Guidelines for Notification of Foods with Function Claims

Established on March 30, 2015 (CFL* Notification No. 141)
Revised on March 31, 2016 (CFL Notification No. 234)
Revised on December 27, 2017 (CFL Notification No. 634)
Revised on March 28, 2018 (CFL Notification No. 156)
Revised on March 26, 2019 (CFL Notification No. 126)
Revised on July 1, 2019 (CFL Notification No. 131)
Revised on April 1, 2020 (CFL Notification No. 123)
Revised on November 30, 2020 (CFL Notification No. 459)
Revised on March 22, 2021 (CFL Notification No. 120)
Revised on April 1, 2022 (CFL Notification No. 136)

* CFL; Food Labeling Division, Consumer Affairs Agency

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The chapters in grey are not translated into English.

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I Purpose

Foods with function claims are foods for which a food-related business operator has notified the Commissioner of the Consumer Affairs Agency (CAA) that the food is expected to provide the specific health benefits indicated on the label under the food-related business operator's responsibility, based on certain scientific evidence regarding safety and functionality as stipulated in Article 2, Paragraph 1, Item 10 of the Food Labeling Standards (Cabinet Office Ordinance No. 10 of 2015) under Article 4, Paragraph 1 of the Food Labeling Act (Act No. 70 of 2013). It should be noted that "foods with function claims" differ from "foods for specified health uses" in that they do not undergo individual review by the CAA Commissioner for scientific evidence. In order for the Food with Function Claims System (hereinafter referred to as "the System") to contribute to consumers' voluntary and rational food selection, it is important to ensure that the scientific evidence necessary for assuring safety and functional claim labeling is provided and that adequate information is provided to consumers through appropriate labeling.

In light of these perspectives, this Guideline has been established to provide a guide for food-related business operators when filing a notification for a food with function claims, with the aim of promoting the appropriate operation of this System. In addition to this Guideline, when filing a notification, please refer to "Questions and Answers on Foods with Function Claims" (CFL Notification No. 463, dated September 29, 2017), "Major Considerations Concerning Advertisements of Foods with Function Claims" (published on June 19, 2015), "Considerations Concerning Health Foods under the Act against Unjustifiable Premiums and Misleading Presentations and the Health Promotion Act" (published on June 30, 2016), "Guidelines for Ensuring Transparency of Ex Post Facto Regulations (Ex Post Facto Checks) Based on Laws and Regulations Concerning Food Labeling, etc., for Foods with Function Claims" (Notification No. 518 of Representation Division, CAA/CFL Notification No. 81, dated March 24, 2020), and other guidelines issued by the CAA. Should you have any further questions regarding the preparation of the notification materials, please contact the Food Labeling Division of the CAA.

Because the current system is based on a completely different concept from the previous functional labeling system, in which the food-related business operators are responsible for labeling functionality based on scientific evidence, the contents of this Guideline shall be reviewed in consideration of the implementation status of the System, and if deemed necessary, measures shall be taken as required based on the results of the review.

II Applicable foods

This System covers all food products (excluding some). In this Guideline, as necessary, food products are divided into the following three categories: processed foods in the form of supplements, processed foods other than processed foods in the form of

supplements (hereinafter referred to as "other processed foods"), and perishable foods. Processed foods in the form of supplements are, for the purpose of this System's operation, foods in the form of tablets, capsules, powders, liquids, and so forth, made from naturally occurring extracts that are fractionated, purified, chemically reacted, or otherwise different in composition from those naturally occurring or made from chemically synthesized products. However, since some tablets, powders, and liquids are consumed without being recognized as supplements by the general population and excessive intake of such foods is unlikely to occur considering their recommended daily intake, foods for which there are reasonable grounds for not causing health hazards may be treated as other processed foods, not as processed foods in the form of supplements. Foods in the capsule form shall be treated as processed foods in the form of supplements.

IV Approach to the preparation of documents

(I) General introduction

Section 1 What are foods with function claims?

Foods with function claims refer to foods that meet the following requirements from 1 to 4, as stipulated in Article 2, Paragraph 1, Item 10 of the Food Labeling Standards.

1. Foods intended for persons not suffering from a disease (excluding minors, pregnant women [including those who are planning to become pregnant], and lactating mothers).
   For the purpose of this Guideline, persons not suffering from a disease are defined as those with symptoms of borderline or lower severity. For example, persons with a disease whose severity is assessed as more than mild, based on diagnostic criteria, are not included.
   Specifically, the following persons are included in this population:
   (i) Persons who are classified as not having the disease based on widely agreed-upon diagnostic criteria for the disease, which are used in official statistics to classify the presence or absence of the disease (this definition appears to be applicable to major lifestyle-related diseases).
   (ii) In cases where the definition in (i) is not necessarily applicable, persons who are found to be free of disease as determined by a physician (preferably a specialist in the relevant field) are included in this population.
   It is not prohibited for persons suffering from a disease, minors, pregnant women (including those who are planning to become pregnant), and lactating mothers to purchase foods with function claims or to sell such foods to these persons.

2. Foods that are labeled on the container or packaging with a statement, based on scientific evidence, that specific health benefits contributing to the maintenance and promotion of health (excluding those related to the reduction of the risk of disease) can be expected from their functional substances.

The basic concept of functional substances and their scientific grounds is as follows:

(1) Functional substances

Functional substances are defined as substances that contribute to specific health-related purposes (excluding those related to the reduction of the risk of disease). The concept of these substances is as follows:

[1] Substances for which the mechanism of action for the proposed functionality has been discussed in *in vitro* and *in vivo* studies or clinical (human) studies[1] and for which direct or indirect qualitative and quantitative validation can be performed.

However, when the functional substance is an "extract[2] and secretion" (hereinafter referred to as "extract, etc.") for which a specific substance that can explain a part of the scientific grounds of functionality has been identified, but the functionality cannot be explained entirely by that specific substance alone, the mechanism of action for the proposed functionality must have been discussed in *in vitro* and *in vivo* studies or clinical (human) studies for at least one indicator substance[3], and the qualitative and quantitative identification of the indicator substance as well as the qualitative identification of the extract, etc. as a whole must be conducted.

Extracts shall be derived from a single plant. The extracts of fungi (including protozoa) and plant extracts to which fermentation or other processing by fungi (including protozoa) has been added are excluded from the scope.

A. The evaluation of the mechanism of action is essentially based on the collection of existing information, and the method of information collection is not required to be a research review (i.e., a systematic literature review, the same applies hereinafter). However, if sufficient information cannot be obtained from the existing information, testing should be conducted.
B. Examples of substances that can be qualitatively and quantitatively identified are summarized in Appendix 1-1.

[2] Substances listed in the first column of Appendix Table 9 of the Food Labeling Standards, including nutrients for which reference intakes have been established in the Dietary Reference Intake (DRI) stipulated by the Minister of Health, Labour and Welfare under Article 16-2, Paragraph 1 of the Health Promotion Act (Act No. 103 of 2002), are excluded from the scope. However, the

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[1] "Clinical (human) studies" in this Guideline refers to "studies in humans" as defined in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (CFL Notice of the Deputy Commissioner of the Consumer Affairs Agency No. 259, dated October 30, 2014).
Note that the World Health Organization (WHO) defines "clinical studies" as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".

