(1) The calculation by multiplying the daily intake of the food items for which the additives to be used by the amount of additive used

The formula for estimating daily intake of the food additive from the daily intake (I) of food products subjected to be used "f" and concentration (C) of food additive "x" is shown as follows:

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

In the formula above, F is the total count of food products with the possibility of containing food additive "x". $C_{xf}$ is the concentration of food additive "x" in food product "f". Thus, [estimated daily intake of food additive] = sum of [intake of food products containing the food additive] × [food additive concentration in the food product].

The daily intake of food products subjected to be used is released as the national health and nutrition survey conducted by the Ministry of Health, Labour and Welfare (MHLW).

· National health and nutrition survey:
http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html
http://www.mhlw.go.jp/english/wp/wp-hw3/dl/2-064_065.pdf

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 daily food product consumption per capita of each food product by the maximum use standards value established for the food product in a respective nation's regulations or internationally, and summing up the resulting values. The TMDI does not consider 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 daily food additive intake by an average food product consumer, and derived by a) actual usage concentrations of the food additive in industry or b) the nearest possible value to actual usage concentrations whenever the minimum necessary usage 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-
www.codexalimentarius.org/input/download/standards/6/cxg_003e.pdf
Reference 2: FDA Guidance for Industry: Estimating Dietary Intake of Substances in Food
http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#ftn1

(2) The market basket method

This method determines the intake of food additives by purchasing food products sold at supermarkets or the like, measuring the amount of food additives contained therein, and multiplying the result by the amount of food ingested. Results of the market basket method conducted by the MHLW are released to the public.

The method is used in cases of amendments to use standards for estimating current intake, and for estimating intake under assumption of replacement of a food additive with an identical purpose at the time of designation request.

· Daily intake surveys of food additives by age bracket according to the market basket method
http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/shokuhin/syokuten/sesshu/

(3) Method according to production amount survey of the additive

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

The method is used in cases of amendments to use standards for estimating current intake, and for estimating intake under assumption of replacement of a food additive with an identical purpose at the time of designation request.

(Examples of description)

① The calculation by multiplying the daily intake of the food items for which the additives to be used by the amount of additive used

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 Product | Intake of food product (g) | Estimated sucrose intake (g) | Advantame addition (ppm) | Estimated advantame intake (mg) | (mg/kg body wt./day) |
|---|---|---|---|---|---|
| Bread (excl. confectionary bread) | 30.7 | 1.842 | 3.00 | 0.09 | 0.00184 |
| Confectionary bread | 5.7 | 1.425 | 12.50 | 0.07 | 0.00143 |
| Sugars, sweeteners | 6.7 | 6.633 | 49.50 | 0.34 | 0.00670 |

| | | | | | |
|---|---|---|---|---|---|
| Leaf pickles | 5.1 | 0.2244 | 2.20 | 0.01 | 0.00022 |
| *Takuan*, 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 |
| Hard candy | 0.3 | 0.3 | 50.00 | 0.02 | 0.00030 |
| Other candy | 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 method and the method of according to production amount survey of the additive

The usage of calcium saccharate is for usage as a sweetener in the same manner as the controlled additive saccharin and sodium saccharate. The physicochemical properties of calcium saccharate are categorically similar to the sodium salt, and evaluation as a group compound of saccharin and sodium saccharate is considered appropriate from a safety perspective. Thus, the use standards (draft) shall be the same as sodium saccharate as described previously. The maximum usage amount is indicated as a total amount together with sodium saccharate for the authorized food products. Consequently, estimation of the daily intake based on current saccharin intake is appropriate.

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 cause of the difference relates to the possibility of shipments as food additives in the method according to production amount survey of the additive, but actual usage other than food product purpose. 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).

iv Draft specifications

In the draft specifications, for the items among ① to ⑱ concerning safety and effectiveness of the subject food additive, establish requirements to assure a certain level of quality

① Name
② English name and other English name
③ Other Japanese name
④ Structural or rational formula
⑤ Molecular or compositional formula, molecular or formula weight
⑥ Chemical name
⑦ CAS (Chemical Abstracts Service) registry number
⑧ Definition
⑨ Content (Assay) or enzyme activity determination
⑩ Description
⑪ Identification
⑫ Specific properties
⑬ Purity
⑭ Loss on drying, loss on ignition, or water content
⑮ Residue on ignition, ash, or acid-insoluble ash
⑯ Microbial limit
⑰ Assay (Method of assay) or enzyme activity determination
⑱ Storage standard

Notes to preparation of content draft specifications

① Name
Establish the common name.

