LD_{50} (mg/kg body weight)		Observed symptoms	Reference
			Males	Females		
XX	Oral	SD rats	＞5,000	＞5,000	Watery stool	XX, Year
		ICR mice	＞4,000	＞4,000	1 death at 1,000 mg/kg body weight	XX, Year
	Percutaneous	F344 rats	2,500	3,000	No symptoms or deaths	XX, Year
	Inhalation	SD rats	＞10	＞10	Diarrhea, blepharoptosis	XX, Year
Metabolite A	Oral	SD rats	＞2,000	＞2,000	Watery stool	XX, Year

(2) Repeated-dose toxicity studies or carcinogenicity studies

<In case of using tables>

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted on the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [period] in XX-old XX [animal species] (X males and females each per group [group establishment]) setting administered group as Table 6 (Ref. X).

Table X: Dosage level

Dosage level (% or ppm)	A, B, C
Equivalent to mg/kg body weight/day	A’, B’, C’

The results showed no treatment-related effects on observation parameters such as general condition, body weight, food consumption, water consumption, blood biochemistry, urinalysis, ophthalmology. Blood biochemistry revealed elevated ALT and AST levels in males and females of the B' mg/kg bodyweight/day and higher dose groups. Elevated sodium level was also observed in males of the B' mg/kg/body weight/day group. This was not considered to be toxic changes because no other related electrolyte changes or dose-response relationships were found.

Analysis of organ weight revealed increases in the absolute and relative weight of the liver in males of the B' mg/kg/ body weight/day and higher dose groups and in females of the C' mg/kg body weight/day dose group. Histopathology revealed centrilobular hepatocyte hypertrophy in males and females of the B' mg/kg body weight/day and higher dose groups, and single cell necrosis of hepatocytes in males of the C' mg/kg body weight/day dose group. These findings were determined to indicate toxicity because they were consistent changes characterized by a dose-response relationship. The NOAEL was, thus, assessed as A' mg/kg/ body weight/day in this study.

Table X: Toxic findings in XX [study title] toxicity study (XX [animal species])

Dose	Males	Females
C' mg/kg body weight/day	Single cell necrosis of hepatocytes	Increases in absolute and relative weight of liver
≥ B' mg/kg body weight/day	Elevated ALT and AST Increases in absolute and relative weight of liver Centrilobular hepatocyte hypertrophy	Elevated ALT and AST Centrilobular hepatocyte hypertrophy

<In case of not using tables>

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant study was conducted on the XX administration [method of administration] of XX [test substance] (XX, XX, XX mg/kg bodyweight/day) for XX [period] in XX-old XX [animal species] (X males and females each per group [group establishment]) setting administered group. The results showed no treatment-related effects on XX [individually noted observation parameters such as general condition, body weight, food consumption, and water consumption, and test parameters such as hematology, blood biochemistry, urinalysis, ophthalmology or other functional tests, necropsy, or histopathology]. XX [findings] in XX [individually noted observation parameters such as general condition, body weight, food consumption, and water consumption, and test parameters such as hematology, blood biochemistry, urinalysis, ophthalmology or other functional tests, necropsy, or histopathology] were noted in XX [males and females] in the XX [dose] group. These findings were (or were not) determined to indicate toxicity based on XX [reasons]. The NOAEL (LOAEL) was, thus, assessed as XX [dose] in this study. (Ref. X)

(3) Reproductive toxicity studies

According to the report by XX [name of author] (XX [year of report]), a GLP-compliant, two-generation reproductive study was conducted on the administration of XX [test substance] mixed with feed (A, B, and C ppm) for in XX-old XX [animal species] (X males and females each per group [group establishment]). The P generation parent animals mated and produced pups twice (offspring animals: F_{1a}, F_{1b}), F_{1b} animals were used as the F_1 generation parent animals, and they mated and produced pups twice (offspring animals: F_{2a}, F_{2b}). Analysis of the parent animals revealed suppressed weight gain in P generation males and females and in F_1 generation females in the C ppm dose group. Food consumption was also lower during the entire study period in P generation females and during the lactation periods of the two F_1 generations. Analysis of the offspring revealed lower 4-day postnatal survival rates in both F_1 and F_2 offspring as well as suppressed weight gain in F_{1b}, F_{2a}, and F_{2b} offspring in the C ppm dose group. These findings appeared to be secondary to the toxic effect of the test substance in parent animals.

The NOAEL in this study was thus B ppm for parent and offspring animals (P males: b mg/kg body weight/day; P females: e mg/kg body weight/day; F_1 males: h mg/kg body weight/day; F_1 females: k mg/kg body weight/ day), with no findings of teratogenicity (Ref. X).

Table X: Mean test article consumption in 2-generation reproductive study (XX [animal species])

Dose group			A ppm	B ppm	C ppm
Mean food consumption (mg/kg body weight/day)	P generation	Males	a	b	c
		Females	d	e	f
	F_1 generation	Males	g	h	i
		Females	j	k	l

Table X: Toxic findings in 2-generation reproductive study (XX [animal species])

	Dose	1st generation (parents: P; offspring: $F_{1a,1b}$)		2nd generation (parents: F_{1b}; offspring: $F_{2a,2b}$)	
		Males	Females	Males	Females
Parent animals	C ppm	Suppressed weight gain	Suppressed weight gain Decreased food consumption	No toxic findings	Suppressed weight gain Decreased food consumption
Offspring animals	C ppm	Lower survival rate in nursing pups	Lower survival rate in nursing pups	Lower survival rate in nursing pups	Lower survival rate in nursing pups

		Suppressed weight gain	Suppressed weight gain	Suppressed weight gain	Suppressed weight gain

(4) Genotoxicity studies (mutagenicity test)

Table X: Summary of *in vitro* genotoxicity studies

Type of test	Test subject	Test substance	Treatment concentration and dose	Results	Reference
Reverse mutation assay	*S. typhimurium* (TA XX, TA XX strain)		X to X mg/plate (+/-S9)	Negative	XX, Year
	S. typhimurium (TA XX, TA XX strain)		X to X mg/plate (+/-S9)	Positive	XX, Year
Chromosomal aberration assay	Chinese hamster ovary cells (CHO cells)		X to X mg/mL (-S9) X to X mg/mL (+S9)	Negative	XX, Year
	Human peripheral blood lymphocytes		X to X mg/mL (-S9) X to X mg/mL (+S9)	Negative Positive	XX, Year

Table X: Summary of *in vivo* genotoxicity studies

Type of test	Test subject	Test substance	Treatment concentration and dose	Results	Reference
Micronucleus assay	XX mice; 5 males and females each (bone marrow cells)		X, X, and X mg/kg body weight (single oral dose)	Negative	XX, Year
	XX mice; 5 males and females each (hepatocytes)		X, X, and X mg/kg body weight (single oral dose)	Positive	XX, Year
Reporter gene transgenic animal mutagenicity	*gpt* delta mice; 5 males and females each (liver, kidneys)		X, X, and X mg/kg body weight (X-week oral dosing)	Negative	XX, Year

assay					

3. Findings in humans

3.1. Explanations and notes

Because the purpose of safety evaluations of food additives is to deduce safety and adverse effects in humans, the available information in humans should be noted.

The following are noted in the assessment guideline by the FSCJ.

Article 3. Findings in humans

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

Studies in humans include epidemiological studies, clinical experience, observations in case studies, research of the effects on health in humans during occupational exposure, reports of poisoning, and allergy studies in volunteers.

Notes

- When existing evaluation reports are cited, the study source should be identified.
- Gender, age, number of individuals, health status, and dosing method and dose should be noted.