[2] An extract is an extracted and concentrated formulation of a base ingredient.
(Reference) "Guidance on the Application for Marketing Approval of Herbal Extract Preparations" (Notification No. 1225 No. 6, dated December 25, 2015)

[3] An indicator substance is a specific substance contained in an extract, etc. that can be identified qualitatively and quantitatively and is used as an indicator to ensure the equivalence of the functional substances.

components of the nutrients listed in the table below may be considered as applicable substances in consideration of the differences in their actions from the said nutrients.
Carbohydrates and sugars, excluding those that are considered to be the main nutritional source (energy source), such as glucose, fructose, galactose, lactose, maltose, starch, may also be considered as applicable substances.

Table Components of nutrients that may be considered as applicable substances

Nutrients for which reference intakes have been established in the DRI	Example components of the nutrients listed on the left that may be considered as applicable substances
Proteins	Amino acids and peptides
n-6 fatty acids	γ-Linolenic acid, arachidonic acid
n-3 fatty acids	α-Linolenic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)
Carbohydrates	Xylitol, erythritol, fructo-oligosaccharide, xylooligosaccharide, galacto-oligosaccharide, lactooligosaccharide (lactosucrose)
Sugars	L-arabinose, palatinose, lactulose
Dietary fiber	Indigestible dextrin, guar gum degradation products
Vitamin A	Provitamin A carotenoid (β-carotene, α-carotene, β-cryptoxanthin)

(2) Scientific evidence

The level of scientific evidence required for foods with function claims must fully take into account the intentions of Japanese consumers and scientific viewpoints and must not mislead consumers while contributing to their voluntary and rational selection of foods. From this perspective, scientific evidence must be explained based on the methods necessary for ensuring safety and functionality labeling as indicated in this Guideline.
With regard to safety, information on eating experience should be evaluated. If the information on eating experience is not sufficient to ensure safety, information from safety studies should be evaluated. In addition, the presence or absence of interactions between the functional substance and pharmaceutical products and, in cases where multiple functional substances are included, the presence or absence of interactions between these substances should be evaluated.
Functionality should be explained by conducting clinical (human) studies using the final product or by reviewing research on the final product or the functional substance.

3. All food products except the following:
   - Foods for special dietary uses and foods with nutrient function claims
   - Alcohol-containing beverages[4]
   - Foods that lead to excessive intake[5] of the nutrients specified in Article 11, Paragraph 2 of the Enforcement Regulations for the Health Promotion Act (Ordinance of Ministry of Health, Labour and Welfare, No. 86 of 2003) as those whose excessive intake affects the maintenance and promotion of people's health in light of the nutritional intake status of the people (e.g., fats, saturated fatty acids, cholesterol, sugar [only monosaccharides or disaccharides that are not sugar alcohols], sodium)[6]

4. Foods for which the content of the labeling; basic information on the food-related business operator, such as their name and contact information; information on the evidence for safety and functionality; information on the production, manufacturing, and quality control; system for collecting information on health hazards; and other necessary information are notified to the Commissioner of the CAA at least 60 days prior to the marketing date.

Section 2 Scope of allowable function claims

1. The labeling of expected health benefits (except for those related to the reduction of the risk of diseases) is permitted to the extent that it conveys that the product is useful or suitable for the maintenance and promotion of the health of persons not suffering from a disease (except for minors, pregnant women [including those who are planning to become pregnant], and lactating mothers)[7,8,9]. Examples of permissible labeling are listed below. When preparing notification materials, the notifier shall also review the information on pharmaceutical products and ensure that there is no risk of misidentification of the product as a pharmaceutical product as defined in Article 2 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Act No. 145 of 1960).

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[4] In light of the purpose of this System, it is also undesirable to include foods made from alcohol-containing beverages or foods containing alcohol (except for foods that are sufficiently heated [e.g., boiled] before consumption and are certain to not result in the ingestion of alcohol [e.g., *udon* noodles to which alcohol has been added to enhance shelf-life]).

[5] The term "excessive intake" refers to the intake of nutrients in excess of what is required, such as when the daily intake of a nutrient exceeds the target amount specified in the DRI due to its additional intake in the normal diet or its intake as a substitute for other nutrients of the same type, although it should be judged based on the characteristics of the food.

[6] In cases where carbohydrates or sugars are used as the functional substances and are contained as syrup together with glucose or fructose, which mainly serve as energy sources, precautions should be provided for their intake so as to not cause excessive intake of sugars.

[7] Medical terms such as "diagnosis", "prevention", "treatment", and "procedure" cannot be used.

[8] Expressions referring to specific parts of the body may be used as long as they relate to the maintenance and promotion of health.

[9] Examples of allowable function claims include expressions accepted for foods for specified health uses (except for those pertaining to the reduction of the risk of disease).

[1] A statement that the product is suitable for maintaining or helping to improve an easily measurable index of the physical condition[10]
[2] A statement that the product is suitable for maintaining or helping to improve the physiological and tissue functions of the body
[3] A statement that the product helps to improve the temporary changes in the physical condition (not ongoing or chronic) that can be perceived by the individual

2. Examples of expressions that are not permitted under the System may include the following:
[1] Expressions implying a therapeutic or preventive effect against a disease
(Examples) "for patients with diabetes mellitus", "for patients with hypertension"
[2] Expressions considered to be claiming intentional health enhancement beyond the scope of health maintenance and promotion
(Examples) "body building", "hair growth", "whitening"
[3] Expressions related to functionality that are not explained by scientific evidence
(Examples) Misleading expressions based on data on limited immune parameters as if the product has an effect on the body's overall immunity; expressions based solely on evidence explained in *in vitro* or *in vivo* studies; and expressions that are scientifically explained based on findings in *in vitro* or *in vivo* studies, such as an increase in antibodies, complement, or immune system cells, but their effects on the living body are unclear.

[10] Indices that have been well evaluated and widely accepted from medical and nutritional perspectives shall be used. Functional claims that can be evaluated only by subjective indices may be acceptable, but such indices should be validated in the Japanese population and be widely agreed upon in the academic community.

(V) Matters related to functionality

Section 1 Materials required to explain scientific evidence for the proposed functionality

When submitting a notification for a food with function claims, the applicant shall prepare any of the materials listed below to explain the scientific evidence for the proposed functionality[18].

(i) Clinical (human) studies using the final product
(ii) Research review on the final product or the functional substance

[18] When multiple functionalities are to be labeled for a single product or when it is intended to demonstrate that the proposed functionality is found in persons of various attributes, multiple materials of either (i) or (ii), or a combination of both, are acceptable. However, care should be taken to keep the combination to the minimum so that the description in the abstract for general consumers is not complicated and, as a result, not difficult for the general consumers to understand.