② English name and other English name
Establish other English name when necessary for labeling.

③ Other Japanese name
Establish when necessary for labeling.

④ Structural or rational formula
Refer to *the Japan's Specifications and Standards for Food Additives*, in the case of organic compounds.

⑤ Molecular or compositional formula, molecular weight (formula weight)
Describe in conformance 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 contents.

⑥ Chemical name
According to International Union of Pure and Applied Chemistry (IUPAC) nomenclature system.

⑦ CAS registry number

Enter the CAS registry number.

⑧ Definition

Describe the origin, preparation method, essence, inclusions, etc., of the subject product. For the chemically synthesized additive which essence cannot be specified by chemical name alone, describe the raw materials, overview of preparation method, or composition of contents if necessary. Describe synthetic materials for high polymer compounds chemically synthesized.

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

- As a general rule, present the standard Japanese name and scientific name of the species for the originating organism 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.

⑨ Content (Assay) or enzyme activity determination

Establish the content (assay) as the value necessary for assuring a consistent quality comparable between safety and effectiveness, based on manufacturing processes, quantitative error, stability, and the like.

The content (assay) for 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 of the food additive, whenever the quantity of main ingredients of additives in the draft specifications are represented under a certain biological action or titer.

⑩ Description

As the items necessary in recognizing 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.

⑪ Identification

Identification is required to testing 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 those listed under identification, these can be included in consideration. For example, selecting chromatography, which has high specificity, for the assay can allow simplification of identification. Moreover, duplicate details do not need to be set forth in the draft specifications.

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.

⑫ Specific properties

Specific properties are analytical values measured according to physicochemical methods, such as absorbance (specific absorbance), freezing 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.

⑬ Purity

Purity is required to determine levels of impurities in the food additive, and specify the purity of the food additive as well as assay. Among substances mixed together 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 testing is established among general testing methods of *the Japan's Specifications and Standards for Food Additives*, use those testing methods as a general rule.

For newly developed testing methods or modified usage 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 in detail and provide verification data of the testing.

Specifications for lead and arsenic are established as a general rule. If deemed unnecessary, describe the grounds within the section for the grounds for establishing the draft specifications. Establish specifications for respective harmful elements as necessary, such as cadmium and mercury.

⑭ Loss on drying, loss on ignition, or water content

A test for loss on drying is usually required to measure substances that is 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.

⑮ Residue on ignition, ash, or acid-insoluble ash

Residue on ignition refers to the remainder after addition of a small quantity of sulfuric acid to, and ignition of the additive. Ordinarily, the test is conducted to learn the amount of inorganic matter contained

as impurity in organic matter. In some cases, analysis is conducted to measure the amount of constituent inorganic matter in the organic matter, or the amount of impurity contained in inorganic matter that volatilizes when heated.

Ash content is the remainder of the additive upon direct ignition. Acid-insoluble ash content is the remainder of ash content obtained upon ignition of insoluble matter after addition and boiling with hydrochloric acid (1 → 4). Testing is ordinarily conducted to learn the amount of inorganic matter contained as impurity in the organic matter, and established for additives originating from animals, plants, or microorganisms as necessary.

⑯ Microbial limit

Establishes limits to bacteria, fungi (mold and yeast), *Salmonella*, *Escherichia coli*, etc. with proliferating ability present in the additives. Microbiology limit shall be conducted according to the tests listed in the general testing methods of *the Japan's Specifications and Standards for Food Additives*.

⑰ Assay (Method of assay) or enzyme activity determination

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

Establish testing with emphasis placed on accuracy, reproducibility, and specificity. If the limit of admixed material is controlled by an appropriate purity test, establish testing that measures absolute amounts with good reproducibility, even if such testing presents a method of low specificity. In such a case, employ a purity test method with high specificity for the portion concerning specificity. These tests must thus complement each other. 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 the test method with emphasis on substrate specificity. Use the units established in the content specification draft, whenever the enzyme activity is represented by titer.