3.2. Examples of description

(1) Intervention studies

According to the report by XX [name of author] (XX [year of report]), a randomized clinical study was conducted in XX Year in XX [location], in which XX- to XX-year old (average age XX) XX [study population] were randomized by a double-blind method to a placebo group (XX subjects) or an XX [test substance] (X mg/kg body weight/day) ingestion group for oral ingestion XX times a day [dosing method (such as capsules at breakfast)] for XX [period]. The results revealed no test substance treatment-related effects on XX [observation parameters such as general condition, hematology, blood biochemistry, urinalysis] (or revealed that XX was affected). (Ref. X)

(2) Cohort studies

According to the report by XX [name of author] (XX [year of report]) cited in the report of XX [assessment document source], an XX-year cohort study was conducted in X [gender] XX subjects (XX to XX years of age) in XX [location]. XX patients contracted XX [disease]. The relative risk for XX [disease] was XX (95% CI = XX to XX) in the X mg/kg body weight/day and higher dose groups when compared to groups with XX [test substance] consumption < X mg/kg bodyweight/day, revealing that XX [test substance] consumption ≥ X mg/kg body weight/day was strongly correlated to increased risk for XX [disease]. (Ref. X)

(3) Other studies

No reports on studies of the oral administration of this test product in humans have been found, but the following related data is available from XX [name of author] (XX [year of report]).

When XX [test substance] (X mg/kg body weight/day) was orally administered for XX [period] to patients with XX, there were no medically abnormal findings in any subjects, and X% of the ingested amount was detected in urine. (Ref. X)

4. Estimation of daily intake

4.1. Explanations and notes

The following are noted in the assessment guideline by the FSCJ.

> Article 4. Estimation of daily intake
>
> 1. The daily intake should be determined based on the Japanese diet. Care should be taken to avoid intake estimations that are too small. In principle, the estimated daily intake is calculated by multiplying the daily intake of the food items for which the additive is to be used by the amount of additive used. The daily intake of 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 gathered using other reliable methods, such as market basket surveys and production analysis, can also be used. The daily intake should be estimated for body weight of 50 kg.
> 2. The estimated daily intake should be compared with the ADI obtained from toxicological tests, and the results of such comparison should be examined. Where necessary, the safety of food additives should also be examined in cases where more than one item of the same kind of food additive, etc. is simultaneously consumed. This can be done by comparing the sum of estimated daily intake to the group ADI, or by any other method.
> 3. 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.

There are generally three methods to estimate the daily intake of a food additive: (1) the method by multiplying the corresponding daily intakes of the individual food products that can contain the food additive by the corresponding intended use levels of the additive, (2) the market basket method, and (3) the method based on production statistics survey (production statistics-based). These methods are outlined below.

(1) The method based on the daily intakes of individual food products and the intended use levels of the additive

The daily intake of the food additive is estimated from the daily intake (I) of food product “f” and the concentration (C) of food additive “x” by the formula:

$$\text{Estimated daily intake of food additive} = \sum_{f=1}^{F} (I_f \times C_{xf})$$

In the formula, F is the total number of food products in which the food additive “x” can be contained.

C_{xf} is the concentration of the food additive "x" in the food product "f". Thus, [estimated daily intake of food additive] = sum of [intake of a food product containing the food additive] × [food additive concentration in the food product].

In Japan, the daily intake of food products is released at the MHLW website as result of the national health and nutrition survey.

[REFERENCE]

The Codex estimates the theoretical maximum daily intake (TMDI) whenever a reference value exists for food additive concentration in food products, and recommends a method of employing the estimated daily intake (EDI) when the TMDI exceeds the ADI.

The TMDI is calculated by multiplying the average per capita daily food consumption for each food product by the maximum use standard level of the food additive established by respective national regulations or internationally, and summing up the resulting values. The TMDI does not take into consideration food consumption by a particular group of population, and therefore should preferably be considered a rough index pertaining to food additive intake. The TMDI calculation assumes the following items:

a) All food products permitted to contain the food additive are cumulative.
b) Food additives are always present at their maximum permitted amount.
c) Food products containing the food additive are consumed at their daily average value per capita.
d) Food additive content does not decrease according to preparation or processing technology.
e) All food products permitted to contain the food additives are consumed and not disposed of.

The EDI is an estimate of the amount of a food additive ingested daily by the average food consumer, and derived by a) actual use concentrations of the food additive by industry or b) the nearest possible value to actual use concentrations whenever the minimum necessary use of food additive is authorized under appropriate manufacture and quality control in conformance with Good Manufacturing Practices.

Reference 1: Guidelines for simple evaluation of food additive intake CAC/GL 03-1989[1]
Reference 2: FDA Guidance for Industry: Estimating Dietary Intake of Substances in Food[2]

(2) The market basket method

This method determines dietary intakes of food additives by purchasing food products distributed on the marketplace, measuring amounts of food additives contained therein, and multiplying the obtained values by

[1] www.codexalimentarius.org/input/download/standards/6/cxg_003e.pdf

[2] http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#ftn1

the amounts of food ingested. Results of MHLW's intake surveys by this method are released to the public at the website.

The method is used in estimating the current intake at the time of the amendment to the use standards, and in estimating an intake at the time of designation request under the assumption that food additives with an identical purpose are replaced with the subject food additive.

(3) Method based on production statistics survey

The results of production statistics survey compiled by the MHLW (surveys by questionnaire method to food additive manufacturers and import distributors in Japan to estimate food additive shipments and distribution) are released to the public.

The method is used in estimating the current intake at the time of the amendment to the use standards, and in estimating an intake at the time of designation request under the assumption that food additives with an identical purpose are replaced with the subject food additive.

Notes

· If maximum use concentrations in individual food products are established in the use standards, the estimation should be based on the method by multiplying the daily intake of each product in which the subject additive is to be used by the amount of the additive used, as a general rule.

· If subject food products in which the additive can be used are increased, applicants should estimate not only the current intake of the additive, but also the increment of the intake with the revised standards.

· The assessment guideline by the FSCJ has noted that the daily intake should be estimated assuming that the body weight is 50 kg. However, based on the FSCJ decision of March 31, 2014 on the change of the average body weight used for evaluation of the effects of foods on human health—食品健康影響評価に用いる平均体重の変更について—the body weight used for estimation of the daily intake should be 55.1 kg instead of 50 kg.

4.2 Examples of description

(Examples of description)

(1) The estimation based on the daily intakes of individual food products and the intended use levels of the additive

Estimated daily intake of sugar and advantame as estimated from intake by food group (total count) from 2008 national health and nutrition survey results (partial excerpt)