For foods with function claims, it is acceptable to claim functionality that can be evaluated only by subjective indices. Therefore, subjective indices may be used as evaluation indices in both (i) and (ii), provided that the indices are validated in the Japanese population and are widely agreed upon academically in the relevant field.
In both (i) and (ii), when evaluating the scientific evidence of functionality for an extract, etc., it is necessary to evaluate the specifications of the extract, etc. and the equivalence of the extract, etc. by pattern analysis or other methods for the food to be submitted for notification and the food used when the scientific evidence of functionality was obtained. Furthermore, if the food to be submitted for notification is in the form of a tablet or a capsule, it is necessary to evaluate the equivalence of the final product by disintegration and dissolution tests and to report the analysis results in an appropriate notification material (Appendix Form (III)-4). For (ii), if the evaluation of equivalence cannot be adequately conducted due to the unavailability of samples of the extract, etc. used when the scientific evidence for functionality was obtained, or due to any other reason, it is necessary to conduct a clinical (human) study on the final product to evaluate its functionality.
If a clinical (human) study or research review on the final product was conducted using a prototype of the product to be actually marketed (e.g., manufactured on a production line for small lots, not for mass production, although the manufacturing principles, etc., are the same), it is necessary to discuss in the notification materials that the two products are identical in their characteristics.
The person who conducts (i) or (ii) is not specified, but the notifier shall be responsible for the materials used for notification of the food with function claims.

Section 2 Conduct of clinical (human) studies using the final product and submission of materials

1 Notes on conducting a clinical (human) study using the final product

(1) Prior registration of the study protocol

For clinical (human) studies to be conducted in Japan, the protocol must be preregistered (before the first participant is enrolled) in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (for clinical [human] studies conducted overseas, this process may be substituted by registration in a database linked to WHO's International Clinical Trial Registry Platform [ICTRP]). It is desirable that all details of the protocol be disclosed at the time of preregistration in the UMIN-CTR. However, in consideration of concerns about the outflow of intellectual property, it is acceptable to disclose the details of the protocol after the preregistration but no later than 1 year after the planned end date of the study. It should be noted that the registration of the protocol details must be complete at the time of preregistration. It is particularly imperative to provide details of the following information at the time of preregistration: the study title, primary outcome endpoints, secondary outcome endpoints (if any), study design, interventions, eligibility (key inclusion and exclusion criteria for participants), target number of participants, research funding organization (funder), approval by an ethics review committee, and date of public release (desired date of release). It should also be noted that studies in

which substantial changes were made after preregistration to items pertaining to the demonstration of functionality (such as primary outcome endpoints, secondary outcome endpoints, study design, interventions, eligibility) cannot be used as scientific evidence for the functionality of the food with function claims.
For studies initiated (the first participant enrolled) within 1 year after the date of enactment of the Food Labeling Standards (March 31, 2016), the preregistration process may be omitted.
When the results of a clinical (human) study using the final product are used as scientific evidence for the functionality of the food with function claims, the registration code of the UMIN-CTR or that of the database linked to the WHO ICTRP shall be provided.

(2) Conduct of clinical (human) studies
The methods of conducting a clinical (human) study (excluding the approach to participant selection) shall, in principle, conform to the testing methods for foods for specified health uses as specified in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (excluding testing methods for standard reference type, labeling for disease risk reduction, and foods for specified health uses with conditions) (for clinical [human] studies whose protocol was approved by the Ethics Review Committee prior to the issuance of the said Notes, it is sufficient to comply with the previous notification for foods for specified health uses). However, the follow-up period required for foods for specified health uses may be omitted. In cases where it is possible to demonstrate functionality without using the test methods for foods for specified health uses as specified in the above notice, other scientifically rational test methods may be used.

Participants in a clinical (human) study shall, in principle, be selected from those who are not suffering from a disease (excluding minors, pregnant women, and lactating mothers), in light of the definition of foods with function claims and the intended consumers of the food. The definition of "persons not suffering from a disease" shall be based on [1] or [2] below [19,20]. Data from patients with diseases that are medically evident to be unrelated to the proposed functionality may be used.

[1] If there are diagnostic criteria for the disease that are widely agreed upon and are used in the official statistics to classify the presence or absence of the disease: Participants shall be selected from those who are classified as not having the disease based on the criteria (those meeting the diagnostic criteria [including those with mild symptoms] shall be included in the exclusion criteria). This definition is applicable, but not limited, to major lifestyle-related diseases.

[2] If the definition in [1] is not necessarily applicable
Participants shall be selected from those who are found to be disease-free through screening by a physician (preferably a specialist in the relevant field). In this case, the specific screening method must be clearly described in the paper (if the specific screening method is not clearly described in a published paper, it is sufficient if the screening method and the fact that the appropriateness of the screening method was confirmed by a physician [preferably a specialist in the relevant field] in an ex post facto manner are described in the notification materials). In the case of clinical (human) studies in sports or other fields in which only those persons who are clearly not suffering from a disease are included, screening by a physician is not mandatory.

For foods for which functionality cannot be expected from the content of the functional substance or the intake of the food containing the substance alone, but which can provide functionality when added to a specific diet, appropriate dietary management and dietary survey must be conducted before and during the clinical (human) study, and the methods and results of such management and survey must be reported in detail in the paper. In such cases, the content of the assumed meal must be clearly stated in the labeling of the functionality of the substance or food containing the substance to be notified to the Commissioner of the CAA (e.g., "This product contains △ mg of ○○ and helps people who consume about □ g/day of seafood [average intake for Japanese adults] to improve XX").

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[19] The use of data involving persons with mild symptoms shall be permitted on an exceptional basis only to the extent described in the testing methods for foods for specified health uses as specified in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (excluding testing methods for standard reference type, labeling for disease risk reduction, and foods for specified health uses with conditions).
Data from persons taking a pharmaceutical product or receiving dietary or exercise guidance by a health care professional shall be excluded (only to the extent that they are related to or affect the proposed functionality).

[20] In addition to the exception stated in footnote 19, when including labeling related to "allergic reactions in the nose and eyes", "medium- to long-term serum uric acid levels", or "increased serum uric acid levels after meals" to indicate that health benefits can be expected, data involving persons with mild symptoms shall be permitted for use on an exceptional basis only to the extent described in Appendix 2.

(3) Documents to be submitted regarding clinical (human) studies
The following [1] to [3] shall be submitted.

[1] Peer-reviewed papers on clinical (human) studies
Papers that were prepared in a format that conforms to the international consensus guidelines so that the results of clinical (human) studies can be appropriately evaluated by anyone (at the time of implementation of this Guideline, these include CONSORT 2010 statement for randomized parallel-group studies [see Appendix 3], although these should in principle be based on the most recent version of the international guidelines) and published as peer-reviewed papers (including papers that have been accepted after peer review and are pending for publication [e.g., in press]; after publication, the published paper should be submitted promptly) shall be submitted. These papers must include a statement that the protocol has received prior approval from the ethics review committee and the name of the ethics review committee. If this information is not included in the paper, it should be provided in Attachment (V)-3, "Supplementary explanatory material on scientific evidence for the proposed functionality", and attached to the material. In addition to this, if a scientifically rational test method different from that for foods for specified health uses was selected, the rationale for the selection shall be provided in Attachment (V)-2.
It is important that the journal in which the paper is published does not have any conflict-of-interest issues with the author(s). For this reason, papers published in journals that may have conflict-of-interest issues shall not be used as scientific evidence for the functionality of a food with function claims.
Papers presenting the results of clinical (human) studies shall be submitted to journals that ensure high transparency of the peer-review process by, for example, disclosing their review policies and standard review period. In addition, the paper should clearly and transparently provide information on the sponsor and co-sponsor of the clinical (human) study (the individual company, research institution, or any other entity responsible for all or any of the conception, administration, and funding of the study) and any conflicts of interest.
For studies initiated (the first participant enrolled) within 1 year after the date of enactment of the Food Labeling Standards (March 31, 2016), it shall be acceptable to report the results in a format that is not compliant with the international guidelines.
If the paper is written in English, it is not always necessary to attach a Japanese translation. If the paper is written in a non-Japanese language other than English, an appropriate translation of the entire paper in correct Japanese must be attached along with the original.
[2] Checklist for scientific evidence of functionality

For materials to be submitted regarding clinical (human) studies, it is desirable to conduct a self-inspection using Attachment (V)-1, "Checklist for scientific evidence of functionality" to prevent omissions and errors in their preparation and submission, and attach it to the submitted materials.