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

⑱ Storage standards

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

New designation

(Appendix 1)

Date

Minister of Health, Labor and Welfare

Address of applicant (For a corporation, principal place of business)

Name (Name and name of its representative in case of a corporation) Seal

I hereby apply for the designation of the following food additive having no risk to human health based on Article 10 of the Food Sanitation Act

(Name of the food additive)

(Notes)

1. Use JIS A4-size paper
2. Use "SUMI," black ink and other like, and type clearly in English or Japanese
3. Give the contact information in Japan, if the applicant lives overseas. Seal may be replaced by the applicant's signature.

Revision of use standards

(Appendix 2)

Date

Minister of Health, Labor and Welfare

Address of applicant (For a corporation, principal place of business)
Name (Name and name of its representative in case of a corporation) Seal

I hereby apply for the revision of a part of specification standards for food additives based on Article 11 (1) of the Food Sanitation Act

(Name of the food additive or a proposed draft for amendments of specification standards)

(Notes)

1. Use JIS A4-size paper
2. Use "SUMI," black ink and other like, and type clearly in English or Japanese
3. Give the contact information in Japan, if the applicant lives overseas. Seal may be replaced by the applicant's signature.

(Appendix 3)

Date

# Accompanying documentation of （the name of a food additive)

Corporate name

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1. Name and usage

2. Origin or details of development

3. Usage in other countries (Use status in foreign countries)

4. Assessments by international organizations and other organizations

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(1) Structural formula

(2) Manufacturing method

(3) Specifications

(4) Safety of food additive

(5) Analytical methods of food additive in food products

(6) Draft of use standards

(7) Other

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2. Toxicological studies

(1) Subchronic toxicity studies and chronic toxicity studies

(2) Carcinogenicity studies

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(4) Reproductive toxicity studies

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(6) Genotoxicity studies

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(8) General pharmacological studies

(9) Other studies

3. Findings in humans

4. Estimation of daily intake

IV. References

I. Overview of the food additive subject to evaluation

1. Name and usage

(1) Name

(2) CAS (Chemical Abstracts Service) registry number.

(3) Usage

2. Origin or details of development

3. Usage in other countries (Use status in foreign countries)

4. Assessments by international organizations and other organizations

5. Physicochemical properties

(1) Structural formula

①Structural or rational formula

②Molecular or compositional formula, molecular weight

(2) Manufacturing method

(3) Specifications

① Draft specifications

| Items | Specifications | Ref. Std. |
|---|---|---|
| ① Japanese Name | | |
| ② English Name | | |
| Other English Name | | |
| ③ Other Japanese Name | | |
| ④ Structural Formula | | |
| ⑤ Molecular or Compositional Formula | | |

| | | |
|---|---|---|
| Molecular or Formula weight | | |
| ⑥ Chemical Name | | |
| ⑦ CAS Registry Number. | | |
| ⑧ Definition | | |
| ⑨ Content (Assay) or Enzyme Activity | | |
| ⑩ Description | | |
| ⑪ Identification | (1) | |
| | (2) | |
| ⑫ (Specific properties) | | |
| ⑬ Purity | (1) | |
| | (2) | |
| ⑭ Loss on Drying, Loss on Ignition or Water Content | | |
| ⑮ Residue on Ignition, Ash, or Acid-insoluble Ash | | |
| ⑯ Microbial Limit | | |
| ⑰ Assay or Enzyme Activity Determination | | |
| ⑱ Storage Standards | | |
| Reference specifications<br>1 :<br>2 :<br>3 :<br>4 : | | |

② Comparison table of draft specifications and existing specifications.

③ Grounds for establishing the draft specifications.