Food Products	Intake of food products (g)	Estimated sucrose intake (g)	Addition of advantame (ppm)	Estimated advantame intake (mg)	(mg/kg body wt./day)
Bread (excl. sweet fine bakery products)	30.7	1.842	3.00	0.09	0.00184
Sweet fine bakery products	5.7	1.425	12.50	0.07	0.00143
Sugars, sweeteners	6.7	6.633	49.50	0.34	0.00670
Leafy vegetable pickles	5.1	0.2244	2.20	0.01	0.00022
Takuan (radish), other pickles	9.5	0.855	4.50	0.04	0.00086
Jams	1.2	0.6	25.00	0.03	0.00060
Fruit juice, fruit drinks	10.0	0.5	2.50	0.03	0.00050
Fish, shellfish (preserved)	0.3	0.03	5.00	0.00	0.00003
Fish, shellfish (paste products)	9.8	0.196	1.00	0.01	0.00020
Fish ham, fish sausage	0.6	0.00996	0.83	0.00	0.00001
Ham, sausage	11.0	0.11	0.50	0.01	0.00011
Fermented milk, lactic acid bacteria beverage	19.9	2.189	5.50	0.11	0.00219
Other dairy products	6.6	0.132	1.00	0.01	0.00013
Japanese confections	12.4	3.1	12.50	0.16	0.00310
Cakes, pastries	6.5	2.275	18.00	0.12	0.00234
Biscuits, cookies	1.7	0.425	12.50	0.02	0.00043
Candies	0.3	0.3	50.00	0.02	0.00030
Other confections	5.8	1.45	12.50	0.07	0.00145
Coffee, cocoa	118.8	3.564	3.10	0.37	0.00737
Other preference drinks	81.2	5.684	9.40	0.76	0.01527
Sauces	1.9	0.19	5.00	0.01	0.00019
Mayonnaise	2.8	0.056	1.00	0.00	0.00006
Other seasonings	61.4	3.07	2.50	0.15	0.00307

Total	409.9	34.86		2.42	0.0484

(2) The market basket- and production statistics-based estimations (Calcium saccharate)

Calcium saccharate is used as a sweetener, the same as saccharin and sodium saccharate, which are designated additives. The substance is similar in physicochemical properties to the sodium salt. It is considered appropriate that the substance is evaluated as a compound categorized in the same group as saccharin and sodium saccharate in terms of safety. Thus, the use standards (draft) are set similarly to for sodium saccharate as described previously. The maximum use amount is expressed as the sum of the respective amounts of this substance and sodium saccharate for each authorized food product. Consequently, the daily intake should be estimated based on the intake as saccharin.

Current Saccharin Intake According to MHLW Surveys

Saccharin is a synthetic chemical substance not present in nature. Saccharin intake according to market basket method presents intake of saccharin and sodium saccharate consumed by people as used in food products. Daily intake per capita ranged from 0.5 to 1 mg between 1982 and 1994. After a high value of 2.88 mg indicated for 1997, the number dropped to 0.65 mg in 2002 and 0.18 mg in 2006, and the overall trend is downward. This decreasing trend is believed to reflect the market launch in recent years of new sweeteners, both synthetic and of natural origin, and the advancement of saccharin substitution.

According to the production amount survey of the additive method, the reported daily intake per capita in survey years 1998 and 2001 was respectively 3.70 mg and 2.68 mg for sodium saccharate and 0.0015 mg and 0.0015 mg for saccharin (Ref. X). These values are higher than the aforesaid values by market basket method. The difference might occurred due to the estimation obtained from the usage of food additive as well as the other product such as pharmaceuticals based on the production survey of the additive. The 0.18 mg/day per capita, which is the latest data by the market basket method above, is equivalent to approximately 0.07% of JECFA ADI 5 mg/kg body wt./day (for 50 kg body weight).

* This example used 50 kg for body weight as this was cited from past application. Notes in this section should be referenced for preparation of documentation.

IV. Guidelines for drafting specifications

As specifications, establish items required to assure a certain level of quality concerning safety and effectiveness of the subject food additive from the following 18 items.

(a) Name
(b) English name and alternative English name
(c) Alternative Japanese name
(d) Structural or rational formula
(e) Molecular formula or molecular weight
(f) Chemical name
(g) CAS registry number
(h) Definition
(i) Assay (Content) or enzyme activity
(j) Description
(k) Identification
(l) Specific properties
(m) Purity
(n) Loss on drying, loss on ignition, or water content
(o) Residue on ignition, ash, or acid-insoluble ash
(p) Microbial limit
(q) (Method of assay) or enzyme activity determination
(r) Storage standards

Notes to preparation of draft specifications

(a) Name

Establish the common name.

(b) English name and alternative English name

Establish an alternative English name when necessary for labeling.

(c) Alternative Japanese name

Establish an alternative Japanese name when necessary for labeling.

(d) Structural or rational formula

Refer to *the Japan's Specifications and Standards for Food Additives*, in the case of organic compounds.

(e) Molecular formula and molecular weight

Conform to the rules of *the Japan's Specifications and Standards for Food Additives*. For mixtures, provide the molecular formulas and molecular weights of the respective components included.

(f) Chemical name

Follow the International Union of Pure and Applied Chemistry (IUPAC) nomenclature system.

(g) CAS registry number

Enter the CAS registry number.

(h) Definition

Describe the origin, preparation method, essence, inclusions, etc., of the subject product. For a chemically synthesized food additive for which the essence cannot be specified by the chemical name alone, describe the raw materials used, an overview of the preparation method, or a composition of the components if necessary. Describe synthetic materials for chemically synthesized polymers.

For a food additive derived from animals or plants, extracts of microorganisms, minerals, or the like, the origin should be provided.

· As a general rule, express the species of the originating organism by the standard Japanese name and scientific name for animals or plants, and the scientific name for microorganisms. Cite the data (source or database) for foundation of the scientific name. Omit the family. When multiple species of the same genus are broadly used, or if the species under the genus is unidentified, denote up to the genus.

· As a rule of plant taxonomy, when the species is indicated, the variety, subspecies, and agricultural species (cultivated variety) are also included. Unless particularly necessary, variety, subspecies, and agricultural species (cultivated variety) below the species are not denoted.

· If two scientific names are used widely as synonyms and the listing of just one could invite misunderstanding, denote the synonym as well.

· If multiple Japanese names exist, select the standard Japanese name or name established within the taxonomy.

· The collective name used generally, though not a species, may be used as necessary for the name of flora or microorganisms.

Examples: grapes, beets, canola, Gram-positive bacteria, actinomycete, filamentous fungus, yeast

· If an appropriate Japanese name does not exist, make a decision for the individual case. For example, flora collected overseas and neither growing naturally nor cultivated in Japan has no established Japanese name in the taxonomy.

(i) Assay (Content) or enzyme activity

Establish the content (assay) as the value necessary for assuring a consistent quality comparable in

safety and effectiveness, based on manufacturing processes, quantitative error, stability, and the like.

The content (assay) as a food additive is presented as a percentage of the effective ingredient(s). If two or more effective ingredients exist, they are denoted respectively.

Enzyme activity determination is listed for enzymes. Use the units established in the draft specifications whenever the quantity of main ingredients are represented under a certain biological action (titer).

(j) Description

As the items necessary for identification and handling at the time of use, ordinarily describe odor, color, and form. For substances with special forms, denote information pertaining to grain size, grain size distribution, and format.

(k) Identification

Identification tests are required to identify whether the substance is the target food additive, based on its characteristics.

If the food additive can be identified from items other than identification tests, these items can be included in consideration. For example, selecting chromatography with high specificity for the assay can allow simplification of identification tests. Duplicate tests do not need to be set forth.

Ordinarily, conceivable methods for identification are based on spectral analysis or chemical reaction. For any chemical reaction, establish one that can appropriately identify the characteristics of the chemical structure.

(l) Specific properties

Specific properties are expressed as analytical values measured according to physicochemical methods, such as absorbance (specific absorbance), congealing point, refraction index, rotation (specific rotation), viscosity (dynamic viscosity), pH, specific gravity, boiling point, melting point, acid value, saponification number, ester value, hydroxyl value, iodine value, etc. Provide the items necessary to secure quality.

(m) Purity

Purity tests are required to determine levels of impurities in the food additive, and specify the purity of the food additive as well as assay. Among substances that may be contained in the food additive (raw materials, intermediates, by-products, decomposition products, reagents and catalysts, heavy metals and inorganic salts, and solvents), target the necessary ones.