[3] Abstracts on clinical (human) studies for general consumers

An abstract shall be prepared in which highly technical terms and information are replaced by plain language as much as possible without causing any misunderstanding, so that even ordinary consumers who do not have specialized knowledge can understand it. Each sentence should be of appropriate length and should not be excessively long in order to make the relationship between the subject and predicate of the text clear. The title of the abstract should not exceed 40 characters and the body text should not exceed 1,000 characters (for both the title and body text, one single-byte alphanumeric character, one single-byte symbol, and one line break should be counted as one character each, and the number of characters for the body text includes the number of characters for section titles, such as "Background"). The abstract should only contain information related to the results of the relevant clinical (human) study and should not contain information related to the results of other clinical (human) studies to avoid misinterpretation by general consumers (if necessary, such information may be included in the "Background" section). In particular, the results of clinical (human) studies in which the subjects and the amount of intake are different from those of the food with function claims to be marketed should never be included in the discussion. However, it is acceptable to include information on the mechanism of action to the extent that it does not mislead the general consumers (it should be described in such a way that it is not confused with the results of the clinical [human] study).

The abstract shall be a structured abstract and be provided in Attachment (I). The information to be included in each section is as follows:

A. Title

Use the clearest possible language. Do not use assertive language such as "〇〇 does △△.".

B. Objectives

Describe the details of "PICO" (Participants, Intervention, Comparison, and Outcome) and provide a statement that the objective is to examine them.

C. Background

Briefly describe what has been clarified or not clarified in the relevant field, and describe that you considered it necessary to examine the PICO through the conduct of the clinical study.

D. Methods

Describe subject characteristics (e.g., number of participants, sex, age, health status), study design, intervention (e.g., type of food or functional substance, amount of intake, duration of intervention [intake]), control (e.g., placebo, no intervention), and conflict-of-interest information. Do not describe statistical analysis methods.

E. Key results

Describe the number of subjects assigned to and dropped out of each of the intervention and control groups, the effect of the intervention on the primary and key secondary outcomes, adverse events, and so forth. If the outcomes are not among the ones commonly observed, describe what the outcomes imply.

While it is important to present the values before and after the intervention, they should be presented in a way that does not lead to misinterpretation. For example, it is not appropriate to present the variability of measurements as the standard error of the mean or to present the arithmetic mean as the representative value of a non-normal distribution.

F. Quality of scientific evidence

Describe the limitations of the study, possible biases (especially selection bias), generalizability, and similar factors as well as the interpretation of the results in light of these factors.

Section 3 Conduct of a research review on the final product or functional substances and submission of materials

1. Notes on the conduct of a research review on the final product or functional substance

(1) Prior registration of the study protocol

Although preregistration of the protocol in the UMIN-CTR or other registries is not mandatory, efforts should be made to preregister it as much as possible and to conduct and publish studies of findings, including new ones, on a regular basis.

(2) Basic approach to the conduct of research reviews

In order to avoid inappropriate evaluation of functionality due to arbitrary selection of research papers, companies should conduct qualitative or quantitative research reviews (meta-analysis) using the "totality of evidence" approach (i.e., the relevant studies selected for the research review are examined, regardless of their positive or negative findings and research design, to determine whether they can be said to be positive from a comprehensive perspective) and adopt only reviews that can be judged as positive as the scientific evidence for the proposed functionality of the food with function claims.

For judgments based on the "totality of evidence" approach, the reasonable grounds for the judgment that the proposed functionality is comprehensively affirmed shall be specifically described in the notification materials.

In conducting a research review, it is desirable to extensively gather peer-reviewed academic papers and other available literature (including primary research papers, unreported research information [e.g., research whose protocol has been preregistered but not yet reported due to reasons such as its ongoing status], and unpublished papers) by appropriately using a literature database appropriate for the relevant field, and review those papers carefully for the evaluation of the functionality. While searching for the literature, to avoid language bias (especially English bias), the search should not only be conducted for English papers using overseas literature

databases, but also for Japanese papers using domestic literature databases. For studies conducted overseas, it is necessary to consider whether the findings can be extrapolated to the Japanese population.
In order to ensure objectivity and transparency of the results of research reviews, the following information shall be included in the notification materials: search criteria; information on accepted and rejected papers; the process leading to the results; sponsors and co-sponsors (individuals, companies, research institutions, or other organizations responsible for all or part of the conception, administration, and funding of the research); and conflict-of-interest information, as well as the results of the evaluation of publication bias.
If, as a result of the research review, there is no peer-reviewed paper (clinical [human] studies for processed foods in the form of supplements or clinical [human] studies or observational studies for other processed foods and perishable foods), or no peer-reviewed paper that supports the proposed function, then scientific evidence for the functional claim shall be deemed insufficient, and the functional claim shall not be made.
If multiple functional substances are to be labeled as functional, it shall be sufficient to demonstrate the functionality of each substance, provided that the safety and efficacy of the substances, including the presence or absence of interactions, have been confirmed.
When conducting a research review on a functional substance, it is a prerequisite that the equivalence of the substance under review and the substance in the final product has been examined.
If a processed food in the form of a supplement is to be marketed, positive results must have been obtained in clinical (human) studies that took into account the amount of intake. For other processed foods and perishable foods to be marketed, positive results must have been obtained in clinical (human) studies or observational studies that took into account the amount of intake. "Clinical (human) studies" in this Guideline refers to "studies in humans" as defined in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use". As for observational studies, only longitudinal studies (e.g., prospective cohort studies and case-control studies) shall be included in the review, in principle. Among observational studies, cross-sectional studies are prone to cause-and-effect reversal. Therefore, when cross-sectional studies are used, they should essentially be combined with clinical (human) studies on the functional substance and used to demonstrate the functionality of the substance.
As for the subjects of clinical (human) studies included in the research review, as stated in Section 2-1(2), those who are not suffering from a disease (excluding minors, pregnant women, and lactating mothers) shall be included, in principle, in light of the definition of food with function claims and the intended consumers of the

food[21,22]. The definition of "persons not suffering from a disease" shall also be based on Section 2-1(2).
As for the subjects of observational studies included in the research review, while they may be suffering from a disease at the time of outcome evaluation in prospective cohort studies and at study entry in case-control studies, they should be confirmed by a physician (preferably a specialist in the field) to be disease-free at the beginning of the follow-up period in prospective cohort studies and at a previous time point (assessment time point) in case-control studies. For an observational study in which only the persons who are clearly not suffering from a disease are included, screening by a physician is not mandatory.
In a research review, data that include some persons who are suffering from a disease may be used if the data have been appropriately stratified and analyzed to exclude such persons.
For foods for which functionality cannot be expected from the intake of the food containing the substance alone, but which can provide functionality when added to a specific diet, an appropriate dietary management and dietary survey (for observational studies, an appropriate dietary survey at the beginning and during the observation period) must be conducted before and during the clinical (human) study, and the methods and results of such management and survey must be reported in detail in the paper included in the research review. In such cases, the content of the assumed meal must be clearly stated in the labeling of the functionality of the functional substance or the food containing the substance to be notified to the Commissioner of the CAA (e.g., "This product contains △ mg/day of ○○. Taking △ mg/day of ○○ has been reported to help people who consume about □ g/day of seafood [average intake for Japanese adults] to improve xx")