④ 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

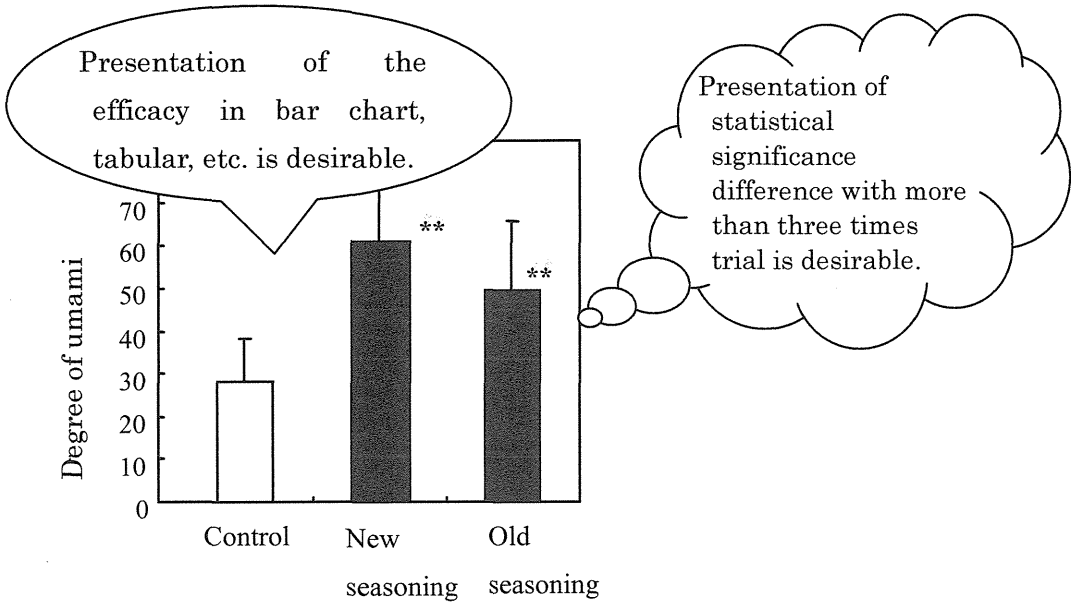
(1) Draft of use standards

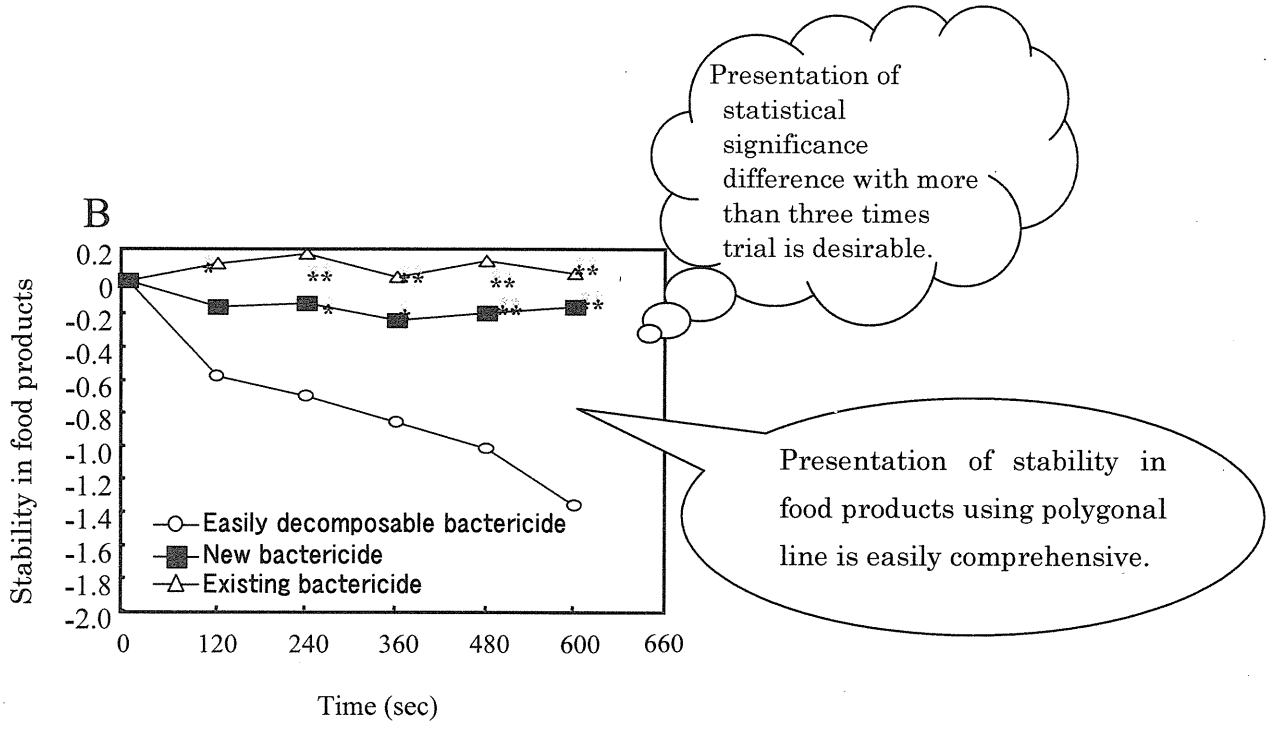
(2) Grounds for establishing the draft of use standards

7. Other

II. Findings regarding effectiveness

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

Enter whether corresponded to GLP.