Whenever methods are established under *General Tests* of *the Japan's Specifications and Standards for Food Additives*, use the testing methods as a general rule.

For newly developed testing methods or a modification of any standard testing methods, explain the reasons for inapplicability of the general testing methods provided in *the Japan's Specifications and Standards for Food Additives*, and describe the testing methods applied in detail and provide verification

data of the methods.

Specifications for lead and arsenic are established as a general rule. If not established, describe the grounds in the Section, "Grounds for establishing the draft specifications." Establish specifications for respective harmful elements as necessary, such as cadmium and mercury.

(n) Loss on drying, loss on ignition, or water content

A test for loss on drying is usually required to measure substances that are present in the food additive and can be lost by drying. The substances include free water, all or part of the crystalline water, and volatile substances. A test for loss on ignition is usually required on an inorganic substance that can lose a part of its components or admixed substances by igniting. Water determination is usually required to determine the water content in the food additive.

(o) Residue on ignition, ash, or acid-insoluble ash

Residue on ignition refers to the residual substance obtained when the food additive is ignited in the presence of a small quantity of sulfuric acid. Ordinarily, the test is conducted to learn the amount of inorganic matter contained as impurities in organic matter. In some cases, the test is conducted to measure the amount of constituent inorganic matter in organic matter or the amount of impurities contained in inorganic matter that volatilize when heated.

Ash is the residual substance obtained when the food additive is ignited. Acid-insoluble ash is the residual substance obtained when ash is boiled with diluted hydrochloric acid (1 in 4) and then the resulting insoluble matter is ignited. The testing is established for additives originating from animals, plants, or microorganisms, as necessary, to learn the amount of inorganic matter contained as impurities in organic matter.

(p) Microbial limit

Establishes limits of bacteria, fungi (mold and yeast), *Salmonella*, *Escherichia coli*, etc. with proliferation ability present in the food additives. Microbial limit tests shall be conducted according to the methods given under *General Test*s of *the Japan's Specifications and Standards for Food Additives*.

(q) Method of assay or enzyme activity determination

An (Method of assay) refers to an analysis to determine the amount of an effective ingredient according to physical, chemical, or biological methods.

Establish a testing method with emphasis placed on accuracy, reproducibility, and specificity. If the limit of admixed material is controlled by an appropriate purity test, a method able to measure absolute amounts with good reproducibility can be established, even if the method presents low specificity. In such a case, employ a purity test method with high specificity to complement the lack of specificity for the assay method. If there are 2 or more components subject to the assay, denote them in the sequence of importance.

For a relative test method like chromatography, establish specifications for the standard substance used in the assay.

Enzyme activity determination measures specific activity of enzymes. Establish a test method with emphasis on substrate specificity. Use the units specified in the corresponding monographs, whenever the enzyme activity is represented by titer.

For establishing new testing methods or applying modified standard testing methods for assay or enzyme activity determination, describe the testing methods in detail and provide verification data of the testing.

(r) Storage standards

Set this item for cases that require particular mention about stability.

V. Examples of findings regarding effectiveness

Example 1. Polysorbate (excerpt from the Report of the Committee on Food Additives Concerning Food Additive Designation) (Japan)

(1) Characteristics as an Emulsifier

Emulsifiers are substances that have a hydrophilic group and lipophilic group in each molecule. Arrayed between water and oil or between water and air, they facilitate emulsification and stabilize mixtures. There are two types of emulsifiers: the O/W type with oil droplets in water and the W/O type with water droplets in oil. As O/W emulsifiers, polysorbates are strongly hydrophilic and have an HLB[*1], the index of the balance between hydrophilic and lipophilic groups, ranging from 10 to 17. Many conventional emulsifiers have a low or medium HLB with high lipophilicity. Sucrose fatty acid esters and glycerin fatty acid esters can be used to prepare emulsifiers with a wide HLB range by respectively varying their degree of esterification or glycerin polymerization, and the type of fatty acid. Nonetheless, it is thought to be difficult to obtain an HLB as high as a polysorbate. HLBs for polysorbates and other emulsifiers are compiled in the following table. (Ref. X)

Name	HLB
Polysorbates	10 -17[a)]
Fatty acid monoglyceride	3 - 4
Sucrose fatty acid esters	3 - 15
Sorbian fatty acid ester	2 - 8
propylene glycol fatty acid ester	3 - 4
Vegetable lecithin	-

[a)] Polysorbate 20: 16.7; Polysorbate 60: 14.9;
Polysorbate 65: 10.5; Polysorbate 80: 15.0

(2) Emulsifying Power Test for O/W Systems

For a blend of 50 g soy oil and 450 g tap water with no emulsifier as control segment, test segments were prepared by adding 5 g each of the emulsifiers provided in the table, such as polysorbate 60 or glycerin fatty acid ester, to either soy oil or tap water. Soy oil, water, and emulsifier (test segment) were then emulsified with a TK Homo Mixer at 60˚C, 10,000 rpm for 5 minutes. The emulsion was transferred to an emulsion test tube and left to stand at room temperature. The amount of separation to the oil layer was measured over time. The test segment employing polysorbate 60 did not result in observation of any oil flotation after 24 hours; however, glycerin fatty acid ester and lecithin caused gelation and uneven emulsification, while

[*1] HLB (Hydrophilic-Lipophilic Balance): The Value shows the degree of affinity to oil and water and takes 0 to 20. Lipophilic property becomes higher as it approaches 0 and hydrophilic property becomes higher as it approaches 20.

sorbitan fatty acid ester and propylene glycol fatty acid ester resulted in 100% oil flotation after 24 hours. Oil droplets were present after 24 hours for sucrose fatty acid ester, demonstrating insufficient emulsifying power. (Ref. X)

Emulsifier	The amount of separation to the oil layer				Addition method	HLB
	0.5h	1h	2h	24h		
None	100%	100%	100%	100%	-	-
Polysorbate 60	0%	0%	0%	0%	Add to soy oil	14.9
Glycerin fatty acid ester	Gelatinization	Gelatinization	Gelatinization	Gelatinization	Add to soy oil	3.8
Sucrose fatty acid esters	0%	0%	0%	0%[a)]	Add to water	11
Sorbian fatty acid ester	100%	100%	100%	100%	Add to soy oil	4.7
propylene glycol fatty acid ester	10%	40%	60%	100%	Add to soy oil	3.4
Lecithin	Gelatinization	Gelatinization	Gelatinization	Gelatinization	Add to soy oil	-

[a)] Oil droplets on its surface

Example 2. Calcium Silicate (excerpt from the Report of the Committee on Food Additives Concerning Food Additive Designation) (Japan)

(1) Fundamental Properties

a. Formability

A mixture (400 mg) of aspirin granules with enteric coating, excipient, and disintegrator at a weight ratio of 1:2:1 was made into a tablet (tableting pressure 100 MPa) to measure the tableting pressure necessary for obtaining a tablet with a hardness of approximately 5 kgf. Consequently, the use of calcium silicate as excipient was found to afford the lowest tableting pressure and to exhibit favorable formability. (Ref. X)

Excipient	Hardness（kgf）	Tableting pressure（MPa）
Calcium silicate	5.9±0.17	6.8±0.07
Synthetic hydrotalcite	6.0±0.28	46.9±0.06
Crystalline cellulose	5.2±0.21	49.9±0.05
Magnesium aluminometasilicate	5.4±0.14	56.2±0.12
Dried aluminum hydroxide gel	5.5±0.32	74.7±0.23
Cornstarch	5.0±0.58	100.5±0.05