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[21] The use of data involving persons with mild symptoms shall be permitted on an exceptional basis only to the extent described in the testing methods for foods for specified health uses as specified in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (excluding testing methods for standard reference type, labeling for disease risk reduction, and foods for specified health uses with conditions).
In this case, in order to contribute to the voluntary and rational food selection of the intended consumers of the food with function claims, a research review of data only from persons not suffering from a disease should also be conducted (from among the papers finally included in the research review including persons with mild symptoms, only those papers containing data from persons not suffering from a disease should be selected for review), and the results shall be reported both in the research review report and in the abstract of research review for general consumers.
Data from persons taking a pharmaceutical product or receiving dietary or exercise guidance by a health care professional shall be excluded (only to the extent that they are related to or affect the proposed functionality).

[22] In addition to the exception stated in footnote 21, when including labeling related to "allergic reactions in the nose and eyes", "medium- to long-term serum uric acid levels", or "increased serum uric acid levels after meals" to indicate that health benefits can be expected, data involving persons with mild symptoms shall be permitted for use on an exceptional basis only to the extent described in Appendix 2.

(3) Procedures for conducting a research review

An example procedure for conducting a research review is provided in Appendix 4.

(4) Documents to be submitted regarding research reviews

The documents listed in A to F below shall be submitted.

A. Research review report

Either of the documents listed in (a) or (b) below shall be submitted.

(a) When a peer-reviewed, published research review paper is used as scientific evidence for the proposed functionality

Submit the paper. If the paper is written in English, it is not always necessary to attach a Japanese translation. If the paper is written in a non-Japanese language other than English, an appropriate translation of the entire paper in correct Japanese must be attached along with the original.

The paper shall, in principle, be prepared in a format compliant with the PRISMA Statement (2009) so that third parties can properly evaluate the reported results. If there is any information that is not sufficiently described in the paper in light of the PRISMA Statement Checklist (2009) (Appendix 5), additional explanation is required using Attachment (V)-3, "Supplementary explanatory material on scientific evidence for the proposed functionality". In particular, if all search formulas used in the search are not listed in the paper in an organized form for each literature database, all search formulas must be listed using the "Database search results" sheet in Attachment (V)-5 or any other appropriate form. If any unreported research information retrieved from a research registry database is not listed in the paper, it is desirable to list such information in the "List of unreported research" sheet of Attachment (V)-9 or any other appropriate form.

For research review papers published as peer-reviewed papers before the enactment of the Food Labeling Standards (including papers that have been accepted after peer review and are pending for publication [e.g., in press]), the above additional explanation may be omitted.

(b) When data not published in a peer-reviewed paper are used as scientific evidence for the proposed functionality

The methods and results of the research review shall be described using Attachment (V)-4 (some information may be described using any other appropriate form), Attachments (V)-5 through (V)-10, and Attachment (V)-14 (Attachment (V)-15 for meta-analysis) and submitted (other appropriate forms may be used in place of the Attachments listed above). The format of the descriptions must be in accordance with the PRISMA Statement Checklist (2009) (Appendix 5).

B. Paper quality assessment sheet

The risk of bias for the papers used in the final evaluation shall be summarized for each outcome using Attachment (V)-11 and Attachment (V)-12, "Paper quality assessment sheet", or other appropriate forms and submitted.

If a peer-reviewed, published research review paper is used and the risk of bias for each paper included in the review paper is summarized in the same level of detail as in the sheet, the preparation and submission of the sheet may be omitted.

C. Body of evidence quality assessment sheet

The body of evidence assessed based on the risk of bias risk for each paper, as described in B, shall be summarized for each outcome using Attachment (V)-13, "Body of evidence quality assessment sheet", or any other appropriate form and submitted.

If a peer-reviewed, published research review paper is used and the risk of bias for the papers included in the review paper is summarized for each outcome in equal or greater detail than in the sheet, the preparation and submission of the sheet may be omitted.

D. Evaluation materials on the relevance of the results of the research review to the proposed functionality

The results of this evaluation (see [10] in Appendix 4) shall be summarized and submitted using Attachment (V)-16, "Evaluation sheet on the relevance of the results of the research review to the proposed functionality" or any other appropriate form.

E. Checklist for scientific evidence of functionality

For materials to be submitted regarding research reviews, it is desirable to conduct a self-inspection using Attachment (V)-1, "Checklist for scientific evidence of functionality" to prevent any omissions or errors in their preparation and submission, and attach it to the submitted materials.

F. Abstracts on research reviews for general consumers

An abstract shall be prepared in which highly technical terms and information are replaced by plain language as much as possible without causing any misunderstanding, so that even ordinary consumers who do not have specialized knowledge can understand it. Each sentence should be of appropriate length and should not be excessively long in order to make the relationship between the subject and predicate of the text clear. The title of the abstract should not exceed 40 characters and the body text should not exceed 1,000 characters (for both the title and body text, one single-byte alphanumeric character, one single-byte symbol, and one line break should be counted as one character each, and the number of characters for the body text includes the number of characters for section titles, such as "Background"). This abstract shall only contain information related to the research review and the reference information used for the discussion to supplement the results of the research review (e.g., findings based on out-of-scope study designs, findings

from studies conducted under conditions slightly different from the intended consumers and intake of the food with function claims to be marketed) shall not be included to avoid misinterpretation by general consumers (if necessary, such information may be included in the "Background" section). However, it is acceptable to include information on the mechanism of action to the extent that it does not mislead the general consumers (it should be described in such a way that it is not confused with the results of the research review).
The abstract shall be a structured abstract and be provided in Attachment (I). The information to be included in each section is as follows:

(a) Title
Use the clearest possible language. Do not use assertive language such as "〇〇 does △△.".

(b) Objectives
Describe the details of "PICO" or "PECO" (Participants, Exposure, Comparison, and Outcome [applicable to observational studies]) and provide a statement that the objective is to examine them.

(c) Background
Briefly describe what has been clarified or not clarified in the relevant field, and describe that you considered it necessary to examine the PICO or PECO through the conduct of the research review.

(d) Characteristics of included studies
Describe the date of the search, the period covered by the search (i.e., papers published from when to when were included in the search), characteristics of the population included (e.g., sex, age, health status), the final number of papers evaluated, study design, and conflict-of-interest information. Do not describe the details of the search method (e.g., database name, search terms, search formulas).