For positive test and *in vitro*, enter the all dosages.

| Index | Type of test | Target of test | Test substance | Dosage | Summary of the test result | Ref No. |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Genetic mutations | reverse mutation assay *(in vitro*, unclear whether corresponded to GLP) | Bacteria (S.typhimurium TA98,TA100) | β-apo-8'-carotenal | Highest dose 0.8 μmol/plate | Negative (Presence or non-presence of metabolic activities) | Azuine et al. (1992) (Reference) |
| 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

| | |
|---|---|
| □ | New designation |
| □ | Revision of use standards |
| □ | Revision of specifications |
| □ | Other ( ) |

2. Applicant information

| | | |
|---|---|---|
| Name (corporate name, or the like) | | |
| Address | | |
| Contact person | Section | |
| | Name | |
| Telephone No. | | |
| FAX No. | | |
| E-mail | | |

3. Food additive information

| | | |
|---|---|---|
| Name of the food additive | | |
| Intended use | | |
| CODEX standard (GSFA, etc.)<br>(Place a checkmark in "Yes" if the additive listed in table 3 of GSFA) | □ Yes | □ No |
| Evaluation results at International Institutions (JECFA, etc.) | □ Yes | □ No |
| Available evaluation results by FSCJ (including evaluations other than as a food additive) | □ Yes | □ No |
| The additive is to be an identical substance as a common component of food by broken down in food or in the digestive tract? | □ Yes | □ N/A |

4. Information on submission materials

(1) Overview of the food additive subject to evaluation

| | | |
|---|---|---|
| Descriptions of usage in other countries (Use status in foreign countries) | □ Yes | □ No |
| Descriptions of assessments by international organizations and other organizations | □ Yes | □ No |
| Descriptions of manufacturing method | □ Yes | □ No |
| Descriptions of draft specifications (including grounds for the establishment) | □ Yes | □ No |
| Descriptions of stability of the food additive | □ Yes | □ No |
| Descriptions of analytical methods of the food additive in food products | □ Yes | □ No |
| Descriptions of draft of use standards (including grounds for the establishment) | □ Yes | □ No |

(3) Findings regarding effectiveness

| | | |
|---|---|---|
| Descriptions of effectiveness as food additives and comparison with other similar food additives | □ Yes | □ No |
| Descriptions of stability in food products | □ Yes | □ No |
| Descriptions of effects on nutritional component in food products | □ Yes | □ No |

(4) Findings regarding safety

| | | |
|---|---|---|
| Descriptions of data on disposition studies | □ Yes | □ No |
| Descriptions of data on subchronic toxicity studies and chronic toxicity studies | □ Yes | □ No |
| Descriptions of data on carcinogenicity studies | □ Yes | □ No |
| Descriptions of data on toxicity/carcinogenicity combination studies with one-year repeated-dose administration | □ Yes | □ No |
| Descriptions of data on reproductive toxicity studies | □ Yes | □ No |
| Descriptions of data on prenatal developmental toxicity studies | □ Yes | □ No |
| Descriptions of data on genotoxicity studies | □ Yes | □ No |
| Descriptions of data on allergenic potential studies | □ Yes | □ No |
| Descriptions of data on general pharmacological studies | □ Yes | □ No |
| Descriptions of data on other studies | □ Yes | □ No |
| Descriptions of data on findings in humans | □ Yes | □ No |
| Descriptions of presence or non-presence of new findings after public announcement of evaluation results by FSCJ | □ Yes | □ No |

| | | |
|---|---|---|
| (Place a checkmark only when applicants have evaluation results by FSCJ) | | |
| Descriptions of estimation of daily intake | □ Yes | □ No |