Table 1. The tableting pressure necessary for obtaining a tablet with a hardness of approximately 5 kgf.

b. Liquid absorption

Dibutyl phthalate was used as oily substance in the measurement of liquid volume absorbed by calcium silicate and other excipients (three kinds of silicate, crystalline cellulose, cornstarch, and calcium monohydrogen phosphate) according to the method provided by JIS K-6220, 26 (1977). The liquid absorption volume of calcium silicate was approximately 7 times its own weight and exhibited liquid retention capacity of approximately 4 to 14 times more than the other excipients, except for light anhydrous silicic acid. (Ref. X)

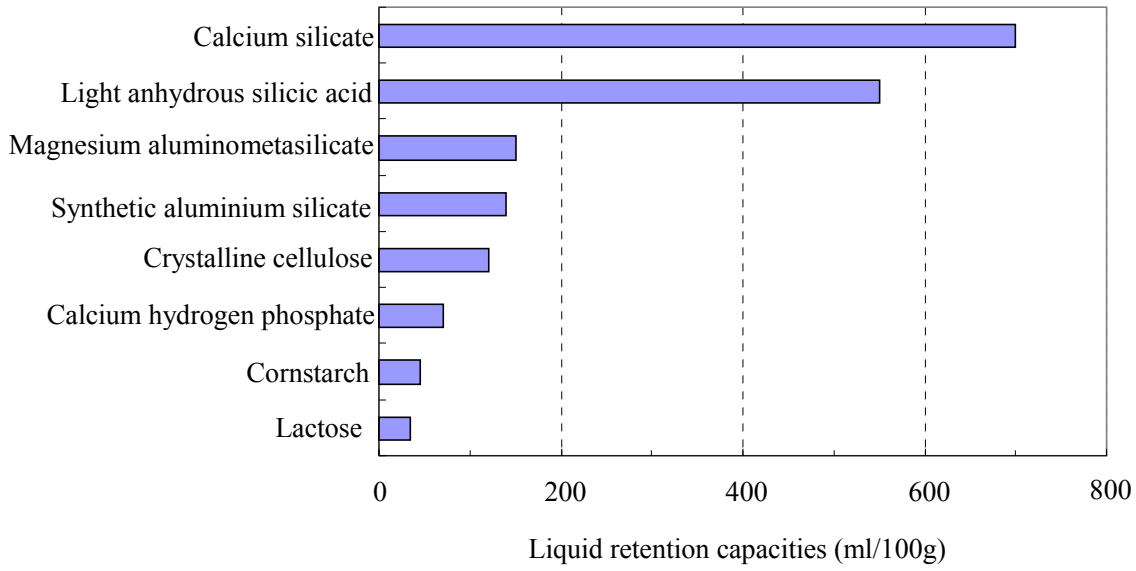


Figure 1. Liquid retention capacities of calcium silicate and the other excipients

(2) Use in Food Products

In the United States, the product is employed as an anti-caking agent in powdered drinks such as iced tea, creamed soup, and cocoa, flavorings such as pork spice, cinnamon, and pork gravy, and sweeteners such as cane sugar and aspartame (Ref. X). In Japan, its properties of oil absorption and formability lend the product to use as an excipient for formulations of vitamin E (which is fat-soluble) as powders, granules, or tablets in the field of pharmaceuticals (Ref. X).

Example 3. Neotame (excerpt from the Report of the Committee on Food Additives Concerning Food Additive Designation) (Japan)

(1) Sweetness

The sweetness of neotame was assessed by sugar-equivalent sweetness (Reference 1). Aqueous neotame solutions with various concentrations (2, 4, 9, 20, 40 ppm) were prepared. Sweetness was assessed according to organoleptic testing, and represented by sugar solution concentrations (sugar-equivalent sweetness: %SE) offering comparable sweetness.

The results are shown in Figure 1 as a sugar-equivalent sweetness curve plotted against neotame concentration. According to the fitted curve, the concentration of neotame that provided the same sweetness as 8% sugar (8% SE) was 10.3 ppm.

Comparison of the sweetness between neotame and sugar (Table 1) revealed that the sweetness of neotame was approximately 7,000 to 13,000 times greater than that of sugar.

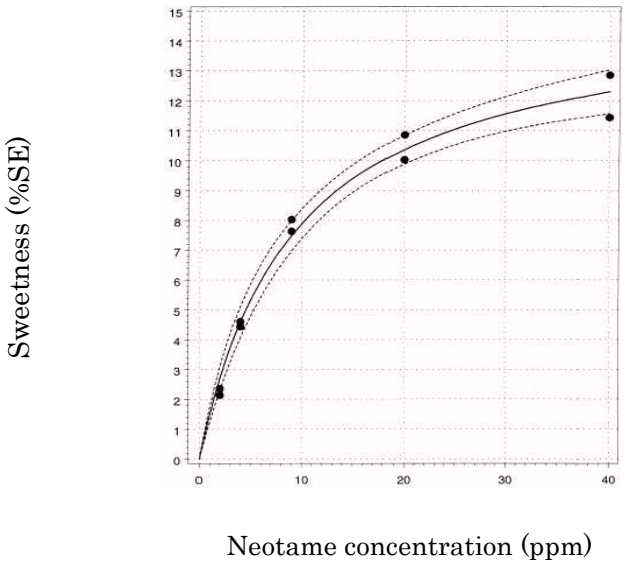


Figure 1. The sugar-equivalent sweetness curve of neotame

● : Measured values ——— : A fitted curve --- : 95% confidence limits

The fitted curve:

$$\text{Sweetness (\%SE)} = \frac{\text{Rmax}}{1/K \times 1/C + 1} = \frac{15.1}{9.18 \times 1/C + 1}$$

Rmax : maximum sweetness (%SE), 1/K : The concentration provided the degree of one half of the maximum sweetness (ppm), C : Concentration (ppm)

Table 1. Comparison of the sweetness between neotame and sugar

Sweetness (%SE)	Sweetness magnification (Sugar / Neotame)
3	13181
4	12092
5	11002
6	9913
7	8824
8	7734
9	6645

(2) Stability

A long-term storage testing (25˚C, 60% RH, 260 weeks) found that neotame was almost stable in the full test period of 260 weeks in terms of items/parameters, including properties and content (Reference 2).

The stability of neotame in solution is affected by pH and temperature. Neotame is relatively stable between the pH range of 3 to 5.5, but becomes more susceptible to hydrolysis at pH3 and below and at 5.5 and above, and as the temperature rises (Reference 6). The half-life of neotame at pH 4.5 was about 30 weeks at 25˚C, about 45 days at 40˚C, and about 40 hours at 80˚C. At pH 7, the half-life was about 2 weeks at 25˚C, about 3 days at 40˚C, and about 4 hours at 80˚C.