(e) Key results
Describe the effects and harms of the intervention or exposure on the primary and key secondary outcomes. If the outcomes are not among the ones commonly observed, describe what the outcomes imply.
While it is important to present numerical data such as effect estimates and their confidence intervals, they should be presented in a manner that does not lead to misinterpretation.

(f) Quality of scientific evidence
The quality of the body of evidence shall be explained based on possible biases (especially publication bias); non-directness (differences in various conditions between the research question and each paper, such as subjects, interventions, comparisons, and outcome measures); inconsistency (i.e., variability of results); and imprecision (e.g., whether small sample sizes or small numbers of events led to wide confidence intervals for effect estimates). It is particularly imperative that the limitations of the study be described.

[References]

- Edited by Fukui T and Yamaguchi N: Minds Guide for Preparation of Treatment Guideline 2014. Igaku-Shoin, 2014.
- Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
- Standards for the reporting of Plain language summaries in new Cochrane Intervention Reviews 2013 Booklet Version 1 September 2013.The Cochrane Collaboration, 2013.

Appendix 2

Handling of data involving patients with mild symptoms

The Food with Function Claims System is intended to label foods for which specific health benefits can be expected from functional substances, targeting people who do not suffer from a disease. Therefore, clinical (human) studies evaluating the functionality of the functional substances must be designed to demonstrate the functionality of foods with function claims for their intended consumers.
Under this System, the clinical (human) studies that provide scientific evidence for the proposed functionality and those that are included in research reviews are the same as the "studies in humans" under the Food for Specified Health Use system, and, in principle, they shall be conducted in accordance with the test methods specified in Attachment 2, "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (CFL Notification No. 259 of the Deputy Commissioner of the CAA, dated October 30, 2014), where the use of the data including persons with mild symptoms is permitted on an exceptional basis only within the scope of the seven health uses listed in the above Notes (related to cholesterol, blood triglycerides in the medium- to long-term, elevated blood triglycerides after eating, blood pressure, elevated blood sugar after eating, body fat, and intestinal regulation).
In addition to this, as scientific evidence for labeling related to "allergic reactions in the nose and eyes", "medium- to long-term serum uric acid levels", or "increased serum uric acid levels after meals" to indicate that health benefits can be expected, data involving persons with mild symptoms may be used on an exceptional basis only within the scope listed below:

1. Allergic reactions in the nose and eyes
   (1) Test methods
   A randomized controlled trial (RCT) design shall be used, in principle. The study can be conducted as a parallel-group comparison study or a crossover comparison study
   For blinding of the study, a double-blind design is recommended, but a single-blind design may be used if a placebo cannot be prepared due to the properties of the functional substance.

   (2) Outcome measures
   Use "nose and eye symptoms" and "degree of interference with daily life". The degree of interference with daily life shall be evaluated together with nose and eye symptoms, based on the assumption that the former will change with changes in the latter.
   Each outcome measure shall be evaluated using the severity grading of allergic rhinitis symptoms as described in the Practical Guideline for the Management of Allergic Rhinitis in Japan 2016, the Japanese Rhinoconjunctivitis Quality of Life

Questionnaire, or similar overseas or validated instruments. Data can be used if they demonstrate the functionality as per any of these instruments.
Even if significant differences in allergen dispersal and study results are found only at some measurement points, they can be considered as valid data if they are properly discussed.

(3) Intake period (study period)
No need to be defined.

(4) Subjects
The subjects shall be healthy persons or healthy persons plus persons with mild symptoms.

Healthy persons:	Persons who have (or have had in the past) allergic symptoms in the nose and eyes and who do not take any allergy medication prior to or during the study period.
Persons with mild symptoms:	Persons who have (or have had in the past) allergic symptoms in the nose and eyes and who occasionally (but not regularly) take allergy medication prior to and during the study period.

(5) Method of confirming functionality
The functionality shall be confirmed in healthy persons or the combined population of healthy persons plus persons with mild symptoms, with a significance level of 5%. If the functionality is to be confirmed in the combined population of healthy persons plus persons with mild symptoms, approximately half or more of the population must consist of healthy persons.
If the percentage of healthy subjects is unknown, it is necessary to provide an appropriate reason to assume that healthy subjects comprise approximately half or more of the population, based on the numerical values of the evaluation parameters.

(6) Handling of data involving persons with diseases outside the scope of the proposed functionality
Even if the values of the test parameters other than those related to the proposed functionality fall within the disease range, such data may be used as valid data, provided it can be confirmed that the study subjects are treated as healthy subjects in the paper. When using data containing test values that fall within the disease range, it must be confirmed whether the test values fall within the disease range, do not fall within the disease range, or are unknown.

2. Medium- to long-term serum uric acid levels
(1) Test methods
A randomized controlled trial (RCT) design shall be used, in principle. It is

recommended that the study be conducted as a parallel-group comparison study, but it may be conducted as a crossover comparison study if required.
For blinding of the study, a double-blind design is recommended, but a single-blind design may be used if a placebo cannot be prepared due to the properties of the functional substance.

(2) Outcome measures
Serum uric acid level

(3) Intake period (study period)
In principle, the intake period shall be 12 weeks, followed by a 4-week follow-up period. Depending on the properties of the functional substance, other scientifically rational test methods may also be used.

(4) Subjects
The subjects shall be healthy persons or healthy persons plus persons with mild symptoms.
Healthy persons: Persons with a serum uric acid level of ≤7.0 mg/dL
Persons with mild symptoms: Persons with a serum uric acid level of 7.1 to 7.9 mg/dL

(5) Method of confirming functionality
The functionality shall be confirmed in healthy persons or the combined population of healthy persons plus persons with mild symptoms, with a significance level of 5%. If the functionality is to be confirmed in the combined population of healthy persons plus persons with mild symptoms, approximately half or more of the population must consist of healthy persons.
If the percentage of healthy subjects is unknown, it is necessary to provide an appropriate reason to assume that healthy subjects comprise approximately half or more of the population, based on the numerical values of the evaluation parameters.

(6) Handling of data involving persons with diseases outside the scope of the proposed functionality
Even if the values of the test parameters other than those related to the proposed functionality fall within the disease range, such data may be used as valid data, provided it can be confirmed that the study subjects are treated as healthy subjects in the paper. When using data containing test values that fall within the disease range, it must be confirmed whether the test values fall within the disease range, do not fall within the disease range, or are unknown.

3. Increased serum uric acid levels after meals
(1) Test methods
A randomized controlled trial (RCT) design shall be used, in principle. It is

recommended that the study be conducted as a crossover comparison study, but it may be conducted as a parallel-group comparison study if required.
For blinding of the study, a double-blind design is recommended, but a single-blind design may be used if a placebo cannot be prepared due to the properties of the functional substance. In order to avoid an excessive increase in serum uric acid levels, it is recommended that the intake of the challenge diet be set for an increase in serum uric acid levels of approximately 1.0 mg/dL.

(2) Outcome measures
Serum uric acid level and AUC

(3) Intake period (study period)
The food shall be consumed once with a challenge diet, or once with a challenge diet after continuous consumption. Serum uric acid levels shall be measured at appropriate time points so that their changes before and after each intake can be evaluated.

(4) Subjects
The subjects shall be healthy persons or healthy persons plus persons with mild symptoms.
Healthy persons: Persons with a serum uric acid level of ≤7.0 mg/dL
Persons with mild symptoms: Persons with a serum uric acid level of 7.1 to 7.9 mg/dL

(5) Method of confirming functionality
The functionality shall be confirmed in healthy persons or the combined population of healthy persons plus persons with mild symptoms, with a significance level of 5%. If the functionality is to be confirmed in the combined population of healthy persons plus persons with mild symptoms, approximately half or more of the population must consist of healthy persons.
If the percentage of healthy subjects is unknown, it is necessary to provide an appropriate reason to assume that healthy subjects comprise approximately half or more of the population, based on the numerical values of the evaluation parameters.

(6) Handling of data involving persons with diseases outside the scope of the proposed functionality
Even if the values of the test parameters other than those related to the proposed functionality fall within the disease range, such data may be used as valid data, provided it can be confirmed that the study subjects are treated as healthy subjects in the paper. When using data containing test values that fall within the disease range, it must be confirmed whether the test values fall within the disease range, do not fall within the disease range, or are unknown.

Appendix 4
Approach to the conduct of systematic reviews (SR) (example)

[1] Establishing a research question appropriate for the proposed functionality

The research question to be examined shall be established in a structured manner using the PICO (for clinical research) or PECO (for observational research) approach (P: participants, I: intervention, E: exposure, C: comparison, O: outcome).

[2] Selection of reviewers

In order to maintain the objectivity of SR, there should be at least two reviewers, in principle. Screening of the related studies shall be conducted independently by two (A and B) or more reviewers, and any discrepancies or questions in their results shall be discussed between them. If the discussion renders it difficult to resolve such issues, another one (C) or more reviewers will arbitrate.

Reviewers A and B are required to have the skills to critically examine academic papers (in English and Japanese) in the relevant field. Reviewer C is required to have, in addition to the above skills, a doctoral or master's degree, experience in writing peer-reviewed academic papers as the first author, and familiarity with SR.

If no one with the above skills is close at hand, it is acceptable to request the cooperation of experts for part or all of the SR work.

In conducting a meta-analysis, a high level of expertise is required, such as knowledge in evaluating heterogeneity among papers. Those who have no experience in SR (e.g., those who have not authored a peer-reviewed SR paper) should avoid conducting a meta-analysis.

[3] Establishing inclusion and exclusion criteria

Inclusion and exclusion criteria appropriate for the PICO or PECO set in [1] shall be established.

In setting these criteria, it is important to take into account the properties of the food with function claims to be marketed, the amount of intake, the intended consumers, the quantitative and qualitative equivalence of the functional substance, and so forth. For example, it is inappropriate to apply the findings of an easily digestible food to an indigestible food or to apply the findings of a food containing multiple substances that are thought to have similar effects to a food containing a single substance. For functional substances, it is also necessary to pay sufficient attention to their origin and extraction method.

[4] Preparation of the review protocol

At the minimum, the following information shall be provided in detail.

A. Search database

- Literature databases
  Although the type of database to be used is not specified, one that is objectively deemed to be appropriate for searching literature in the relevant field shall be selected.
  Representative databases for English-language papers in the medical field (including papers in which only the abstract is written in English) include The Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. It should, however, be noted that there are many papers in certain fields that are not included in PubMed.
- Clinical study registries (e.g., UMIN-CTR)
  In order to ensure that the research question can be reevaluated based on new findings in the future, a search shall be conducted for unreported research information (e.g., research whose protocol has been preregistered but not yet reported due to reasons such as its ongoing status, research that have not been reported although the implementation period has ended).

B. Hand search
- Whether or not a hand search was conducted.
- If conducted, the method used.

C. Handling of gray literature, such as meeting abstracts and administrative materials

D. Selection method
- Primary screening
  Whether a paper should be excluded shall, in principle, be determined based on its title and abstract.
- Secondary screening
  The entire paper shall be read carefully, in principle, to determine whether it should be excluded. Papers that are deemed not to be used as scientific evidence for the proposed functionality, such as studies in which part* or all of the subjects were suffering from a disease at the beginning of the study or survey (data in which subjects with disease were excluded through appropriate stratified analysis or data from patients with diseases that are medically clearly not related to the proposed functionality may be used), studies conducted overseas that are unlikely to be extrapolated to the Japanese population, and studies in which bias due to conflicts of interest is strongly suspected, shall be excluded at this stage.

  * Data involving persons with mild symptoms may be used only to the extent described in the testing methods for foods for specified health uses as specified in Attachment 2 "Notes on Preparation of Application Forms for Food for Specified Health Use" of "Permission etc. for Labeling of Food for Specified Health Use" (CFL Notification No. 259, dated October 30, 2014) (excluding testing methods for standard reference type, labeling for disease risk reduction, and foods for specified health uses with conditions).

Data from persons taking a pharmaceutical product or receiving dietary or exercise guidance by a health care professional shall be excluded (only to the extent that they are related to or affect the proposed functionality).

E. Target study design
- Handling of certain types of clinical (human) studies, especially quasi-RCTs and non-RCTs.

F. Risk of bias and other endpoints in individual studies and their evaluation methods
- See ‘A’ and ‘B’ in [7] and the "Paper quality assessment sheet" (Attachment (V)-11 and (V)-12).

G. Evaluation items for the body of evidence
- See [9] and the "Body of evidence quality assessment sheet" (Attachment (V)-13).

H. Method for integrating individual study results (if meta-analysis is performed)
- Method of testing for heterogeneity
- Selection of models (e.g., fixed-effects model, random effects model)
- Name and version of the software to be used

I. Additional analyses (if meta-analysis is performed)
- Whether or not an additional analysis was conducted.
- If performed, the method used (e.g., sensitivity analysis, meta-regression analysis).

[5] Search formula setting

Search formulas shall be developed for each literature database by appropriately combining free and controlled terms (e.g., MeSH in PubMed) to allow for an exhaustive search.

As described in section (V)-3-1(2) of this document, the search shall include at least English- and Japanese-language papers to avoid language bias.

[6] Conducting a search

The search for relevant studies shall be conducted according to the inclusion and exclusion criteria determined in advance in [3] and the review protocol developed in [4]. If duplicates of the same paper are retrieved across literature databases, the duplicates shall be excluded.

[7] Quality assessment of individual papers

A. Assessment of bias risk

Papers that meet the inclusion criteria in the secondary screening shall be evaluated for quality in terms of bias risk.

Methods of assessing bias risks for clinical (human) studies may include the following:

(a) Risk of selection bias

- Randomization

  Assess whether randomization was done appropriately.

  For example, the risk of selection bias due to the randomization method shall be assessed as "low" if a computer-generated random number table is used; "high" if the randomization is based on parameters such as birth date, individual ID, or odd/even study enrollment date; and "unknown" if the relevant information is not sufficiently described in the paper.

- Allocation concealment

  Prior to the allocation, assess whether allocation concealment was properly performed.

  For example, the risk of selection bias due to the method of allocation concealment shall be assessed as "low" if both the participants and providers of the clinical (human) study could not predict the allocation because of a centralized enrollment process (i.e., the intervention provider is not involved in the allocation, and a third-party organization performs centralized enrollment and issues the allocation codes); "high" if the method of concealment appears to be inadequate; and "unknown" if the relevant information is not sufficiently described in the paper.