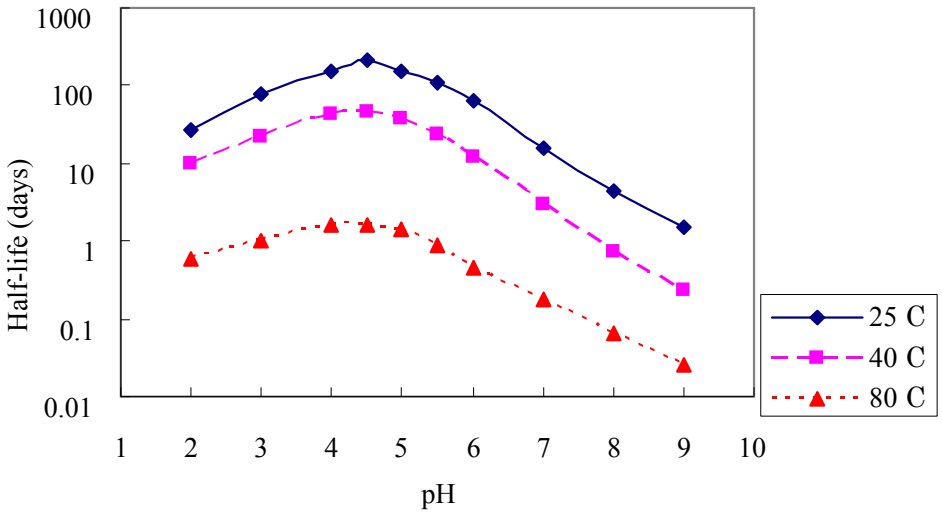


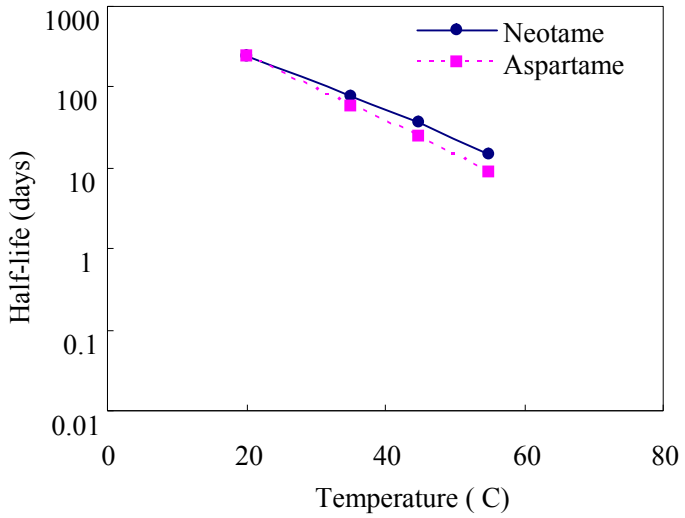
Figure 2. The effects of pH and temperature on the stability of neotame

The report regarding neotame stability compared to aspartame and regarding stability in food products was as follows.

Stability Comparison to Aspartame

The comparison of half-life between neotame and aspartame at pH 3.2 and pH 7 is shown below. Under the described conditions, the half-life of neotame was longer. Neotame can be considered as or more stable than aspartame.

(a) pH 3.2



(b) pH 7

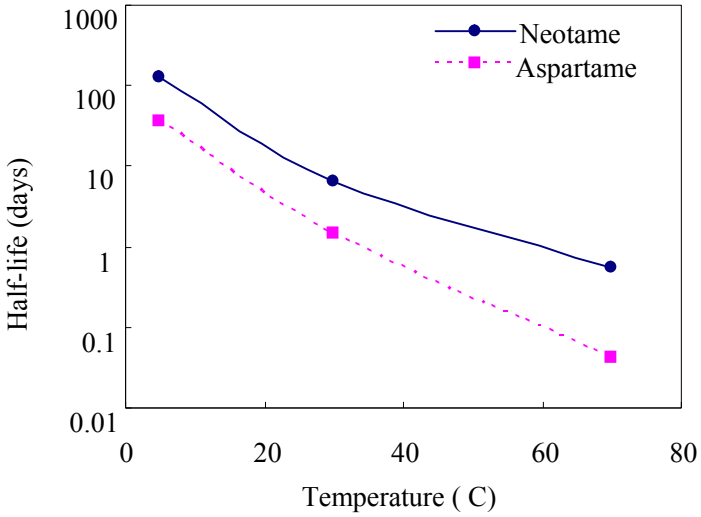


Figure 3. The comparison of half-life between neotame and aspartame

a. Thermal stability

Neotame (25 ppm) and aspartame (500 ppm) were respectively added to milk (1% fat, pH 6.5). After the respective mixtures were homogenized, they were subjected to UHT[*1] processing for 8 seconds at 142˚C. The sweetener content both before and after UHT processing was analyzed to study the impact of UHT processing of milk on neotame stability. The residual ratios of neotame and aspartame after UHT processing were 91.0% and 69.0%, respectively (Reference 3).

The stability of neotame (25 ppm) and aspartame (525 ppm) after HTST[*2] processing for 40 seconds at 85 C was also compared during yogurt manufacture operation. The residual ratios of neotame and aspartame after HTST processing were 98.7% and 89.5%, respectively (Reference 4).

The heat resistance of neotame (35 ppm) and aspartame (about 2,700 ppm) was also compared during a baking process of yellow cake. The residual ratios of neotame and aspartame were 85.1% and 59.3%, respectively (Reference 5).

[*1] UHT: Ultra-high temperature pasteurization (Ministerial ordinance on Milk and Milk products Concerning Compositional Standards, etc. sets this method of pasteurizing more than one second and less than three seconds between 120 C and 150 C using continuous ultrahigh-temperature sterilizer with automatic control device.)

[*2] HTST: High-temperature short-time pasteurization (Ministerial ordinance on Milk and Milk products Concerning Compositional Standards, etc. sets this method of pasteurizing 15 seconds or more at 72 C or more using continuous ultrahigh-temperature and short-time sterilizer with automatic control device.)

b. Resistance property for fermentation

The stability of neotame and aspartame was compared during a fermentation process of yogurt (for 6 hours at 40 C). The residual ratios of neotame and aspartame during the fermentation process were 87.9% and 56.0%, respectively (Reference 4).

c. Preservation stability

After refrigerating 8 weeks of yogurt, the stability of neotame and aspartame was favorable without decrease (Reference 3).

After 5 days storage of yellowcake at 25 C and 60% RH, the residual ratios of neotame and aspartame were 94.6% and 83.9%, respectively (Reference 5).

Production / storage	Food	sweetener	pH	temperature	Relative humidity	time	Concentration at early phase		Concentration after processing		Residue ratio of sweetness[b)] (%)
							ppm	%SE[a)]	ppm	%SE[a)]	
UHT processing	Milk[c)] (1%fat)	Neotame	6.5	142 C	-	8 seconds	25.0	11.0	22.8	10.8	97.4
		Aspartame	6.5	142 C	-	8 seconds	500.0	7.7	345.0	6.1	80.2
HTST processing	Yogurt[d)] (milk)	Neotame	6.5	85 C	-	40 seconds	24.0	10.9	23.7	10.9	99.6
		Aspartame	6.5	85 C	-	40 seconds	519.0	7.8	464.5	7.3	94.0
baking	Yellow cake[e)]	Neotame	-	177 C	-	30 minutes	35.1	12.0	29.9	11.5	96.5
		Aspartame	-	177 C	-	30 minutes	2624.7	13.8	1556.1	12.2	88.5
fermentation	Yogurt[c)]	Neotame	-	40 C	-	6 hours	23.7	10.9	20.8	10.5	96.3
		Aspartame	-	40 C	-	6 hours	464.5	7.3	260.3	5.1	69.2
storage	Yellow cake[e)]	Neotame	-	25 C	60%	5 days	29.9	11.5	28.3	11.4	98.7
		Aspartame	-	25 C	60%	5 days	1556.1	12.2	1306.0	11.6	94.9
storage	Yogurt[d)]	Neotame	4.4	5 C	-	8 weeks	20.8	10.5	20.8	10.5	100.0
		Aspartame	4.4	5 C	-	8 weeks	260.3	5.1	254.0	5.0	98.3

[a)] The values were calculated using the concentration of neotame or aspartame (A ppm) and the following formula (sugar-equivalent sweetness curve (Reference 2)).

$$\text{Sugar-equivalent sweetness of neotame (\%SE)} = \frac{15.1}{9.18 \times 1/A+1}$$

$$\text{Sugar-equivalent sweetness of aspartame (\%SE)} = \frac{17.1}{610 \times 1/A+1}$$

[b)] Residual ratio of sweetness (%) = the sweetness after processing (%SE) / the sweetness at early phase (%SE) x 100

[c)] Reference 5

[d)] Reference 6

[e)] Reference 7

Above results actually applied to foods indicates that neotame can be considered as or more stable than

aspartame, analogical sweetener.

The stability and chronological change of sweetness in carbonated drink

A Coca-Cola type carbonated drink containing 17 ppm of neotame (approximately pH3.2) was prepared and stored 26 weeks at 25±2 C. The change of neotame content during preservation period was measured. The chronological change of sweetness was also evaluated using organoleptic test (Reference 7).

The residual concentration after 8weeks was 12.2 ppm (72% of early phase), and 5.9 ppm (35%) after 26 weeks. The sweetness was maintained through 22 weeks (the final residual concentration of neotame was 41% of early phase).

Resolvents from a carbonated drink (200 ppm) after preservation for 8 weeks at 20 C were N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine(NC-00751), N-[N-(3,3-dimethylbutyl)-L-β-aspartyl]-L- phenylalanine 1-methyl ester (NC-00764), N-[N-(3,3-dimethylbutyl)-L-aspartimide]-L-phenylalanine 1-methyl ester (NC-00777） and N-[N-(3,3-dimethylbutyl)-L- aspartimide]-L- phenylalanine （NC-00779）.

The stability and chronological change of sweetness in black tea

Black tea containing 8 ppm of neotame (approximately pH3.2) was prepared and stored 26 weeks at 25±2 C. The change of neotame content during preservation period was measured. The chronological change of sweetness was also evaluated using organoleptic test (Reference 8).

The residual concentration after 8weeks was 6.14 ppm (77% of early phase), and 4.09 ppm (52%) after 26 weeks. The half-life period was estimated to be week 31. At sweetness judgment after 26 weeks storage, 71% of inspectors judged the sweetness was weak or not enough. The sweetness was maintained until approximately week 25.

The stability and chronological change of sweetness in chewing gum

A chewing gum containing 250 ppm of neotame was prepared and stored 26 weeks at 25±2 C and 60±5% RH. The change of neotame content in week 0, 4, 8, 16 and 26, respectively, was measured. The chronological change of sweetness was also evaluated using organoleptic test (Reference 9). (Table 2)

The residual ratio after 26 weeks was 43% of early phase. The half-life period of neotame in chewing gum was estimated to be week 21.3. At organoleptic test after 26 weeks storage, 80% of inspectors judged the chewing gum has enough sweetness.

Table 2 Chronological change of amount of neotame in chewing gum (0 ~ 26 weeks storage)

	0 week	4 weeks	8 weeks	16 weeks	26 weeks
Neotame (ppm)	242.7[a)]	222.2[b)]	192.0[b)]	149.9[b)]	103.5[b)]
Residual ratio of neotame (%)	100	92	79	62	43
Sweetness equivalence to sugar (% SE)	14.5	14.5	14.4	14.2	13.9

[a)] Average of repeated 18 times storage [b)] Average of repeated 6 times storage

With above results, it is reported that neotame retains its sweetness for certain period although influenced from pH and temperature and resolves over time.

Example 4. Sodium carboxymethylcellulose (CMC) (excerpt from safety evaluation)
(Australia and New Zealand)

3.1 Technological justification

3.1.1 Use of the additive in wine and sparkling wine

The Application requests an extension of use of CMC to enable it to be used in wine and sparkling wine production as an additional tool for preventing clouding and sediment formation resulting from the precipitation of tartrate crystals during storage. Tartrate occurs naturally in wine and is mainly in the potassium form however calcium tartrate can also be present. As a result of change in storage temperature during transport tartrate can crystallize in wine resulting in cloudy wine with sediment which is undesirable to many consumers. Current methods used in Australia to control tartrate crystallization in wine can be divided into two categories: 1) encouraging and accelerating crystal growth followed by removing the crystals by filtering 2) inhibiting crystal precipitation.

The Application explains that the additive works by inhibiting crystal growth in wine. The additive acts as a protective colloid which prevents tartrate crystals seeding and subsequently precipitating. CMC is added to the wine towards the end of the production process unlike other existing tartrate crystal control methods chilling or filtration steps are not required.

Information provided by the applicant states that in contrast to metatartaric acid the effectiveness of this additive is temperature insensitive and thus crystal stability is obtained even with temperature fluctuations, such as those which occur during storage and transport. However other currently available methods for tartrate crystal control need to be retained as under certain circumstances e.g. for high quality wine, wine which is strongly saturated with tartrate or wines with high levels of calcium tartrate the existing methods may be more suitable.

A maximum use level of 100 mg/L is proposed in the application. Information provided with the application, namely results of tests to investigate the degree of tartrate crystal precipitation overtime is deemed sufficient by FSANZ to demonstrate that the use of CMC at this proposed level is effective.

3.1.2 Evidence of the effectiveness of the additive in wine

The Applicant stated that the additive has been trialled by several major companies, including in Australia, and has provided information to show increased stability of wines treated with CMC compared with untreated or metatartic acid treated wine.

Storage of additive treated wine at 17^0C for 10 months followed by storage at -4^0C for 8 days did not result in visual evidence of crystal precipitation. This test is an OIV accepted method to test the stability of tartrate crystals. In addition storage of additive treated wine at 17^0C for 10 months followed by checking the difference in conductivity by means of the minicontact process, showed the additive treated wine had a low difference in

conductivity compared with untreated (Control) or metatartaric acid treated wine. The Applicant provided a paper which stated that low difference in conductivity means high stability with respect to tartrate. This information was provided by the Applicant to demonstrate stability of the wine treated with additive over time.

3.1.3 Cost and environmental advantages

As indicated in Section 3.1.1 above use of CMC for tartrate crystal control does not involve chilling or filtration step, both of which are energy dependent. The Applicant explains that the absence of these steps in wine production utilising CMC results in a more cost effective process with environmental advantages over other existing methods of control.