(b) Risk of blindness bias (participants)

Assess whether the allocated intervention was adequately concealed (blinded) from the participants and parties involved (including the providers) in the clinical (human) study to ensure proper conduct of the study in the participants (intervention and control groups).

For example, the risk of performance bias due to the blinding method shall be assessed as "low" if both parties were adequately blinded or if the blinding was inadequate but its impact on the outcome is judged to be low; "high" if the impact of inadequate blinding on the outcome is of concern; and "unclear" if the relevant information is not sufficiently described in the paper.

(c) Risk of blindness bias (outcome assessors)

Assess whether the outcome assessors were blinded to the assigned interventions to ensure proper assessment of outcomes.

For example, the risk of detection bias due to the blinding method shall be assessed as "low" if the outcome assessors were adequately blinded or if the blinding was inadequate but its impact on the outcome assessment is judged to be low; "high" if the impact of inadequate blinding on the outcome assessment is of concern; and "unknown" if the relevant information is not sufficiently described in the paper.

(d) Risk of attrition bias
Assess whether there are systematic differences between the groups being compared due to reduced sample size.
For example, the risk of attrition bias shall be assessed as "low" if the number and reasons for missing outcome data are judged to be similar between the intervention and control groups; "high" if the number and reasons for missing outcome data are unbalanced between the intervention and control groups or if the analysis was based on the actual intervention performed (per-protocol set [PPS] analysis), instead of the original assignment-based analysis because many subjects withdrew from the assigned intervention; and "unknown" if the relevant information is not sufficiently described in the paper.

(e) Risk of bias due to reporting of selective outcomes
Assess whether there is any bias due to reporting of selective outcomes.
For example, the risk of reporting bias shall be assessed as "low" if all the primary and secondary outcomes described in the study protocol and preregistered study plan are analyzed and reported in accordance with the protocol; "high" if not all the prespecified primary outcomes are reported or if non-prespecified measurement or analysis methods (e.g., sub-analysis or interim analysis that were not part of the original plan) were used; and "unknown" if the relevant information is not sufficiently described in the paper.

(f) Risk of other biases
Assess whether there is any bias other than the above.
For example, the risk of bias other than the above shall be assessed as "low" if there seems to be no other bias factors; "high" if there seems to be potential bias related to the study design, suspected fraud, or some other problems; and "unknown" if the relevant information is not sufficiently described in the paper.

The risk of biases in observational studies shall be assessed for the following: [1] selection bias in selecting participants (e.g., bias due to selecting exposed and unexposed groups from different populations); [2] measurement bias (e.g., bias due to different investigation methods between exposed and unexposed groups in prospective cohort studies, bias due to differences in the amount and accuracy of past memories between patients and controls in case-control studies [recall bias]); [3] attrition bias (e.g., bias due to incomplete follow-up); and [4] other biases (e.g., inadequate adjustment for confounding factors).

B. Assessment of non-directness
In addition to the above, the non-directness of each paper to the PICO or PECO of SR (i.e., differences in various conditions between the research question and each paper, such as subjects, interventions, comparisons, and outcome measures) shall also be assessed.

[8] Data extraction from each paper
Extract sufficient data from each paper to evaluate the body of evidence. To evaluate the body of evidence as described in [9], the following pieces of information, for example, need to be extracted at a minimum.

A. Clinical (human) studies
Study design, setting (e.g., where the study was conducted [for studies conducted overseas, the name of the country must also be identified]), subject characteristics, intervention (e.g., type of food or functional substance, amount of intake, duration of intervention [intake]), control (e.g., placebo, no intervention), analysis method (e.g., intention-to-treat [ITT], full analysis set [FAS], PPS), primary and secondary outcomes, adverse events, whether or not the study was peer reviewed.

B. Observational studies
Study design, setting (e.g., where the study was conducted [for studies conducted overseas, the name of the country must also be identified]), subject characteristics, exposure (e.g., type of food or functional substance, amount of intake, duration of exposure [intake]), control (e.g., no exposure), adjustment variables, primary and secondary outcomes, adverse events, whether or not the study was peer reviewed.

In order to prevent omissions and errors in data extraction, it is recommended that at least two or more reviewers conduct the data extraction independently.

[9] Evaluation of the body of evidence
Papers that are included in the final evaluation shall be categorized by the study design and then further summarized by the type of comparison (e.g., test diet vs. placebo), type of outcome, and type of subjects. Based on the summarization results (body of evidence), the strength of the evidence shall be evaluated.
Because clinical studies and observational studies have different potential biases due to the study design, the results of both types of studies should not simply be combined for evaluation. For observational studies, the results of prospective studies (e.g., prospective cohort studies) and retrospective studies (e.g., case-control studies) should not simply be combined for evaluation.
When evaluating the body of evidence, it is important to appropriately assess [1] risk of bias, [2] nondirectness, [3] inconsistency (variation in results), [4] imprecision (e.g., whether the confidence interval for the effect estimate is wide due to small

sample size or small number of events), and [5] publication bias. Methods for assessing publication bias include, but are not limited to, graphical evaluation of funnel plots as well as Begg's test and Egger's test.

To quantitatively integrate the results by meta-analysis, the heterogeneity among papers shall be assessed by the chi-square test of Cochran Q statistics or I^2 statistics, and based on the results, an appropriate statistical method (model) shall be selected. Specifically, if the heterogeneity is likely to be low, either a fixed-effects model (depending on the type of outcome, an appropriate one shall be selected from among the Mantel-Haenszel, Peto, or inverse variance methods) or a random-effects model (depending on the type of outcome, an appropriate one shall be selected from among the DerSimonian-Laird method or the restricted maximum-likelihood method) may be selected. In contrast, if the heterogeneity is likely to be high, it is preferable to adopt a random effects model and explain the causes of the heterogeneity by a subgroup analysis or sensitivity analysis. In cases of high bias risks or markedly high heterogeneity among papers, quantitative integration of results should not be performed, and only qualitative evaluation should be conducted.

It should also be noted that when submitting a notification for a food with function claims, it shall be confirmed by both qualitative and quantitative SR that the proposed functionality is demonstrated in peer-reviewed papers based on the "totality of evidence" approach. Although papers that have not been peer-reviewed or papers on studies conducted in out-of-scope designs may not be used as materials for determining the scientific validity of the proposed functionality (as stated in section (V)-3-1(2) of this document, for example, when a food with function claims in the form of a supplement is to be marketed, the findings from a prospective cohort study may not be used as materials for determining the presence or absence of the proposed functionality), these papers may be used as reference information for discussing the functionality. Findings from studies conducted under conditions slightly different from the intended consumers and intake of the food with function claims to be marketed may also be used, although they must not be so different that the extrapolation potential is largely lost.

[10] Evaluation of the relevance of the SR results to the proposed functionality

Evaluate how effective the SR results are as scientific evidence for the functionality to be labeled on the food with function claims, and clarify the limitations, if any. It is particularly essential to discuss the following aspects:

- Food properties (e.g., digestibility of food, effects of nonfunctional substances on the functional substance)
- Subjects
- Qualitative properties of the functional substance (only if applicable)
- Recommended daily intake
- Relationship between outcome measures in SR and the proposed function

[References]

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