VI. A list of URLs

Institute	Type of information	URL
MHLW	Uses and use standards	http://www.ffcr.or.jp/zaidan/FFCRHOME.nsf/pages/stanrd.use
	Daily intake of food products (result of the national health and nutrition survey)	http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html
	Survey of daily intake of food additives (the market basket method)	http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/shokuhin/syokuten/sesshu/
FSCJ	Evaluation results	https://www.fsc.go.jp/english/evaluationreports/additives_e3.html
Codex	INS number and uses (technological purposes) (Class names and the International Numbering System for food additives (CAC/GL 36-1989))	http://www.codexalimentarius.org/download/standards/13341/CXG_036e_2014.pdf
	INS number and use standards (GSFA (CODEX STAN 192-1995))	http://www.codexalimentarius.net/gsfaonline/docs/CXS_192e.pdf
	INS number, uses and use standards (GSFA online)	http://www.codexalimentarius.net/gsfaonline/index.html?lang=en
JECFA	Evaluation results (TRS and FAS)	http://www.who.int/foodsafety/publications/jecfa-reports/en/ (TRS) http://www.who.int/foodsafety/publications/monographs/en/ (FAS)
	Specifications	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/

EU	Authorization status and use standards (Food Additives Database)	https://webgate.ec.europa.eu/sanco_foods/main/?event=substances.search&substances.pagination=1
	Evaluation results (Scientific Opinion (Evaluation of EFSA))	http://www.efsa.europa.eu/
	Evaluation results (Opinion (Evaluation of SCF))	http://ec.europa.eu/food/fs/sc/scf/reports_en.html
	Specifications	http://ec.europa.eu/food/food/fAEF/additives/specifications_en.htm
The United States	Authorization status and use standards (21 CFR)	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
	Authorization status and use standards (GRAS Notice Inventory)	http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing
	Evaluation results (SCOGS list)	http://www.accessdata.fda.gov/scripts/fdcc/?set=SCOGS
	Evaluation results (NTIS website)	http://www.ntis.gov/
	Freedom of Information request to FDA	http://www.fda.gov/regulatoryinformation/foi/default.htm
	Specifications (FCC) (*pay services)	http://www.usp.org/store/products-services/food-chemicals-codex-fcc
Australia and New Zealand	Authorization status and use standards (Food Standards Code)	http://www.foodstandards.gov.au/code/Pages/default.aspx
	Evaluation results (Approval Report)	http://www.foodstandards.gov.au/code/applications/Pages/default.aspx
IPCS	Evaluation results (INCHEM)	http://www.inchem.org/

(Appendix 1)

Designation

Date

Minister of Health, Labour and Welfare

Address of applicant (For a corporation, principal place of business)
Name of applicant (For a corporation, its name and the representative's name)

I/We hereby apply for the designation of the substance given below, based on Article 12 of the Food Sanitation Act, as a food additive unlikely to cause damage to human health.

Name of the substance

(Notes)
1. Use JIS A4-size paper.
2. Use black ink, and type in clear block letters in Japanese.
3. Give the contact information in Japan, if the applicant lives overseas.

(Appendix 2)

Revision of standards

Date

Minister of Health, Labour and Welfare

Address of applicant (For a corporation, principal place of business)
Name (For a corporation, its name and the representative's)

I/We hereby apply for partial revision of the specifications/standards for food additives, as given below, based on Article 13 Paragraph 1 of the Food Sanitation Act.

Name of the food additive
Draft revision of specifications/standards

(Notes)
1. Use JIS A4-size paper.
2. Use black ink, and type in clear block letters in Japanese.
3. Give the contact information in Japan, if the applicant lives overseas.

(Appendix 3)

Date

The Overview Documentation should be in Japanese.

The Overview Documentation of XXX (the name of a food additive)

Corporate name

Table of contents

I. Overview of the food additive

1. Name and uses

(1) Name

(2) CAS registry number.

(3) Uses

2. Origin or details of development

3. Use status in other countries

4. Assessments by national and international organizations

5. Physicochemical properties

(1) Structural formula

(i) Structural or rational formula

(ii) Molecular formula or molecular weight

(2) Manufacturing method

(3) Specifications

(i) Draft specifications 以下表　修正案 (エクセル file) あり

Items		Specifications	Ref. Spec.
(a) Japanese Name			
(b) English Name			
(c)	Alternative English Names		
	Alternative Japanese Name		
(d) Structural Formula			
(e) Molecular or Compositional Formula			
Molecular or Formula			

Weight		
(f) Chemical Name		
(g) CAS Registry Number.		
(h) Definition		
(i) Assay(Content) or Enzyme Activity		
(j) Description		
(k) Identification	(1)	
	(2)	
(l) (Specific Properties)		
(m) Purity	(1)	
	(2)	
(n) Loss on Drying, Loss on Ignition or Water Content		
(o) Residue on Ignition, Ash, or Acid-insoluble Ash		
(p) Microbial Limit		
(q) Method of Assay or Enzyme Activity Determination		
(r) Storage Standards		
Reference specifications 1 : 2 : 3 : 4 :		

(ii) Comparison table of draft and existing specifications

(iii) Grounds for establishing the draft specifications.

(iv) Verification data of test methods and test results.

(4) Stability of the food additive

(5) Analytical methods of the food additive in food products

6. Draft of use standards

(1) Draft of use standards

(2) Grounds for establishing the draft of use standards

7. Other

II. Findings regarding effectiveness

(1) Efficacy as food additives and comparison with other similar food additives

(2) Stability in food products

(3) Effects on nutritional component in food products

III. Findings regarding safety

1. Disposition studies

2. Toxicological studies

(1) Subchronic toxicity studies and chronic toxicity studies

(2) Carcinogenicity studies

(3) Toxicity/carcinogenicity combination studies with one-year repeated-dose administration

(4) Reproductive toxicity studies

(5) Prenatal developmental toxicity studies

(6) Genotoxicity studies

Index	Type of test	Target of test	Test substance	Dosage	Summary of the test result	Ref No.
Geneticmutations						
Chromosomal aberration						

(7) Allergenic potential studies

(8) General pharmacological studies

(9) Other studies

3. Findings in humans

4. Estimation of daily intake

IV. References

(Appendix 4)

Checklist

1. Type of application

□	Designation
□	Revision of use standards
□	Revision of specifications
□	Other ( )

2. Applicant information

Name (corporate name,)		
Address		
Contact person	Affiliation	
	Name	
Telephone No.		
FAX No.		
E-mail		

3. Food additive information

Name of the food additive		
Intended uses		
CODEX standards (GSFA, etc.) (Place a checkmark in "Yes" for the additive listed in table 3 of GSFA)	□ Presence	□ Absence
Evaluation by international organizations (JECFA, etc.)	□ Presence	□ Absence
Available evaluation by FSCJ (including evaluations other than as a food additive)	□ Presence	□ Absence
Is the additive broken down in the food or in the digestive tract to common food components by?	□ Yes	□ No

4. Information on submission materials

(1) Overview of the food additive subject to evaluation

Use status in foreign countries	□ Presence	□ Absence
Assessments by international and national organizations	□ Presence	□ Absence
Manufacturing methods	□ Presence	□ Absence
Draft specifications (including grounds for the establishment)	□ Presence	□ Absence

Stability of the food additive	□ Presence	□ Absence
Analytical methods of the food additive in food products	□ Presence	□ Absence
Draft use standards (including grounds for the establishment)	□ Presence	□ Absence

(2) Findings regarding effectiveness

Effectiveness as food additive and comparison with other similar food additives	□ Presence	□ Absence
Stability in food products	□ Presence	□ Absence
Effects on nutritional components in food products	□ Presence	□ Absence

(3) Findings regarding safety

Data on disposition studies	□ Presence	□ Absence
Data on subchronic and chronic toxicity studies	□ Presence	□ Absence
Data on carcinogenicity studies	□ Presence	□ Absence
Data on combined one-year toxicity/carcinogenicity studies	□ Presence	□ Absence
Data on reproductive toxicity studies	□ Presence	□ Absence
Data on prenatal developmental toxicity studies	□ Presence	□ Absence
Data on genotoxicity studies	□ Presence	□ Absence
Data on allergenic potential studies	□ Presence	□ Absence
Data on general pharmacological studies	□ Presence	□ Absence
Data on other studies	□ Presence	□ Absence
Data on findings in humans	□ Presence	□ Absence
Presence or absence of new findings obtained after the publication of FSCJ evaluation results (Place a checkmark only when FSCJ evaluation results are available)	□ Presence	□ Absence
Estimation of daily intake	□ Presence	□ Absence